



National Comprehensive  
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Non-Small Cell Lung Cancer

Version 7.2019 — August 30, 2019

**NCCN.org**



Download Clinical Guidelines

NCCN Guidelines for Patients® available at [www.nccn.org/patients](http://www.nccn.org/patients)

**Continue**



**\*David S. Ettinger, MD/Chair †**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**\*Douglas E. Wood, MD/Vice Chair ¶**  
Fred Hutchinson Cancer Research Center/Seattle  
Cancer Care Alliance

**Charu Aggarwal, MD, MPH †**  
Abramson Cancer Center at the  
University of Pennsylvania

**Dara L. Aisner, MD, PhD ≠**  
University of Colorado Cancer Center

**Wallace Akerley, MD †**  
Huntsman Cancer Institute at the University of Utah

**Jessica R. Bauman, MD ‡ †**  
Fox Chase Cancer Center

**Ankit Bharat, MD ¶**  
Robert H. Lurie Comprehensive Cancer Center of  
Northwestern University

**Debora S. Bruno, MD, MS †**  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer  
Center and Cleveland Clinic Taussig  
Cancer Institute

**Joe Y. Chang, MD, PhD §**  
The University of Texas MD Anderson Cancer  
Center

**Lucian R. Chirieac, MD ≠**  
Dana-Farber/Brigham and Women's Cancer Center

**Thomas A. D'Amico, MD ¶**  
Duke Cancer Institute

**Thomas J. Dilling, MD, MS §**  
Moffitt Cancer Center

**Michael Dobelbower, MD, PhD §**  
University of Alabama at Birmingham  
Comprehensive Cancer Center

**Scott Gettinger, MD † ¶**  
Yale Cancer Center/Smilow Cancer Hospital

**Ramaswamy Govindan, MD †**  
Siteman Cancer Center at Barnes-Jewish  
Hospital and Washington University School of  
Medicine

**Matthew A. Gubens, MD, MS †**  
UCSF Helen Diller Family Comprehensive  
Cancer Center

**Mark Hennon, MD ¶**  
Roswell Park Cancer Institute

**Leora Horn, MD, MSc †**  
Vanderbilt-Ingram Cancer Center

**Rudy P. Lackner, MD ¶**  
Fred & Pamela Buffett Cancer Center

**Michael Lanuti, MD ¶**  
Massachusetts General Hospital Cancer Center

**Ticiana A. Leal, MD †**  
University of Wisconsin Carbone Cancer Center

**Jules Lin, MD ¶**  
University of Michigan Rogel Cancer Center

**Billy W. Loo, Jr., MD, PhD §**  
Stanford Cancer Institute

**Renato G. Martins, MD, MPH †**  
Fred Hutchinson Cancer Research Center/  
Seattle Cancer Care Alliance

**Gregory A. Otterson, MD †**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Sandip P. Patel, MD ‡ † ¶**  
UC San Diego Moores Cancer Center

**Karen L. Reckamp, MD, MS † ‡**  
City of Hope National Medical Center

**Gregory J. Riely, MD, PhD † ¶**  
Memorial Sloan Kettering Cancer Center

**Steven E. Schild, MD §**  
Mayo Clinic Cancer Center

**Theresa A. Shapiro, MD, PhD ≠**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**James Stevenson, MD †**  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer  
Center and Cleveland Clinic Taussig  
Cancer Institute

**Scott J. Swanson, MD ¶**  
Dana-Farber/Brigham and Women's  
Cancer Center

**Kurt W. Tauer, MD †**  
St. Jude Children's Research Hospital/  
University of Tennessee Health Science Center

**Stephen C. Yang, MD ¶**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**NCCN**

**Kristina Gregory, RN, MSN, OCN**  
**Miranda Hughes, PhD**

**Continue**

† Medical oncology	φ Diagnostic/Interventional radiology
¶ Surgery/Surgical oncology	≠ Patient advocate
§ Radiation oncology/Radiotherapy	¶ Internal medicine
≠ Pathology	*Discussion Section Writing Committee
‡ Hematology/Hematology oncology	





### [NCCN Non-Small Cell Lung Cancer Panel Members](#) [Summary of Guidelines Updates](#)

### [Lung Cancer Prevention and Screening \(PREV-1\)](#) [Clinical Presentation and Risk Assessment \(DIAG-1\)](#) [Initial Evaluation and Clinical Stage \(NSCL-1\)](#) [Evaluation and Treatment:](#)

- [Stage I \(T1abc-2a, N0\), Stage II \(T1abc-2ab, N1; T2b, N0\), Stage IIB \(T3, N0\), and Stage IIIA \(T3, N1\) \(NSCL-2\)](#)
- [Stage IIB \(T3 invasion, N0\) and Stage IIIA \(T4 extension, N0-1; T3, N1; T4, N0-1\) \(NSCL-4\)](#)
- [Stage IIIA \(T1-2, N2\); Stage IIIB \(T3, N2\); Separate Pulmonary Nodules \(Stage IIB, IIIA, IV\) \(NSCL-7\)](#)

### [Multiple Lung Cancers \(N0-1\) \(NSCL-10\)](#)

### [Stage IIIB \(T1-2, N3\); Stage IIIC \(T3, N3\) \(NSCL-11\)](#)

### [Stage IIIB \(T4, N2\); Stage IIIC \(T4, N3\); Stage IVA, M1a: Pleural or Pericardial Effusion \(NSCL-12\)](#)

### [Stage IVA, M1b \(NSCL-13\)](#)

### [Surveillance After Completion of Definitive Therapy \(NSCL-15\)](#)

### [Therapy for Recurrence and Metastasis \(NSCL-16\)](#)

### [Systemic Therapy for Advanced or Metastatic Disease \(NSCL-17\)](#)

### [Principles of Pathologic Review \(NSCL-A\)](#)

### [Principles of Surgical Therapy \(NSCL-B\)](#)

### [Principles of Radiation Therapy \(NSCL-C\)](#)

### [Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy \(NSCL-D\)](#)

### [Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\)](#)

### [Cancer Survivorship Care \(NSCL-F\)](#)

### [Principles of Molecular and Biomarker Analysis \(NSCL-G\)](#)

### [Emerging Biomarkers to Identify Patients with for Therapies \(NSCL-H\)](#)

### [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#)

### [Systemic Therapy for Advanced or Metastatic Disease \(NSCL-J\)](#)

### [Staging \(ST-1\)](#)

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

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/clinicians.aspx](#).

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2019.



Updates in Version 7.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2019 include:

### [NSCL-24](#)

- Entrectinib added as a preferred treatment option for *ROS1* rearrangement positive advanced or metastatic NSCLC.

### [NSCL-26](#)

- Entrectinib added as a treatment option for *NTRK* gene fusion positive advanced or metastatic NSCLC.

### [NSCL-G 4 of 5](#)

- Sentence modified: The FDA-approved IHC assay for PD-L1 utilizes a cutoff of ~~50%~~  $\geq 1\%$  tumor proportion score for first-line and 1% tumor proportion score for second-line therapy with pembrolizumab.

### [NSCL-I 1 of 2](#)

- Entrectinib added for *ROS1* rearrangement positive and *NTRK* gene fusion positive advanced or metastatic NSCLC, including the reference.

### [MS-1](#)

- Discussion section updated based on the changes in the algorithm.

Updates in Version 6.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2019 include:

### [NSCL-27](#)

- The following footnote was added: An FDA-approved biosimilar is an appropriate substitute for bevacizumab. (also applies to NSCL-I 1 of 2, NSCL-J 2 of 4)

### [MS-1](#)

- Discussion section updated based on the changes in the algorithm.

[Continued](#)

**UPDATES**



Updates in Version 5.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2019 include:

### [NSCL-27](#)

Clarifications made for PD-L1 expression positive ( $\geq 1\%$ ) treatment options:

- Adenocarcinoma, large cell, NSCLC NOS: (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1 if PD-L1  $\geq 50\%$ ) (category 1 and preferred if PD-L1 1-49%)
- Squamous cell carcinoma: (Carboplatin or cisplatin) + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (carboplatin combination: [category 1 if PD-L1  $\geq 50\%$ ] [category 1 and preferred if PD-L1 1-49%])

### [MS-1](#)

- Discussion section updated based on the changes in the algorithm.

Updates in Version 4.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 3.2019 include:

### [NSCL-17](#)

- PD-L1 expression percentage changed from  $\geq 50\%$  to  $\geq 1\%$  (also applies to NSCL-27, NSCL-I 1 of 2)

### [NSCL-27](#)

- Pembrolizumab monotherapy added for PD-L1 1-49% with a category 2B designation.
- Footnote bbb added: Pembrolizumab monotherapy can be considered in PD-L1 1-49%, in patients with poor PS or other contraindications to combination chemotherapy.

### [MS-1](#)

- Discussion section updated based on the changes in the algorithm.

Updates in Version 3.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 2.2019 include:

### [NSCL-17](#)

- Footnote jj added: Testing should include the neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion; if positive, see NSCL-26.

### [NSCL-26](#)

- New page added to address the treatment of metastatic NSCLC that is positive for the *NTRK* gene fusion.

### [NSCL-I 1 of 2](#)

- Larotrectinib added for *NTRK* gene fusion positive, including reference.

### [MS-1](#)

- Discussion section updated based on the changes in the algorithm.

Updates in Version 2.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 1.2019 include:

### [NSCL-22](#)

- *ALK* rearrangement positive metastatic NSCLC: Lorlatinib added as a treatment option after progression on crizotinib and alectinib, brigatinib, or ceritinib.

### [NSCL-23](#)

- *ALK* rearrangement positive metastatic NSCLC: Lorlatinib added as a treatment option, after progression on alectinib, brigatinib, or ceritinib

### [NSCL-24](#)

- *ROS1* rearrangement positive metastatic NSCLC: Lorlatinib added as a treatment option, after progression on crizotinib or ceritinib.

[Continued](#)

**UPDATES**



Updates in Version 1.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2018 include:

### **DIAG-2**

- Footnote g modified: "Non-solid (~~ground-glass~~), ~~partially solid~~, or ~~ground-glass~~ nodules may require longer follow-up to exclude indolent adenocarcinoma." (also applies to DIAG-3)

### **DIAG-3**

- Solitary pure ground-glass nodules
  - ▶ ≥6 mm
    - ◊ Follow-up modified: "CT at 6–12 mo to confirm ~~persistence~~, *no growth or change in solid component*, then CT every 2 y until 5 y"
- Solitary part-solid nodule(s); sub-categories modified
  - ▶ "Persistent and <6 mm"
  - ▶ "Persistent and ≥6 mm"
    - ◊ Follow-up modified: CT at 3–6 mo to confirm ~~persistence~~; *no growth or change in solid component*, then annual CT for 5 y

### **DIAG-A 3 of 3**

- Bullet added: "An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection." (also added to footnote h on NSCL-2)
- Bullet modified: "TTNA and anterior mediastinotomy (ie, Chamberlain procedure) provide additional access to anterior mediastinal (station 5 and 6) lymph nodes if these are clinically suspicious. *If TTNA is not possible due to proximity to aorta, VATS biopsy is also an option.*"

### **NSCL-2**

- Durvalumab changed from a category 2A to a category 1 recommendation. (also applies to NSCL-5, 6, 8, 11, 12, E)
- Footnote k added: "If MRI is not possible, CT of head with contrast." (also applies to NSCL-4, 7, 9, 11, 12, 13, 16)

### **NSCL-5**

- Footnote removed: "If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy." (also applies to NSCL-6, NSCL-11, NSCL-12)
- Footnote text moved to Principles of Radiation Therapy: "RT should continue to definitive dose without interruption if patient is not a surgical candidate." (also applies to NSCL-6)

### **NSCL-9**

- Footnote o added: "After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative."

### **NSCL-13**

- Footnote bb added: "Including selected patients with stage M1c and limited number and volume of metastatic lesions amenable to definitive local therapy. Limited number is undefined but clinical trials have included up to 3 to 5 metastases."

### **NSCL-16**

- Clinical presentation modified: "Locoregional recurrence *or symptomatic local disease*"
- SVC obstruction
  - ▶ Treatment options clarified with the addition of "± SVC stent" to concurrent chemoradiation and external-beam RT.
- Severe hemoptysis
  - ▶ Treatment options clarified with addition of "Any combination of the following"

[Continued](#)

**UPDATES**



Updates in Version 1.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2018 include:

### **NSCL-17**

- Adenocarcinoma/Large cell/NSCLC not otherwise specified (NOS); Testing
  - ▶ PD-L1 testing changed from category 2A to category 1
- Squamous cell carcinoma; Testing
  - ▶ *ROS1* and *BRAF* testing clarified with additional wording: "in small biopsy specimens or mixed histology"
  - ▶ PD-L1 testing changed from category 2A to category 1
- PD-L1  $\geq 50\%$  positive: "*ROS1*, *BRAF* negative or unknown removed." (also applies to NSCL-26)
- Footnote gg modified: "If repeat biopsy is not feasible, plasma biopsy-testing should be considered."
- Footnote removed: "PD-L1 expression levels  $\geq 50\%$  are a positive test result for first-line pembrolizumab therapy."

### **NSCL-18**

- First-line therapy for sensitizing EGFR mutation positive metastatic NSCLC
  - ▶ Osimertinib listed as preferred.
  - ▶ Dacomitinib added as a category 1 treatment option.

### **NSCL-19**

- Subsequent Therapy
  - ▶ Asymptomatic
    - ◇ "Consider local therapy" changed to "Consider definitive local therapy (eg, SABR or surgery) for limited lesions" (also applies to NSCL-20, NSCL-22, and NSCL-23)
    - ◇ Continue dacomitinib added as a treatment option.
  - ▶ Brain
    - ◇ "Consider local therapy" changed to "Consider definitive local therapy (eg, SRS) for limited lesions" (also applies to NSCL-20, NSCL-22, and NSCL-23)
    - ◇ Continue dacomitinib added as a treatment option.
  - ▶ Isolated lesion
    - ◇ "Consider local therapy" changed to "Consider definitive local therapy (eg, SABR or surgery)" (also applies to NSCL-20, NSCL-22, and NSCL-23)
    - ◇ Continue dacomitinib added as a treatment option.
- Footnote pp modified: "~~If tissue biopsy is not feasible, plasma biopsy should be considered. Consider reflex to tissue-based testing, if plasma test is negative for the T790M mutation.~~ Plasma-based testing should be considered at progression on EGFR TKIs for the T790M mutation. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral."
- Footnote rr added: In the randomized phase III trial of dacomitinib, patients with brain metastases were not eligible for enrollment. In the setting of brain metastases, consider other options.
- Footnote tt modified: "The data in the second-line setting suggest that immunotherapy *PD-1/PD-L1 inhibitor monotherapy* is less effective, irrespective of PD-L1 expression, in tumors with an actionable mutation *EGFR+ or ALK+ NSCLC.*" (also applies to NSCL-20, NSCL-22, NSCL-23)
- Footnote removed: "For rapid radiologic progression or threatened organ function, alternate therapy should be instituted." (also applies to NSCL-22, NSCL-23)

**Continued**  
**UPDATES**



Updates in Version 1.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2018 include:

### [NSCL-21](#)

- **ALK rearrangement discovered prior to first-line systemic therapy:** Brigatinib added as a category 1 treatment option.
- **ALK rearrangement discovered during first-line systemic therapy**
  - ▶ Alectinib noted as preferred.
  - ▶ Brigatinib added as a treatment option.

### [NSCL-22](#)

- **Symptomatic brain progression:** "continue crizotinib" removed.
- **Footnote removed:** "If considering WBRT, consider switching ALK inhibitor before using WBRT." (also applies to NSCL-23)

### [NSCL-23](#)

- **Subsequent therapy:** Continue brigatinib added as a treatment option.

### [NSCL-24](#)

- **The following categories added:** "*ROS1* rearrangement discovered during first-line systemic therapy" with the recommendation to "Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by crizotinib (preferred) or ceritinib."
- **Footnote removed:** "The data in the second-line setting suggest that immunotherapy is less effective, irrespective of PD-L1 expression, in tumors with an actionable mutation."

### [NSCL-25](#)

- **The following category added:** "*BRAF V600E* mutation discovered during first-line systemic therapy" with the recommendation to "Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by dabrafenib + trametinib."
- **Footnote removed:** "At this point, there are no published data on the progression-free survival (PFS) of patients treated in the first-line setting."

### [NSC-26](#)

- **PD-L1 category modified** with the addition of "and no contraindications to the addition of pembrolizumab or atezolizumab"
- **Histology and performance status added** as treatment criteria
- **Adenocarcinoma/Large cell/NSCLC NOS**
  - ▶ Pembrolizumab noted as preferred
  - ▶ **The following regimens added as category 1**
    - ◇ (Carboplatin or cisplatin) + pemetrexed + pembrolizumab
    - ◇ Carboplatin + paclitaxel + bevacizumab + atezolizumab
  - ▶ **Continuation maintenance**
    - ◇ Pembrolizumab added as a category 1 recommendation.
- **Squamous cell carcinoma**
  - ▶ Pembrolizumab noted as preferred
  - ▶ **The following regimens added as category 1**
    - ◇ Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab
  - ▶ **The following regimens added as category 2A**
    - ◇ Cisplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab

[Continued](#)  
**UPDATES**





Updates in Version 1.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2018 include:

#### [NSC-26](#)

- Footnote zz added: "Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene which would predict lack of benefit. If contraindications, refer to NSCL-27 (adenocarcinoma) or NSCL-28 (squamous cell carcinoma)." (Also applies to NSCL-J 2 of 4, NSCL-J 3 of 4)
- Footnote aaa added: "If pembrolizumab monotherapy given."
- Footnote ddd added: "If patient has not received platinum-doublet chemotherapy refer to 'systemic therapy.' If patient received platinum chemotherapy and anti-PD-1/PD-L1, refer to 'subsequent therapy.'"

#### [NSCL-27](#)

- Footnote tt added: "The data in the second-line setting suggest that PD-1/PD-L1 monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR+/ALK+* NSCLC." (also for NSCL-28)
- Footnote ggg added: "If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended." (also applies to NSCL-28, NSCL-J 2 of 4, NSCL-J 3 of 4)

#### [NSCL-A 1 of 4](#)

- Bullet 2 modified: "Formalin-fixed paraffin-embedded (FFPE) material is suitable for most molecular analyses, except bone biopsies that were previously treated with acid decalcifying solutions. Non-acid decalcification approaches may be successful for subsequent molecular testing. ~~Many molecular pathology laboratories also accept cytopathology specimens such as direct smears or touch preparations. While many molecular pathology laboratories currently also accept cytopathology specimens such as cell blocks, direct smears, or touch preparations, laboratories that do not currently do so are strongly encouraged to identify approaches to testing on non-FFPE cytopathology specimens.~~"

#### [NSCL-B 1 of 4](#)

- Evaluation, bullet 3 modified: "*For medically operable disease*, resection is the preferred local treatment modality (other modalities include SABR, *thermal ablation such as* radiofrequency ablation and cryotherapy). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where SABR is considered for high-risk or *borderline operable* patients, a multidisciplinary evaluation including a radiation oncologist is recommended."

#### [NSCL-C 1 of 10](#)

- General Principles; bullet 2, sentence 2 modified: "Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with *stage III NSCLC, early-stage disease who are medically inoperable, refuse surgery, or are high-risk surgical candidates, and stage IV disease that may benefit from local therapy.*"

#### [NSCL-C 2 of 10](#)

- Radiation Therapy Simulation, Planning, and Delivery; bullet 4 modified: "IGRT—including (but not limited to) orthogonal pair planar imaging and/or volumetric imaging (such as CBCT or CT on rails)—is recommended when using SABR, ~~and~~ 3D-CRT/IMRT, *and proton therapy* with steep dose gradients around the target, when OARs are in close proximity to high-dose regions, and when using complex motion management techniques."



Updates in Version 1.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2018 include:

### [NSCL-C 3 of 10](#)

#### • General Treatment Information

##### ▶ Early-Stage NSCLC (Stage I, selected node negative Stage IIA)

- ◊ **Bullet 1 modified:** "SABR (also known as SBRT) is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation. SABR has achieved *good* primary tumor control rates and overall survival, *higher than conventionally fractionated radiotherapy, although not proven equivalent* comparable to lobectomy and higher than 3D-CRT in nonrandomized and population-based comparisons in medically inoperable or older patients."
- ◊ **Bullet 2 modified:** "SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years], poor lung function). ~~SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control.~~"
- ◊ **Bullet removed:** "A combined analysis of two randomized trials (that individually did not complete accrual) of SABR vs. lobectomy in operable patients found similar cancer-specific outcomes and improved toxicity profile and survival for SABR compared to surgery.<sup>14</sup> This analysis does not provide sufficient data to change the standard of care for good surgical candidates but strengthens the indication for SABR in patients with relative contraindications for surgery or who refuse surgery."
- ▶ **SABR for Node-Negative Early-Stage NSCLC**
  - ◊ **Dosing regimen;** sentence added: "However, particular attention should be paid to tumors abutting the bronchial tree and esophagus to avoid severe toxicity."

### [NSCL-C 4 of 10](#)

#### • Locally Advanced NSCLC (Stage II/III)

- ▶ **Bullet 1 modified:** "Concurrent chemotherapy/RT is recommended for patients with inoperable stage II (node positive) and stage III NSCLC ~~followed by consolidation durvalumab for stage III.~~"
- ▶ **Bullet removed:** "RT has a role before or after surgery."
- ▶ **Bullet 4 modified** with the addition of this sentence: "RT should be planned up front such that it continues to a definitive dose without interruption if the patient does not proceed to surgery as initially planned."
- ▶ **Bullet 7 modified:** "Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy ~~PORT with concurrent chemotherapy can be administered safely in medically fit patients and is recommended and concurrently with chemotherapy for positive resection margins.~~"

### [NSCL-C 5 of 10](#)

#### • Advanced/Metastatic NSCLC (Stage IV)

- ▶ **Bullet 2 modified:** "Definitive RT to oligometastases (*limited number is not universally defined but clinical trials have included up to 3–5 metastases*), particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites. *In 2* randomized phase II trials, significantly improved progression-free survival was found for local consolidative therapy (RT or surgery) to oligometastatic lesions versus maintenance systemic therapy or observation for patients not progressing on systemic therapy ~~for local consolidative therapy.~~"
- ▶ **Bullet 3 added:** "In the setting of progression at a limited number of sites on a given line of systemic therapy (oligoprogression), local ablative therapy to the oligoprogressive sites may extend the duration of benefit of the current line of systemic therapy."
- ▶ **Bullet 4 added:** "When treating oligometastatic/oligoprogressive lesions, if SABR is not feasible, other dose-intensive accelerated/hypofractionated conformal radiation therapy regimens may be used."
- **Palliative RT for Advanced Metastatic NSCLC**
  - ▶ **Second sentence modified:** "Shorter courses of RT are preferred for patients with poor performance status and/or shorter life expectancy because they provide similar pain relief as longer courses, although there is a higher potential need for retreatment, ~~and are preferred for patients with poor performance status and/or shorter life expectancy.~~"

[Continued](#)  
**UPDATES**



Updates in Version 1.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2018 include:

### [NSCL-C 8 of 10](#)

- Table 5 title change to include "With Concurrent Chemotherapy"

- ▶ Lung

- ◊ V20 modified to  $\leq 35\text{--}40\%$ ; V5 removed

- ▶ Heart

- ◊ V50  $\leq 25\%$  added; V40, V45, V60 removed

- ◊ Mean changed from  $\leq 26$  Gy to  $\leq 20$  Gy

- ▶ Esophagus

- ◊ V60  $\leq 17\%$  added

- ◊ "Contralateral sparing is desirable" added

- ▶ Brachial plexus modified: "Max/Median dose  $\leq 6669$  Gy"

- The following footnotes added:

- ▶ "These constraints represent doses that generally should not be exceeded. Because the risk of toxicity increases progressively with dose to normal tissues, a key principle of radiation treatment planning is to keep normal tissue doses 'as low as reasonably achievable' while adequately covering the target. The doses to any given organ at risk should typically be lower than these constraints, approaching them only when there is close proximity to the target volume."

- ▶ "Use V20  $< 35\%$ , especially for the following: elderly  $\geq 70$  years, taxane chemotherapy, and poor PFTs (such as FEV1 or DLCO  $< 50\%$  normal). Use more conservative limits with a diagnosis or radiologic evidence of idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) (the tolerance of these patients is lower though not well characterized)."

- The following footnote removed: "RTOG 0617 data suggest that even lower radiation doses to the heart than previously appreciated may be detrimental to survival after thoracic RT, and more stringent constraints may be appropriate."

### [NSCL-C 9 of 10](#) and [NSCL-10 of 10](#)

- References 4, 19, 26, 42, 64, 90, 94 added.

### [NSCL-G 1 of 5](#)

- Specimen Acquisition and Management; bullet 1 modified: "Although tumor testing has been primarily focused on use of formalin-fixed paraffin-embedded (FFPE) tissues, increasingly, laboratories accept other specimen types, notably cytopathology smear-preparations *not processed by FFPE methods. Although testing on cell blocks is not included in the FDA approval for multiple companion diagnostic assays, testing on these specimen types is highly recommended when it is the only or best material.*"
- Testing Methodologies; bullet 1 modified: "Next-generation sequencing (NGS) is ~~increasingly utilized~~ used in clinical laboratories. Not all types of alterations are detected by individual NGS assays and it is important to be familiar with the types of alterations identifiable in individual assays or combination(s) of assays."

### [NSCL-G 4 of 5](#)

- Bullet removed: "EGFR mutations: Limited mutation-specific antibodies are available for EGFR. While these antibodies have good specificity, the sensitivity is lacking, and it is not recommended to use EGFR mutation-specific antibodies except in circumstances of extremely limited tissue, because many sensitizing EGFR mutations are not detected with this approach."



Updates in Version 1.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2018 include:

### [NSCL-G 5 of 5](#)

- Section added:

- ▶ **Plasma Cell-Free/Circulating Tumor DNA Testing:**

- ▶ Cell-free/circulating tumor DNA testing should not be used in lieu of a tissue diagnosis.
- ▶ Some laboratories offer testing for molecular alterations examining nucleic acids in peripheral circulation, most commonly in processed plasma (sometimes referred to as 'liquid biopsy').
- ▶ Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to 30% false-negative rate.
- ▶ Standards for analytical performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.
- ▶ Cell-free tumor DNA testing can identify alterations that are unrelated to a lesion of interest, for example, clonal hematopoiesis of indeterminate potential (CHIP).
- ▶ The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably:
  - ◊ If a patient is medically unfit for invasive tissue sampling
  - ◊ In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified"

### [NSCL-H](#)

- Title changed to "Emerging Biomarkers to Identify Patients for Therapies"
- "Tumor Mutation Burden" added
  - ▶ Available Targeted Agents: "Nivolumab + ipilimumab and Nivolumab" added
  - ▶ References 10, 11 added.
  - ▶ Footnote added: "TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB."

### [NSCL-I 1 of 2](#)

- PD-L1 expression changed to PD-L1  $\geq 50\%$ 
  - ▶ First-line therapy
    - ◊ The following regimens added:
      - (Carboplatin or cisplatin)/pemetrexed/pembrolizumab (nonsquamous)
      - Carboplatin + paclitaxel/bevacizumab/atezolizumab (nonsquamous)
      - (Carboplatin or cisplatin)/(paclitaxel or albumin-bound paclitaxel)/pembrolizumab (squamous)
  - ▶ Subsequent therapy removed.
- Description of Maintenance Therapy Added.

### [NSCL-I 2 of 2](#)

- References 3, 10, 25-27 added.



Updates in Version 1.2019 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2018 include:

### [NSCL-J 1 of 4](#)

- Monitoring clarified as during initial therapy or during subsequent therapy

The following text removed:

- **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 ( $\approx 25\%$ – $35\%$ ), 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 Systemic 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."

### [NSCL-J 2 of 4](#)

- Categories added:

- ▶ "No contraindications to the addition of pembrolizumab or atezolizumab"
- ▶ "Contraindications to the addition of pembrolizumab or atezolizumab"

- The following regimens noted as preferred:

- ▶ (Carboplatin or cisplatin)/pemetrexed/pembrolizumab

- Footnote c added: "PD-1/PD-L1 contraindications may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene which would predict lack of benefit." (also applies to NSCL-J 3 of 4)

### [NSCL-J 3 of 4](#)

- Categories added:

- ▶ No contraindications to the addition of pembrolizumab
- ▶ Contraindications to the addition of pembrolizumab

- The following regimens noted as category 1 and preferred:

- ▶ Pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel)

- The following regimens added as category 2A:

- ▶ Pembrolizumab/cisplatin/(paclitaxel or albumin-bound paclitaxel)

**LUNG CANCER PREVENTION AND SCREENING**

- Lung cancer is a unique disease in that the major etiologic agent is an addictive product that is made and promoted by an industry. Approximately 85% to 90% of cases are caused by voluntary or involuntary (second-hand) cigarette smoking. Reduction of lung cancer mortality will require effective public health policies to prevent initiation of smoking, U.S. Food and Drug Administration (FDA) oversight of tobacco products, and other tobacco control measures.
- Persistent smoking is associated with second primary cancers, treatment complications, drug interactions, other tobacco-related medical conditions, diminished quality of life, and reduced survival.
- Reports from the Surgeon General on both active smoking ([http://www.cdc.gov/tobacco/data\\_statistics/sgr/2004/pdfs/executivesummary.pdf](http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf)) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk for lung cancer from second-hand smoke exposure associated with living with a smoker (<http://www.ncbi.nlm.nih.gov/books/NBK44324/>). Every person should be informed of the health consequences, addictive nature, and mortal threat posed by tobacco consumption and exposure to tobacco smoke, and effective legislative, executive, administrative, or other measures should be contemplated at the appropriate governmental level to protect all persons from exposure to tobacco smoke ([www.who.int/tobacco/framework/final\\_text/en/](http://www.who.int/tobacco/framework/final_text/en/)).
- Further complicating this problem, the delivery system of lung carcinogens also contains the highly addictive substance, nicotine. Reduction of lung cancer mortality will require widespread implementation of Agency for Healthcare Research and Quality (AHRQ) Guidelines (<http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html>) to identify, counsel, and treat patients with nicotine habituation.
- Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.
- Lung cancer screening using low-dose CT (LDCT) is recommended in select high-risk smokers and former smokers (see the [NCCN Guidelines for Lung Cancer Screening](#)).
- See the [NCCN Guidelines for Smoking Cessation](#).

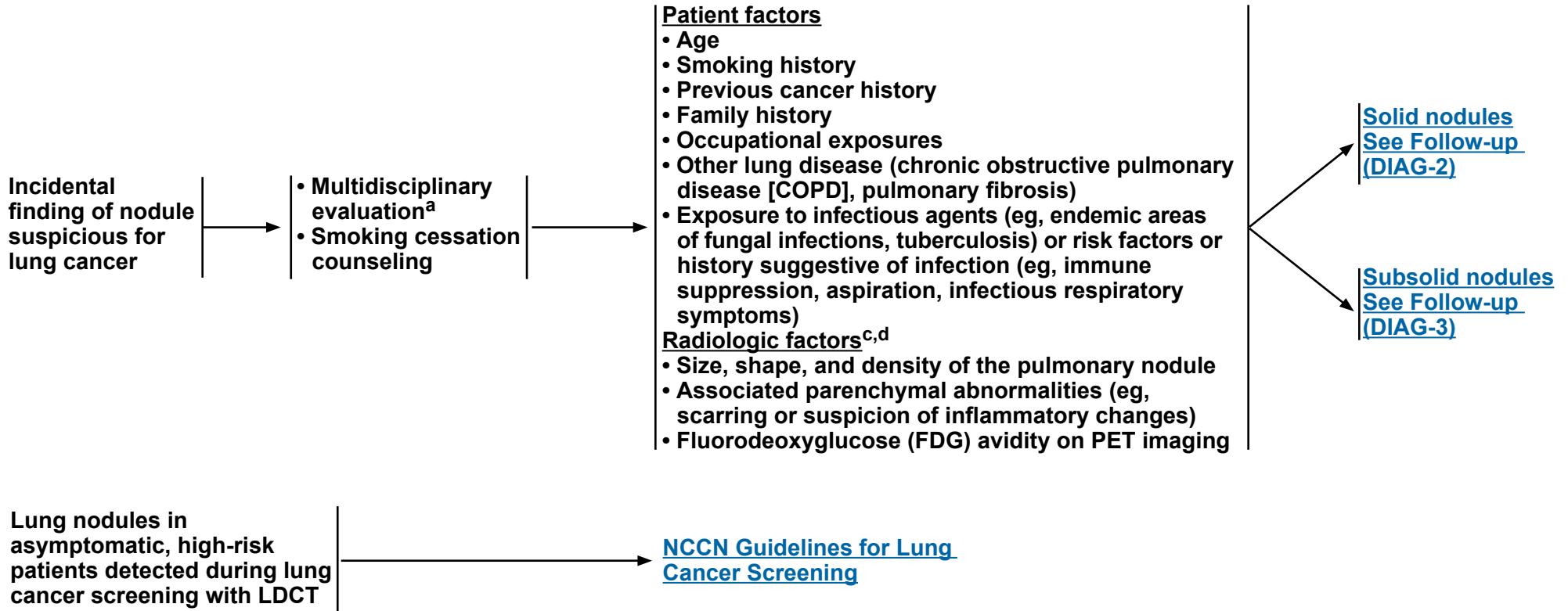
**Note:** All recommendations are category 2A unless otherwise indicated.

**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.



### CLINICAL PRESENTATION

### RISK ASSESSMENT<sup>b</sup>



<sup>a</sup>Multidisciplinary evaluation including thoracic surgeons, thoracic radiologists, and pulmonologists to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy.

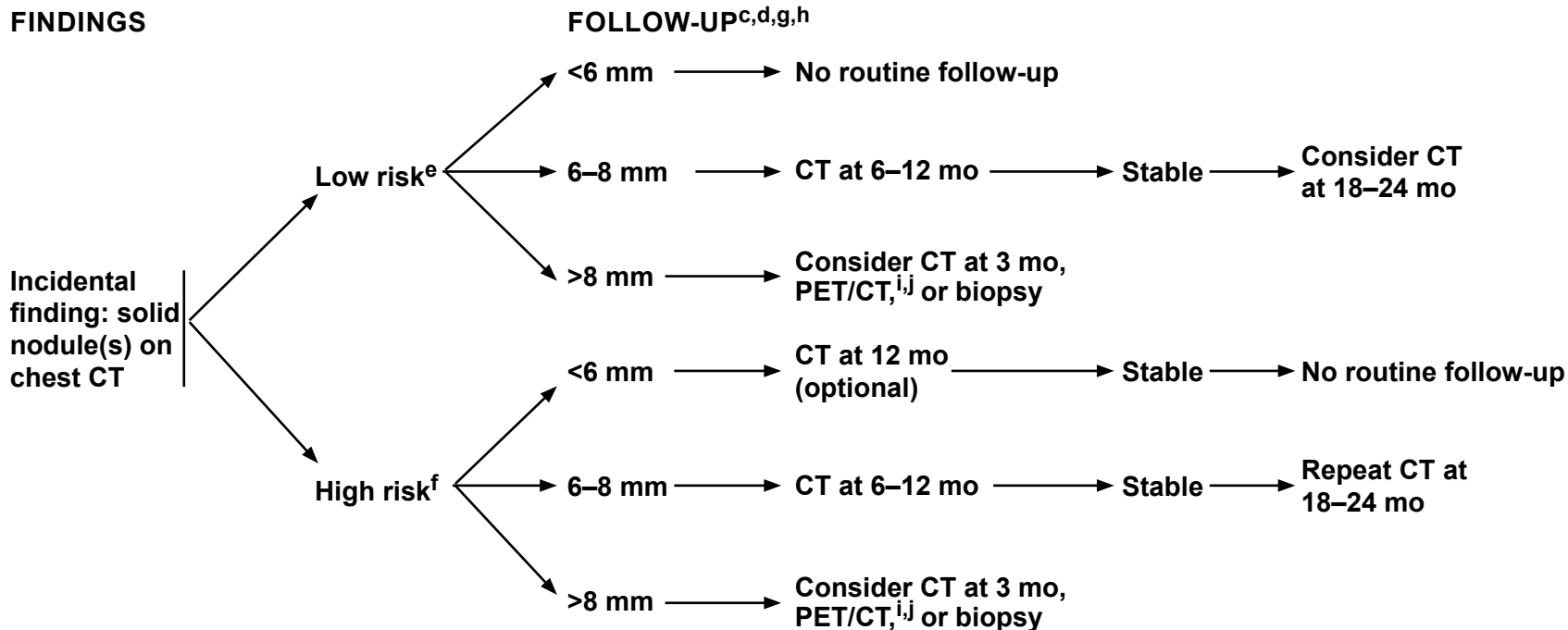
<sup>b</sup>Risk calculators can be used to quantify individual patient and radiologic factors but do not replace evaluation by a multidisciplinary diagnostic team with substantial experience in the diagnosis of lung cancer.

<sup>c</sup>[See Principles of Diagnostic Evaluation \(DIAG-A 1 of 3\).](#)

<sup>d</sup>The most important radiologic factor is change or stability compared with a previous imaging study.

**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.**





<sup>c</sup>See Principles of Diagnostic Evaluation (DIAG-A 1 of 3).

<sup>d</sup>The most important radiologic factor is change or stability compared with a previous imaging study.

<sup>e</sup>Low risk = minimal or absent history of smoking or other known risk factors.

<sup>f</sup>High risk = history of smoking or other known risk factors. Known risk factors include history of lung cancer in a first-degree relative; exposure to asbestos, radon, or uranium.

<sup>g</sup>Non-solid (ground-glass) nodules may require longer follow-up to exclude indolent adenocarcinoma.

<sup>h</sup>Adapted from Fleischner Society Guidelines: MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner Society 2017. *Radiology* 2017;284:228-243. ©Radiological Society of North America. Fleischner Society Guidelines do not direct whether or not contrast is necessary or if an LDCT is appropriate. LDCT is preferred unless there is a reason for contrast enhancement for better diagnostic resolution.

<sup>i</sup>PET/CT performed skull base to knees or whole body. A positive PET result is defined as a standardized uptake value (SUV) in the lung nodule greater than the baseline mediastinal blood pool. A positive PET scan finding can be caused by infection or inflammation, including absence of lung cancer with localized infection, presence of lung cancer with associated (eg, postobstructive) infection, and presence of lung cancer with related inflammation (eg, nodal, parenchymal, pleural). A false-negative PET scan can be caused by a small nodule, low cellular density (nonsolid nodule or ground-glass opacity [GGO]), or low tumor avidity for FDG (eg, adenocarcinoma in situ [previously known as bronchoalveolar carcinoma], carcinoid tumor).

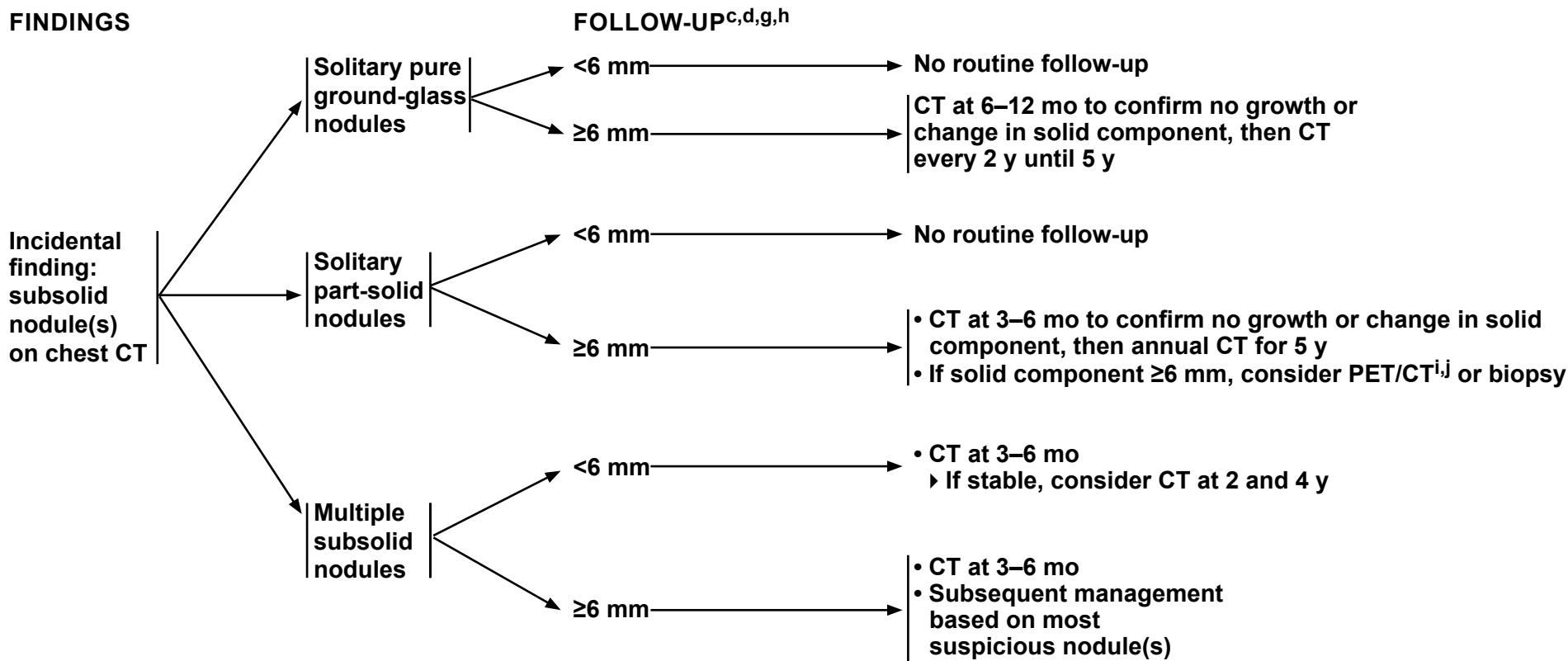
<sup>j</sup>Patients with a suspicion of lung cancer after PET/CT require histologic confirmation before any nonsurgical therapy. When a biopsy is not possible, a multidisciplinary evaluation should be done including radiation oncology, surgery, and interventional pulmonology.

**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.**



### FINDINGS



<sup>c</sup>See Principles of Diagnostic Evaluation (DIAG-A.1 of 3).

<sup>d</sup>The most important radiologic factor is change or stability compared with a previous imaging study.

<sup>g</sup>Non-solid (ground-glass) nodules may require longer follow-up to exclude indolent adenocarcinoma.

<sup>h</sup>Adapted from Fleischner Society Guidelines: MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner Society 2017. Radiology 2017;284:228-243. ©Radiological Society of North America. Fleischner Society Guidelines do not direct whether or not contrast is necessary or if an LDCT is appropriate. LDCT is preferred unless there is a reason for contrast enhancement for better diagnostic resolution.

<sup>i</sup>PET/CT performed skull base to knees or whole body. A positive PET result is defined as a standardized uptake value (SUV) in the lung nodule greater than the baseline mediastinal blood pool. A positive PET scan finding can be caused by infection or inflammation, including absence of lung cancer with localized infection, presence of lung cancer with associated (eg, postobstructive) infection, and presence of lung cancer with related inflammation (eg, nodal, parenchymal, pleural). A false-negative PET scan can be caused by a small nodule, low cellular density (nonsolid nodule or ground-glass opacity [GGO]), or low tumor avidity for FDG (eg, adenocarcinoma in situ [previously known as bronchoalveolar carcinoma], carcinoid tumor).

<sup>j</sup>Patients with a suspicion of lung cancer after PET/CT require histologic confirmation before any nonsurgical therapy. When a biopsy is not possible, a multidisciplinary evaluation should be done including radiation oncology, surgery, and interventional pulmonology.

**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.**

**PRINCIPLES OF DIAGNOSTIC EVALUATION**

- **Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.**
  - ▶ **A biopsy adds time, costs, and procedural risk and may not be needed for treatment decisions.**
  - ▶ **A preoperative biopsy may be appropriate if a non-lung cancer diagnosis is strongly suspected that can be diagnosed by core biopsy or fine-needle aspiration (FNA).**
  - ▶ **A preoperative biopsy may be appropriate if an intraoperative diagnosis appears difficult or very risky.**
  - ▶ **If a preoperative tissue diagnosis has not been obtained, then an intraoperative diagnosis (ie, wedge resection, needle biopsy) is necessary before lobectomy, bilobectomy, or pneumonectomy.**
- **Bronchoscopy should preferably be performed during the planned surgical resection, rather than as a separate procedure.**
  - ▶ **Bronchoscopy is required before surgical resection ([see NSCL-2](#)).**
  - ▶ **A separate bronchoscopy may not be needed for treatment decisions before the time of surgery and adds time, costs, and procedural risk.**
  - ▶ **A preoperative bronchoscopy may be appropriate if a central tumor requires pre-resection evaluation for biopsy, surgical planning (eg, potential sleeve resection), or preoperative airway preparation (eg, coring out an obstructive lesion).**
- **Invasive mediastinal staging is recommended before surgical resection for most patients with clinical stage I or II lung cancer ([see NSCL-2](#)).**
  - ▶ **Patients should preferably undergo invasive mediastinal staging (mediastinoscopy) as the initial step before the planned resection (during the same anesthetic procedure), rather than as a separate procedure. For patients undergoing endobronchial ultrasound (EBUS)/endoscopic ultrasound (EUS) staging, this may require a separate procedure to allow evaluation if onsite rapid cytology interpretation is not available.**
  - ▶ **A separate staging procedure adds time, costs, coordination of care, inconvenience, and an additional anesthetic risk.**
  - ▶ **Preoperative invasive mediastinal staging may be appropriate for a strong clinical suspicion of N2 or N3 nodal disease or when intraoperative cytology or frozen section analysis is not available.**
- **In patients with suspected non-small cell lung cancer (NSCLC), many techniques are available for tissue diagnosis.**
  - ▶ **Diagnostic tools that should be routinely available include:**
    - ◊ **Sputum cytology**
    - ◊ **Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)**
    - ◊ **Image-guided transthoracic needle core biopsy (preferred) or FNA**
    - ◊ **Thoracentesis**
    - ◊ **Mediastinoscopy**
    - ◊ **Video-assisted thoracic surgery (VATS) and open surgical biopsy**
  - ▶ **Diagnostic tools that provide important additional strategies for biopsy include:**
    - ◊ **EBUS–guided biopsy**
    - ◊ **EUS–guided biopsy**
    - ◊ **Navigational bronchoscopy**

**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.



### PRINCIPLES OF DIAGNOSTIC EVALUATION

- **The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.**
  - ▶ **Factors to be considered in choosing the optimal diagnostic step include:**
    - ◊ **Anticipated diagnostic yield (sensitivity)**
    - ◊ **Diagnostic accuracy including specificity and particularly the reliability of a negative diagnostic study (ie, true negative)**
    - ◊ **Adequate volume of tissue specimen for diagnosis and molecular testing**
    - ◊ **Invasiveness and risk of procedure**
    - ◊ **Efficiency of evaluation**
      - **Access and timeliness of procedure**
      - **Concomitant staging is beneficial, because it avoids additional biopsies or procedures. It is preferable to biopsy the pathology that would confer the highest stage (ie, to biopsy a suspected metastasis or mediastinal lymph node rather than the pulmonary lesion). Therefore, PET imaging is frequently best performed before a diagnostic biopsy site is chosen in cases of high clinical suspicion for aggressive, advanced-stage tumors.**
    - ◊ **Technologies and expertise available**
    - ◊ **Tumor viability at proposed biopsy site from PET imaging.**
  - ▶ **Decisions about the optimal diagnostic steps for suspected stage I to III lung cancer should be made by thoracic radiologists, interventional radiologists, and board-certified thoracic surgeons who devote a significant portion of their practice to thoracic oncology. Multidisciplinary evaluation should also include a pulmonologist or thoracic surgeon with expertise in advanced bronchoscopic techniques for diagnosis.**

**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.**



### PRINCIPLES OF DIAGNOSTIC EVALUATION

- ▶ **The least invasive biopsy with the highest yield is preferred as the first diagnostic study.**
  - ◇ **Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.**
  - ◇ **Patients with peripheral (outer one-third) nodules may benefit from navigational bronchoscopy, radial EBUS, or transthoracic needle aspiration (TTNA).**
  - ◇ **Patients with suspected nodal disease should be biopsied by EBUS, EUS, navigational bronchoscopy, or mediastinoscopy.**
    - **EBUS provides access to nodal stations 2R/2L, 4R/4L, 7, 10R/10L, and other hilar nodal stations if necessary.**
    - **An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.**
    - **EUS-guided biopsy provides additional access to stations 5, 7, 8, and 9 lymph nodes if these are clinically suspicious.**
    - **TTNA and anterior mediastinotomy (ie, Chamberlain procedure) provide additional access to anterior mediastinal (stations 5 and 6) lymph nodes if these are clinically suspicious. If TTNA is not possible due to proximity to aorta, VATS biopsy is also an option.**
  - ◇ **EUS also provides reliable access to the left adrenal gland.**
  - ◇ **Lung cancer patients with an associated pleural effusion should undergo thoracentesis and cytology. A negative cytology result on initial thoracentesis does not exclude pleural involvement. An additional thoracentesis and/or thoroscopic evaluation of the pleura should be considered before starting curative intent therapy.**
  - ◇ **Patients suspected of having a solitary site of metastatic disease should have tissue confirmation of that site if feasible.**
  - ◇ **Patients suspected of having metastatic disease should have confirmation from one of the metastatic sites if feasible.**
  - ◇ **Patients who may have multiple sites of metastatic disease—based on a strong clinical suspicion—should have biopsy of the primary lung lesion or mediastinal lymph nodes if it is technically difficult or very risky to biopsy a metastatic site.**

**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.**



# NCCN Guidelines Version 7.2019

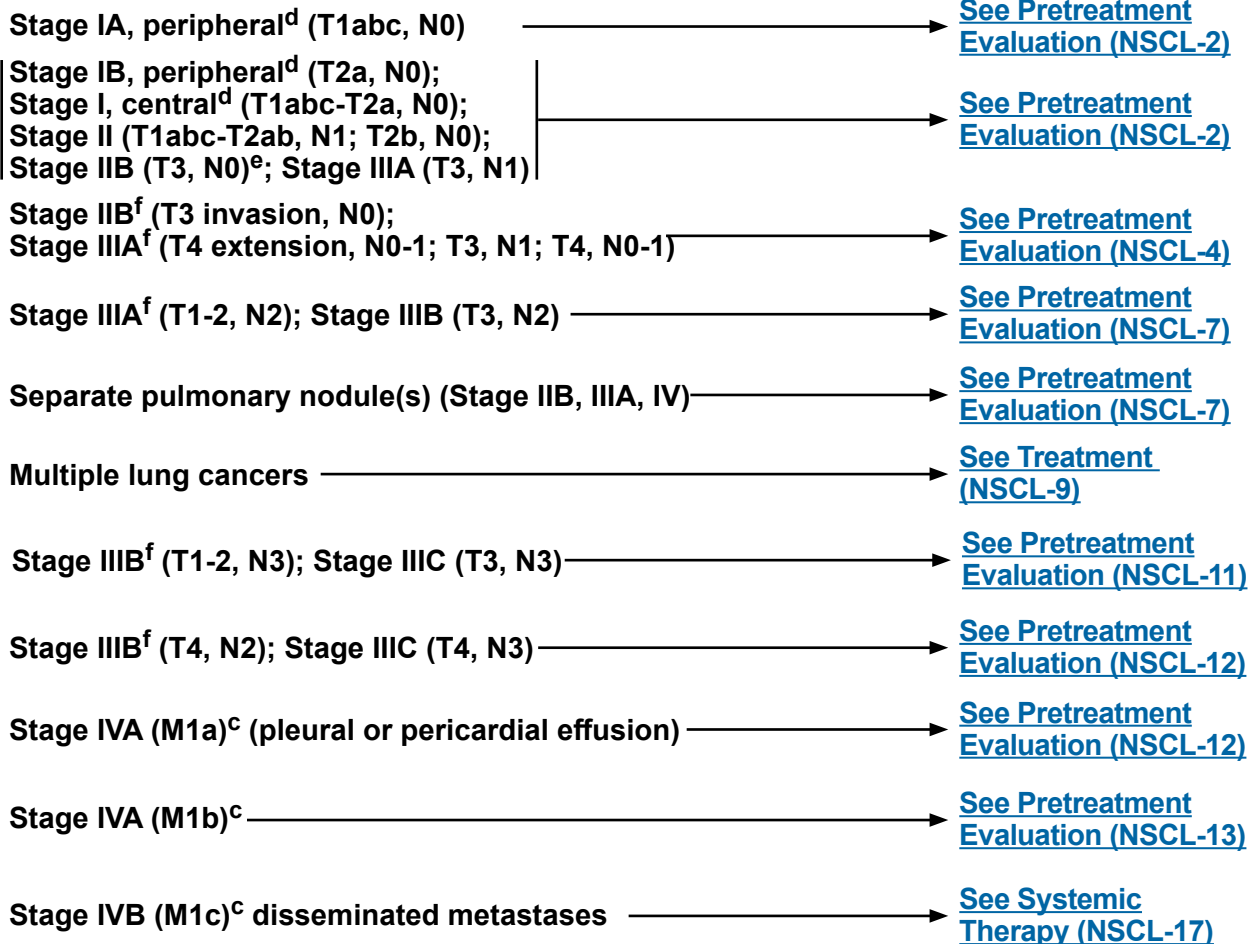
## Non-Small Cell Lung Cancer

### PATHOLOGIC DIAGNOSIS OF NSCLC

### INITIAL EVALUATION

### CLINICAL STAGE

- NSCLC →
- Pathology review<sup>a</sup>
  - H&P (include performance status + weight loss)<sup>b</sup>
  - CT chest and upper abdomen with contrast, including adrenals
  - CBC, platelets
  - Chemistry profile
  - Smoking cessation advice, counseling, and pharmacotherapy
    - ▶ Use the 5 A's Framework: Ask, Advise, Assess, Assist, Arrange
    - <http://www.ahrq.gov/clinic/tobacco/5steps.htm>
  - Integrate palliative care<sup>c</sup> ([See NCCN Guidelines for Palliative Care](#))



<sup>a</sup>See [Principles of Pathologic Review \(NSCL-A\)](#).

<sup>b</sup>Enhanced frailty or geriatric assessments may predict complications better following treatment modalities, particularly surgery. A preferred frailty assessment system has not been established.

<sup>c</sup>Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. *N Engl J Med* 2010;363:733-742.

<sup>d</sup>Based on the CT of the chest: Peripheral = outer third of lung; Central = inner two thirds of lung.

<sup>e</sup>T3, N0 related to size or satellite nodules.

<sup>f</sup>For patients considered to have stage IIB and stage III tumors, where more than one treatment modality (surgery, radiation therapy, or chemotherapy) is usually considered, a multidisciplinary evaluation should be performed.

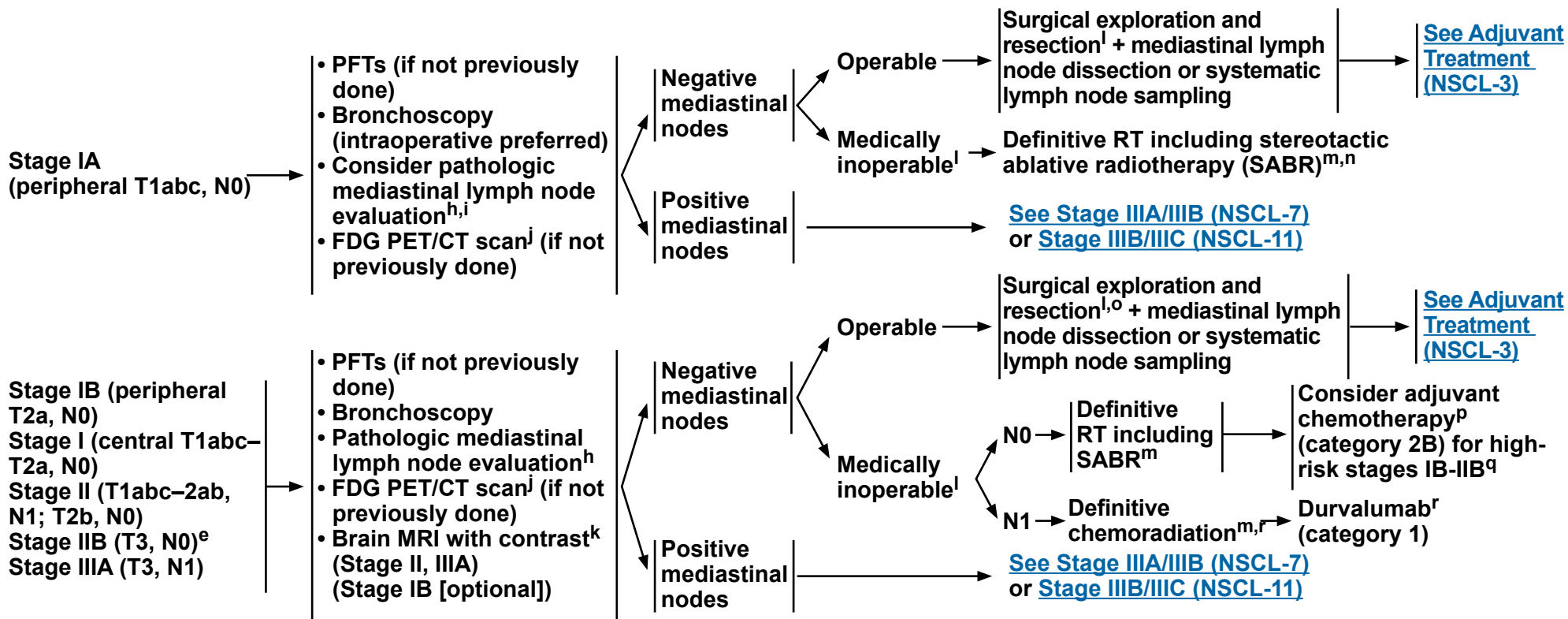
**Note: All recommendations are category 2A unless otherwise indicated.**

**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.**





## CLINICAL ASSESSMENT    PRETREATMENT EVALUATION<sup>g</sup>



<sup>e</sup>T3, N0 related to size or satellite nodules.

<sup>g</sup>Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.

<sup>h</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.

<sup>i</sup>There is low likelihood of positive mediastinal lymph nodes when these nodes are CT and PET negative in solid tumors <1 cm and purely non-solid tumors <3 cm. Thus, pre-resection pathologic mediastinal evaluation is optional in these settings.

<sup>j</sup>PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>k</sup>If MRI is not possible, CT of head with contrast.

<sup>l</sup>[See Principles of Surgical Therapy \(NSCL-B\)](#).

<sup>m</sup>[See Principles of Radiation Therapy \(NSCL-C\)](#).

<sup>n</sup>Interventional radiology ablation is an option for selected patients.

<sup>o</sup>After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

<sup>p</sup>[See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy \(NSCL-D\)](#).

<sup>q</sup>Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

<sup>r</sup>[See Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\)](#).

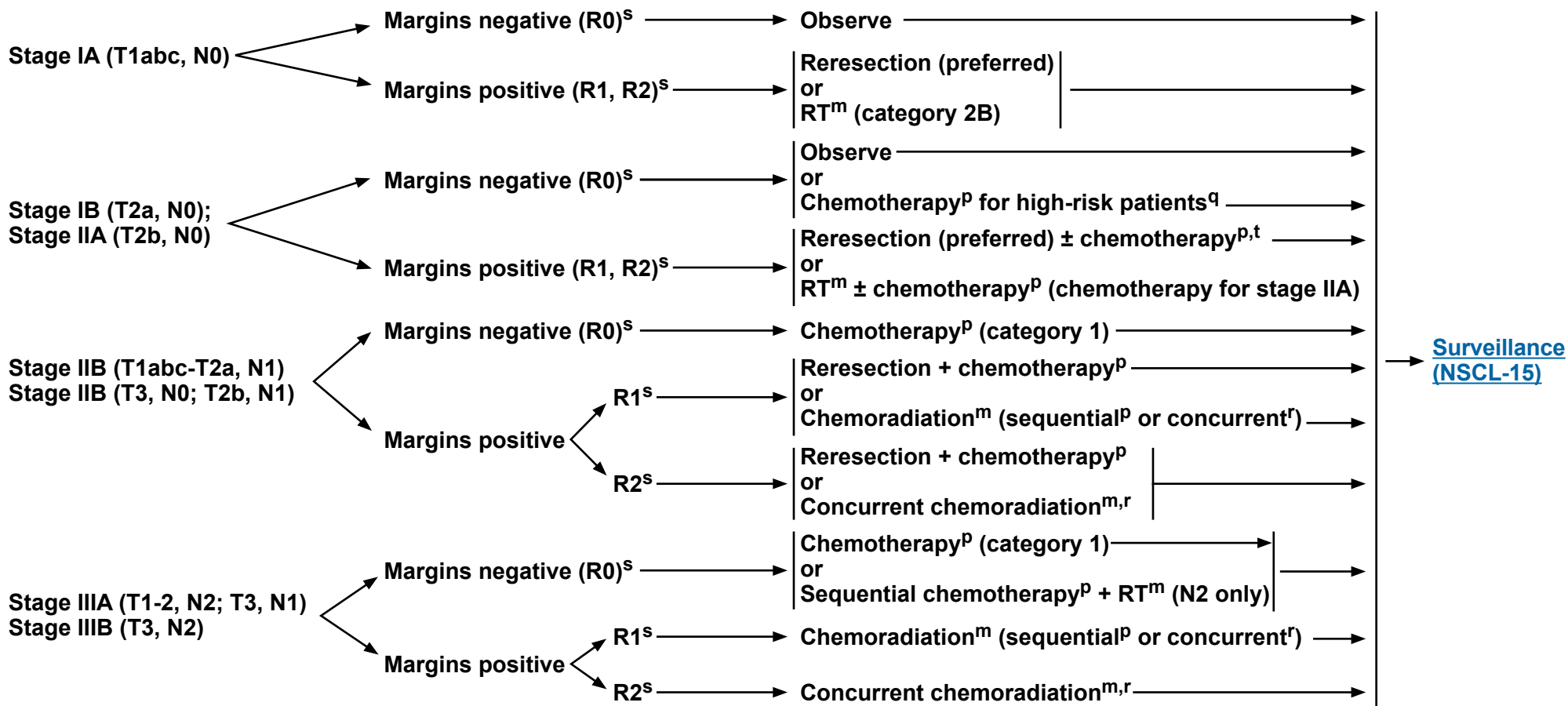
**Note: All recommendations are category 2A unless otherwise indicated.**

**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.**



### FINDINGS AT SURGERY

### ADJUVANT TREATMENT



<sup>m</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>p</sup>See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

<sup>q</sup>Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

<sup>r</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

<sup>s</sup>R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

<sup>t</sup>Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

**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.**



### CLINICAL ASSESSMENT

### PRETREATMENT EVALUATION

### CLINICAL EVALUATION

Stage IIB (T3 invasion, N0)  
Stage IIIA (T4 extension,  
N0-1; T3, N1; T4, N0-1)

- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation<sup>h</sup>
- Brain MRI with contrast<sup>k</sup>
- MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine or subclavian vessels
- FDG PET/CT scan<sup>j</sup> (if not previously done)

Superior sulcus tumor → [See Treatment \(NSCL-5\)](#)

Chest wall → [See Treatment \(NSCL-6\)](#)

Proximal airway or mediastinum → [See Treatment \(NSCL-6\)](#)

Stage IIIA (T4, N0-1) → [See Treatment \(NSCL-6\)](#)

Unresectable disease → [See Treatment \(NSCL-6\)](#)

Metastatic disease → [See Treatment for Metastasis limited sites \(NSCL-13\) or distant disease \(NSCL-16\)](#)

<sup>k</sup>If MRI is not possible, CT of head with contrast.

<sup>h</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

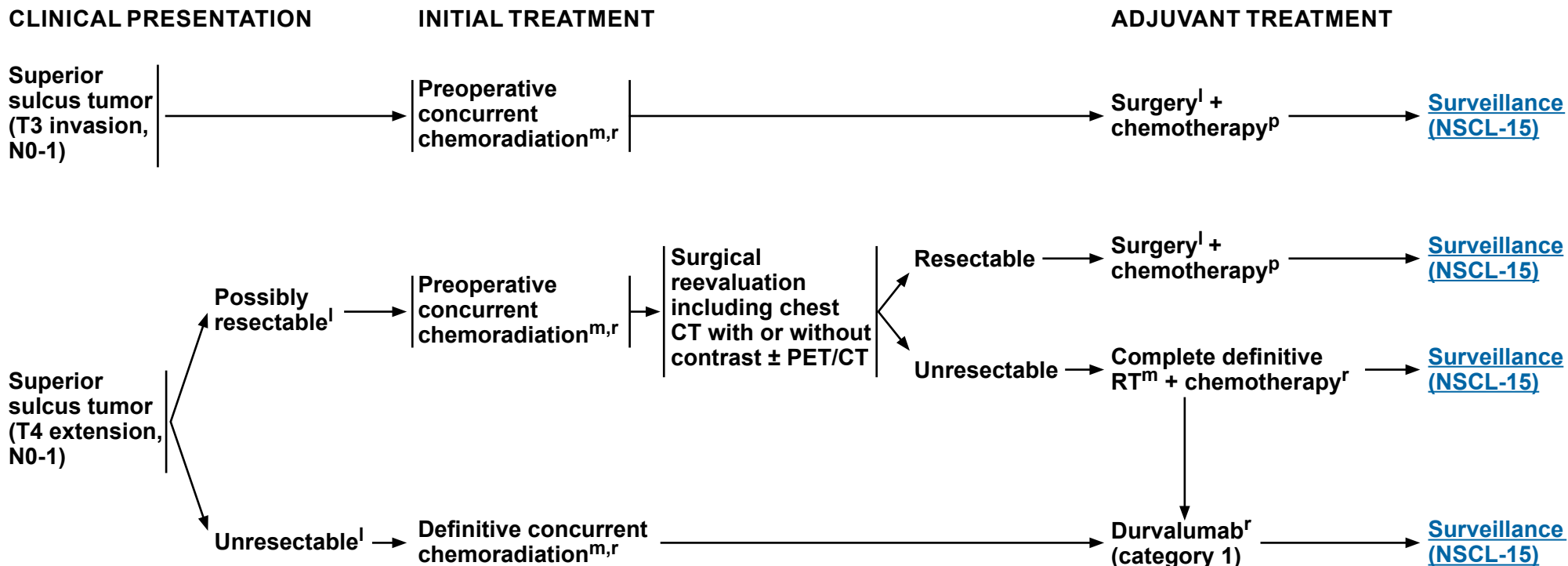
<sup>j</sup>PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

**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.**







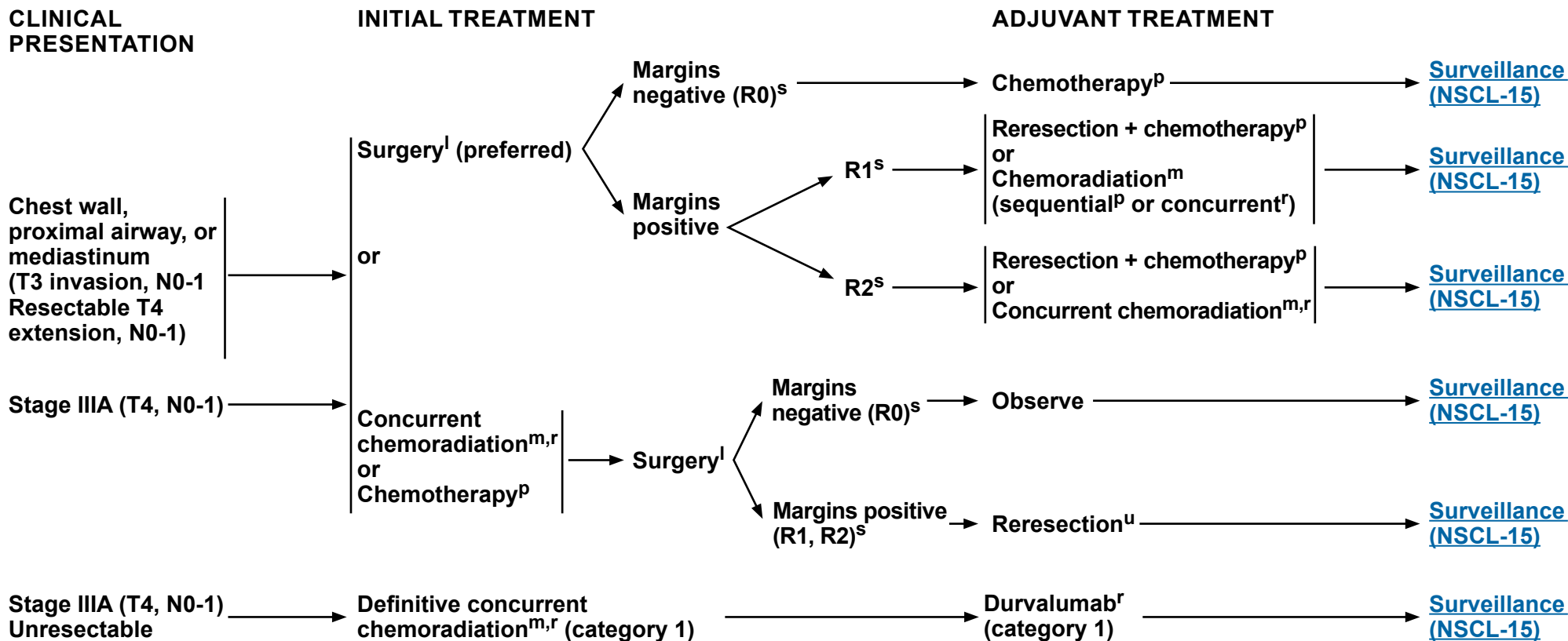
<sup>l</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>m</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>p</sup>See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

<sup>r</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

**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.**



<sup>l</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>m</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>p</sup>See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

<sup>r</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

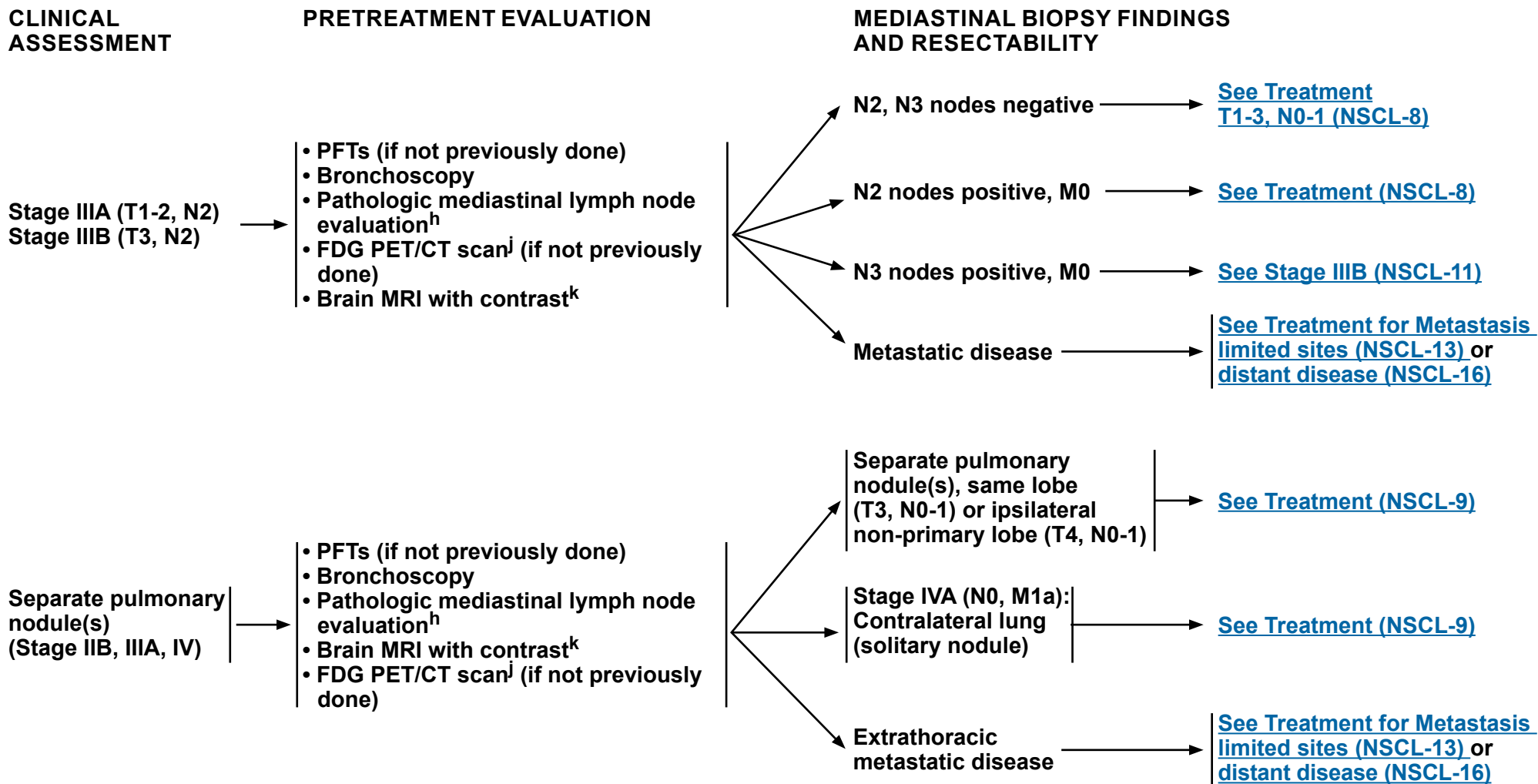
<sup>s</sup>R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

<sup>u</sup>Consider RT boost if chemoradiation is given as initial treatment.

**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.**



# NCCN Guidelines Version 7.2019 Non-Small Cell Lung Cancer



<sup>h</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

<sup>j</sup>PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>k</sup>If MRI is not possible, CT of head with contrast.

**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.**

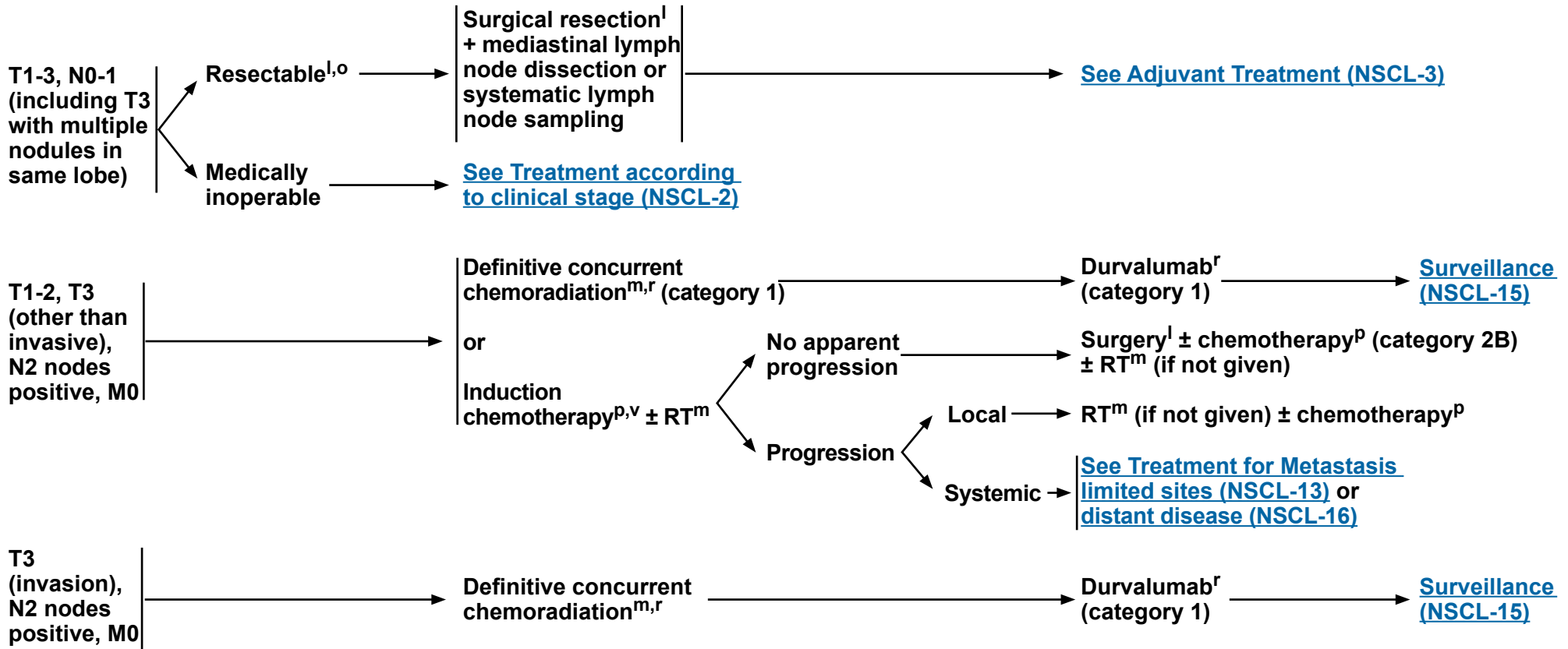




### MEDIASTINAL BIOPSY FINDINGS

### INITIAL TREATMENT

### ADJUVANT TREATMENT



<sup>l</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>m</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>o</sup>After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

<sup>p</sup>See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

<sup>r</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

<sup>v</sup>Chest CT with contrast and/or PET/CT to evaluate progression.

**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.**



## CLINICAL PRESENTATION

Separate pulmonary nodule(s), same lobe (T3, N0-1), or ipsilateral non-primary lobe (T4, N0-1)

Surgery<sup>l,o</sup>

N0-1

Margins negative (R0)<sup>s</sup>

N2

Margins positive

R1<sup>s</sup>

R2<sup>s</sup>

## ADJUVANT TREATMENT

Chemotherapy<sup>p</sup>

Chemotherapy<sup>p</sup> (category 1) or Sequential chemotherapy<sup>p</sup> + RT<sup>m</sup>

Chemoradiation<sup>m</sup> (sequential<sup>p</sup> or concurrent<sup>r</sup>)

Concurrent chemoradiation<sup>m,r</sup>

[Surveillance \(NSCL-15\)](#)

[Surveillance \(NSCL-15\)](#)

[Surveillance \(NSCL-15\)](#)

[Surveillance \(NSCL-15\)](#)

Stage IVA (N0, M1a): Contralateral lung (solitary nodule)

Treat as two primary lung tumors if both curable

[See Evaluation \(NSCL-1\)](#)

Suspected multiple lung cancers (based on the presence of biopsy-proven synchronous lesions or history of lung cancer)<sup>w,x</sup>

• Chest CT with contrast  
• FDG PET/CT scan (if not previously done)<sup>j</sup>  
• Brain MRI with contrast<sup>k</sup>

Disease outside of chest

No disease outside of chest

[See Systemic Therapy for Metastatic Disease \(NSCL-17\)](#)

Pathologic mediastinal lymph node evaluation<sup>h</sup>

N0-1

N2-3

[See Initial Treatment \(NSCL-10\)](#)

[See Systemic Therapy for Metastatic Disease \(NSCL-17\)](#)

<sup>h</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

<sup>j</sup>PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>k</sup>If MRI is not possible, CT of head with contrast.

<sup>l</sup>[See Principles of Surgical Therapy \(NSCL-B\)](#).

<sup>m</sup>[See Principles of Radiation Therapy \(NSCL-C\)](#).

<sup>o</sup>After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

<sup>p</sup>[See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy \(NSCL-D\)](#).

<sup>r</sup>[See Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\)](#).

<sup>s</sup>R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

<sup>w</sup>Lesions with different cell types (eg, squamous cell carcinoma, adenocarcinoma) may be different primary tumors. This analysis may be limited by small biopsy samples. However, lesions of the same cell type are not necessarily metastases.

<sup>x</sup>For guidance regarding the evaluation, workup, and management of subsolid pulmonary nodules, please see the diagnostic evaluation of a nodule suspicious for lung cancer ([DIAG-1](#)).

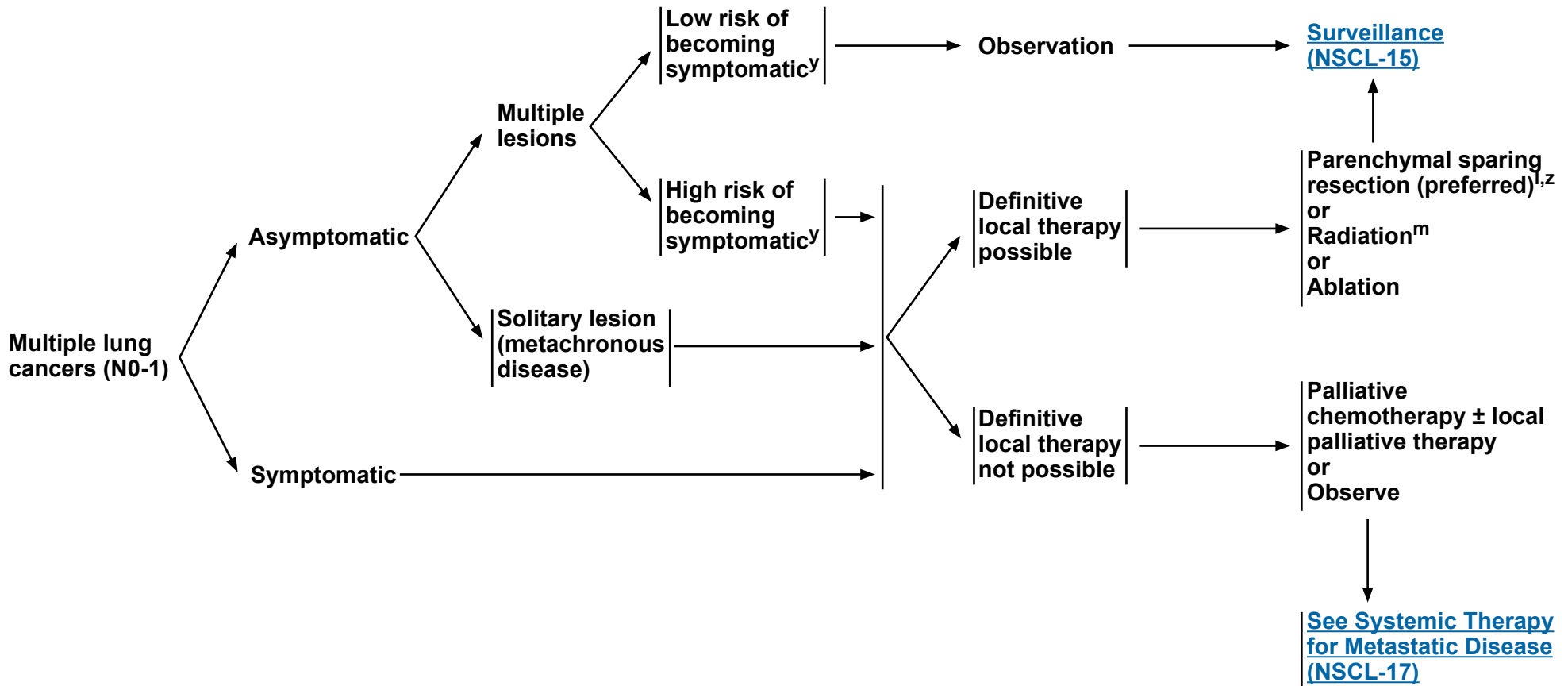
**Note: All recommendations are category 2A unless otherwise indicated.**

**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.**



### CLINICAL PRESENTATION

### INITIAL TREATMENT



<sup>1</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>m</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>y</sup>Lesions at low risk of becoming symptomatic can be observed (eg, small subsolid nodules with slow growth). However, if the lesion(s) becomes symptomatic or becomes high risk for producing symptoms (eg, subsolid nodules with accelerating growth or increasing solid component or increasing FDG uptake, even while small), treatment should be considered.

<sup>z</sup>Lung-sparing resection is preferred, but tumor distribution and institutional expertise should guide individual treatment planning. Patients should be evaluated in a multidisciplinary setting (ie, surgery, radiation oncology, medical oncology).

**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.**

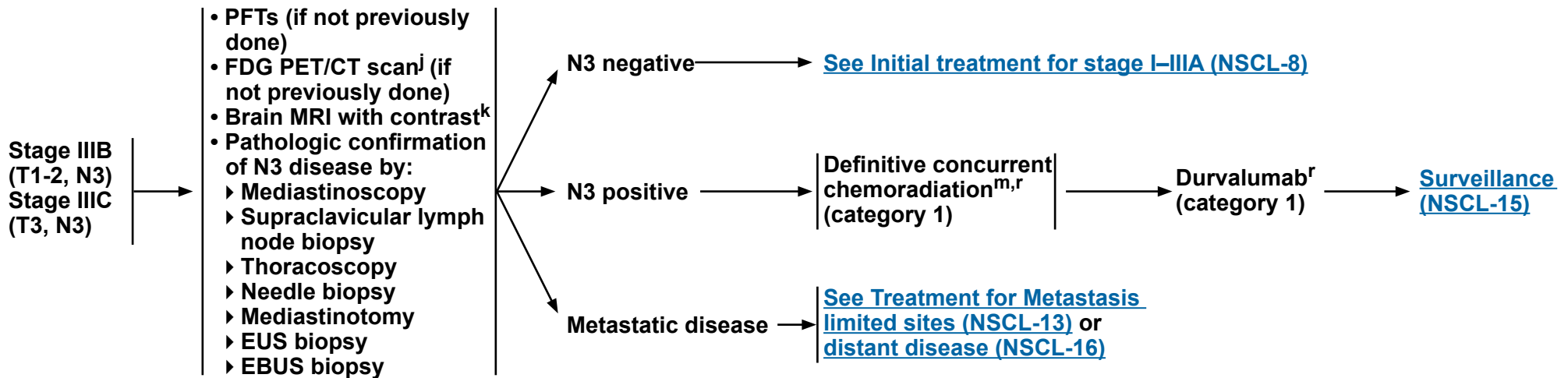




**CLINICAL ASSESSMENT**

**PRETREATMENT EVALUATION**

**INITIAL TREATMENT**



<sup>j</sup>PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>k</sup>If MRI is not possible, CT of head with contrast.

<sup>m</sup>See [Principles of Radiation Therapy \(NSCL-C\)](#).

<sup>r</sup>See [Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\)](#).

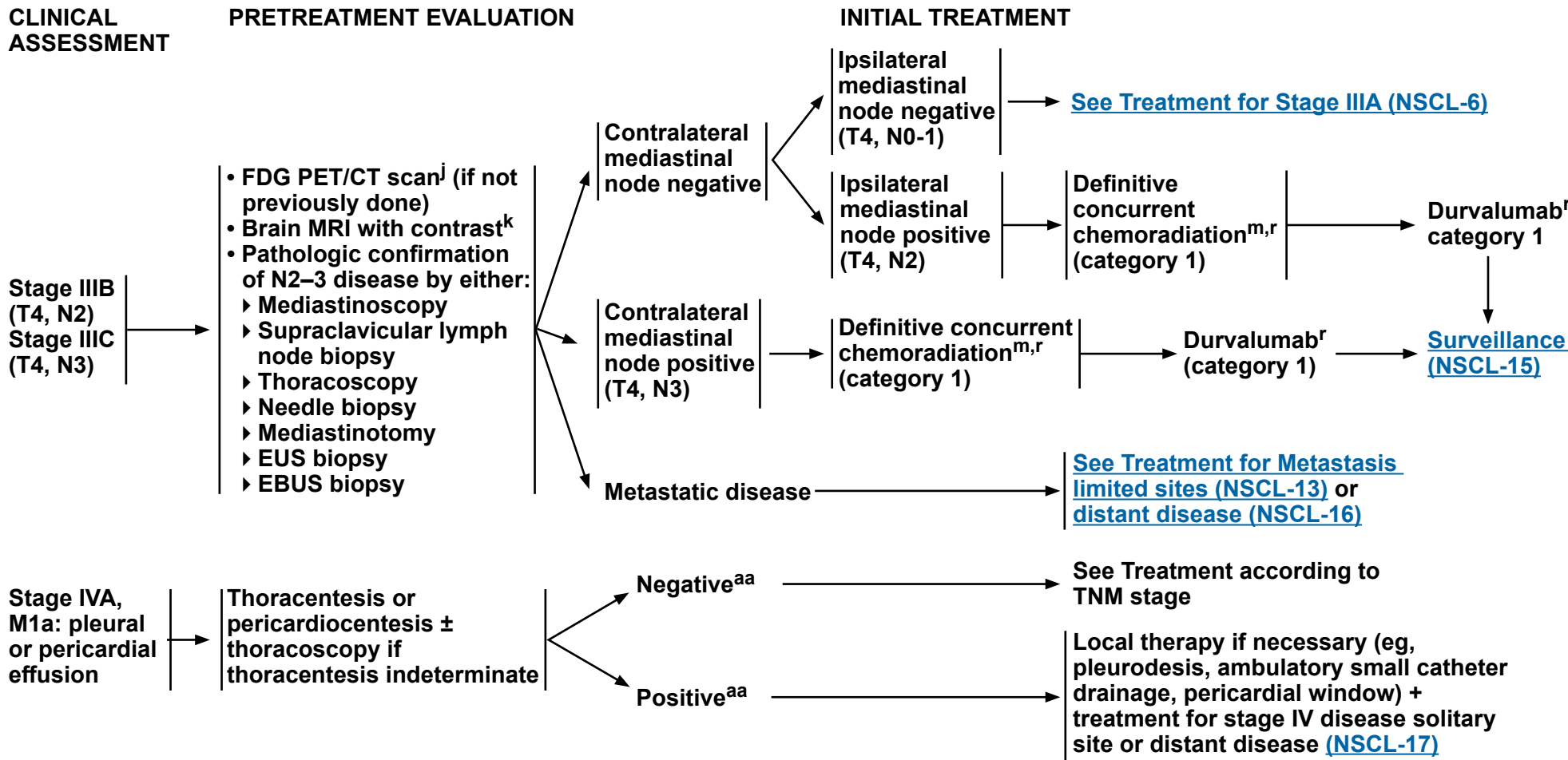
**Note: All recommendations are category 2A unless otherwise indicated.**

**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.**





# NCCN Guidelines Version 7.2019 Non-Small Cell Lung Cancer



<sup>j</sup>PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>k</sup>If MRI is not possible, CT of head with contrast.

<sup>m</sup>See [Principles of Radiation Therapy \(NSCL-C\)](#).

<sup>r</sup>See [Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\)](#).

<sup>aa</sup>Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and fluid is non-bloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

**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.**

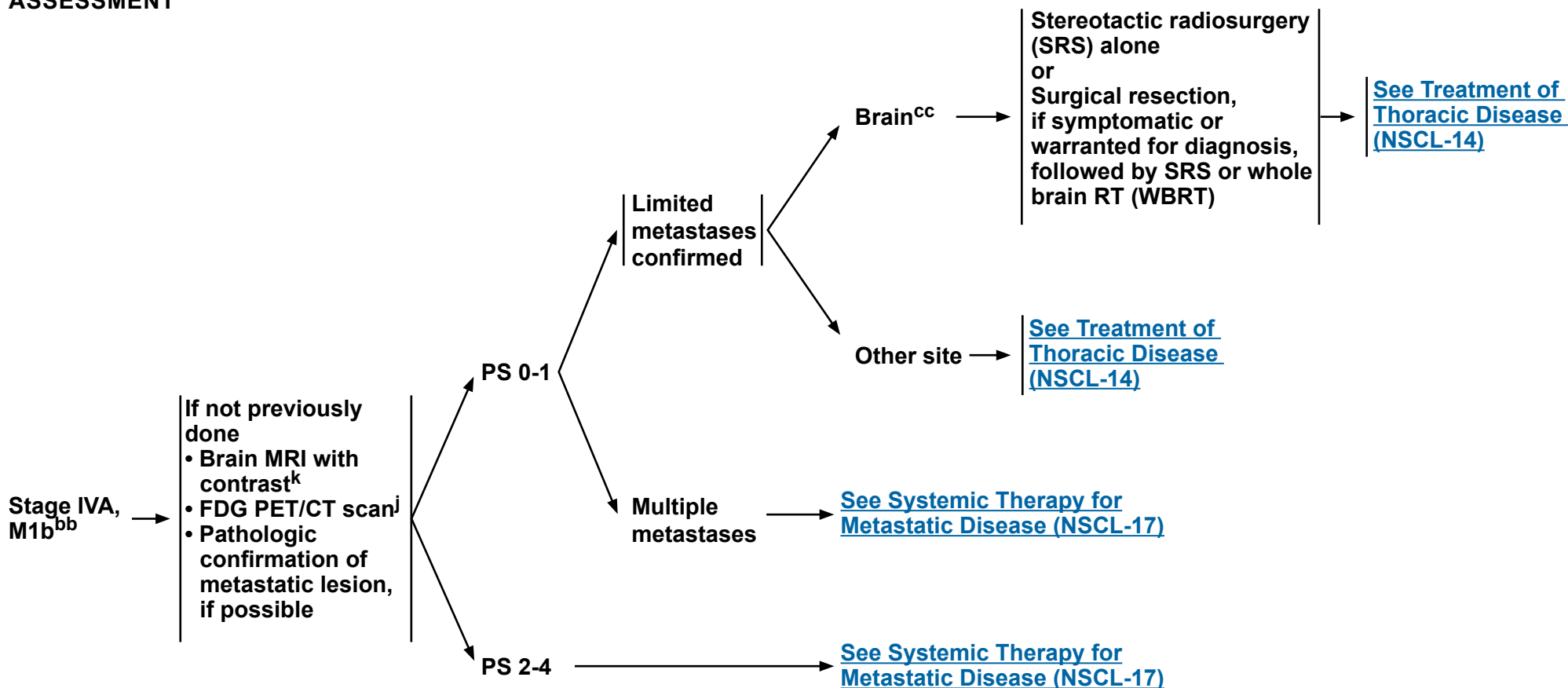




**CLINICAL ASSESSMENT**

**PRETREATMENT EVALUATION**

**INITIAL TREATMENT<sup>cc</sup>**



<sup>j</sup>PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>k</sup>If MRI is not possible, CT of head with contrast.

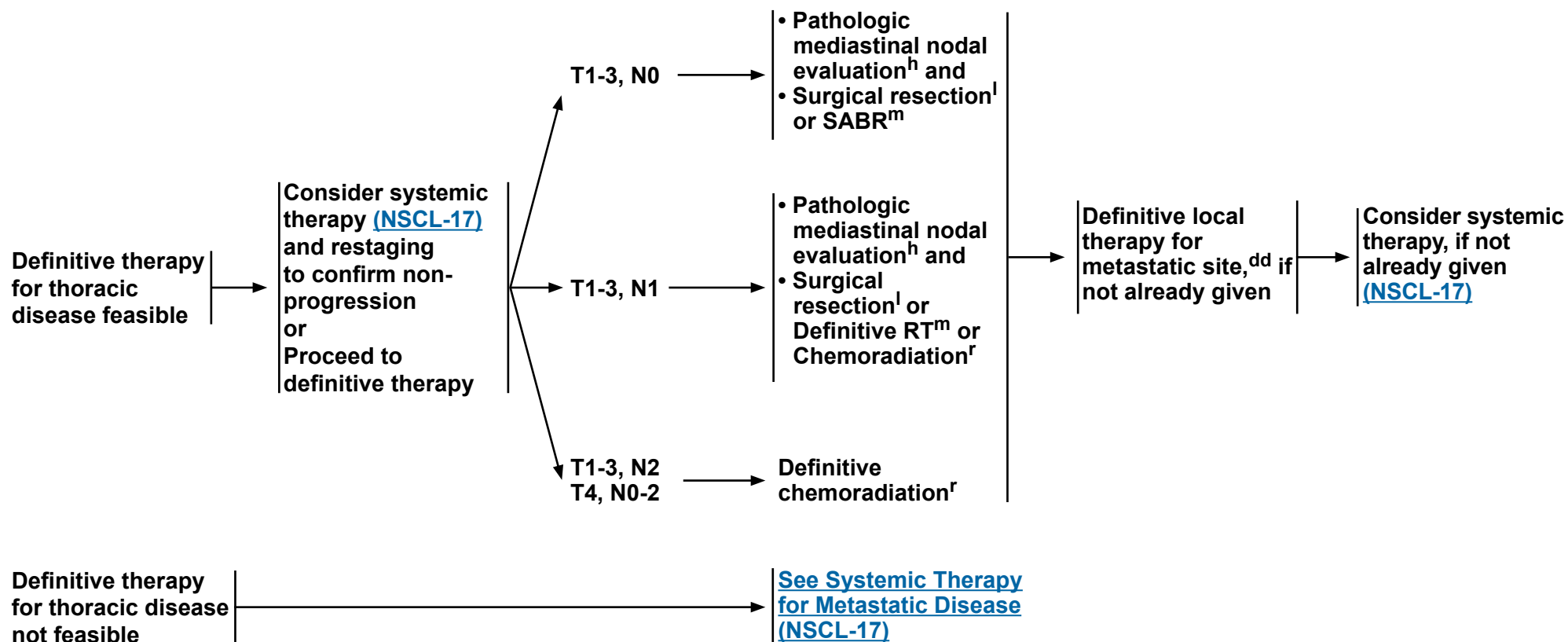
<sup>bb</sup>Including selected patients with stage M1c and limited number and volume of metastatic lesions amenable to definitive local therapy. Limited number is undefined but clinical trials have included up to 3 to 5 metastases.

<sup>cc</sup>[See NCCN Guidelines for Central Nervous System Cancers.](#)

**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.**

### TREATMENT OF THORACIC DISEASE



<sup>h</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

<sup>l</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>m</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>r</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

<sup>dd</sup>Typically, RT (including SABR) or surgical resection.

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

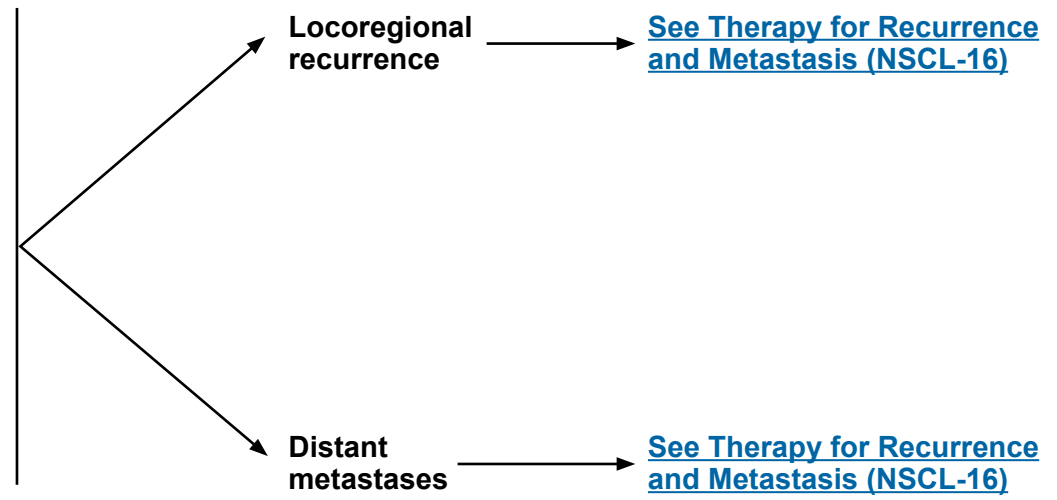
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



**SURVEILLANCE AFTER COMPLETION  
OF DEFINITIVE THERAPY**

**No evidence of clinical/radiographic disease**

- Stage I–II (primary treatment included surgery ± chemotherapy)
  - ▶ H&P and chest CT ± contrast every 6 mo for 2–3 y, then H&P and a low-dose non-contrast-enhanced chest CT annually
- Stage I–II (primary treatment included RT) or stage III or stage IV (oligometastatic with all sites treated with definitive intent)
  - ▶ H&P and chest CT<sup>ee</sup> ± contrast every 3–6 mo for 3 y, then H&P and chest CT ± contrast every 6 mo for 2 y, then H&P and a low-dose non-contrast-enhanced chest CT annually
    - ◊ Residual or new radiographic abnormalities may require more frequent imaging
- Smoking cessation advice, counseling, and pharmacotherapy
- PET/CT<sup>ff</sup> or brain MRI is not routinely indicated
- [See Cancer Survivorship Care \(NSCL-F\)](#)



<sup>ee</sup>Timing of CT scans within Guidelines parameters is a clinical decision.

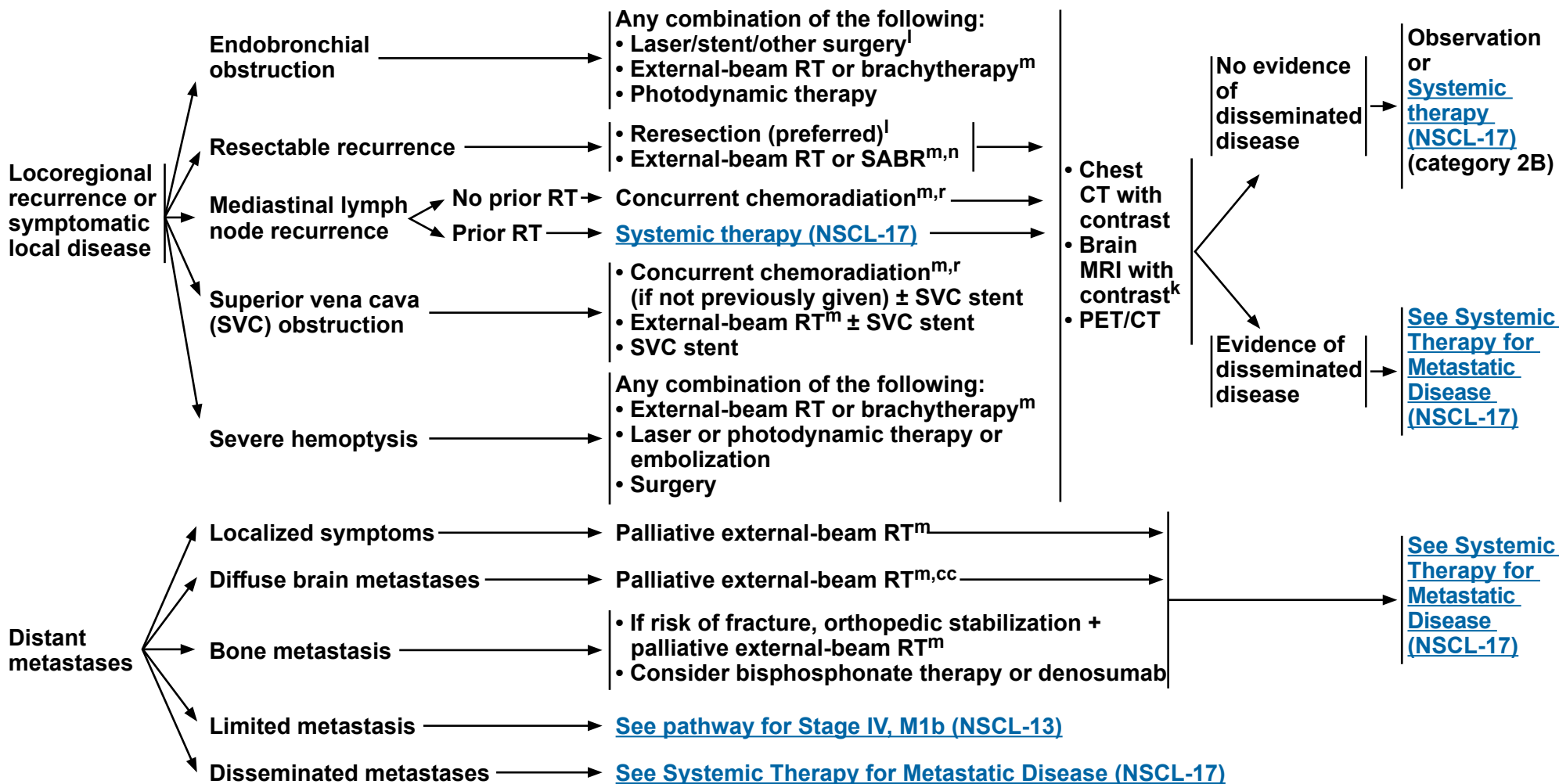
<sup>ff</sup>FDG PET/CT is currently not warranted in the routine surveillance and follow-up of patients with NSCLC. However, many benign conditions (such as atelectasis, consolidation, and radiation fibrosis) are difficult to differentiate from neoplasm on standard CT imaging, and FDG PET/CT can be used to differentiate true malignancy in these settings. However, if FDG PET/CT is to be used as a problem-solving tool in patients after radiation therapy, histopathologic confirmation of recurrent disease is needed because areas previously treated with radiation therapy can remain FDG avid for up to 2 years.

**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.**





### THERAPY FOR RECURRENCE AND METASTASIS



<sup>k</sup>If MRI is not possible, CT of head with contrast.  
<sup>l</sup>[See Principles of Surgical Therapy \(NSCL-B\)](#).  
<sup>m</sup>[See Principles of Radiation Therapy \(NSCL-C\)](#).

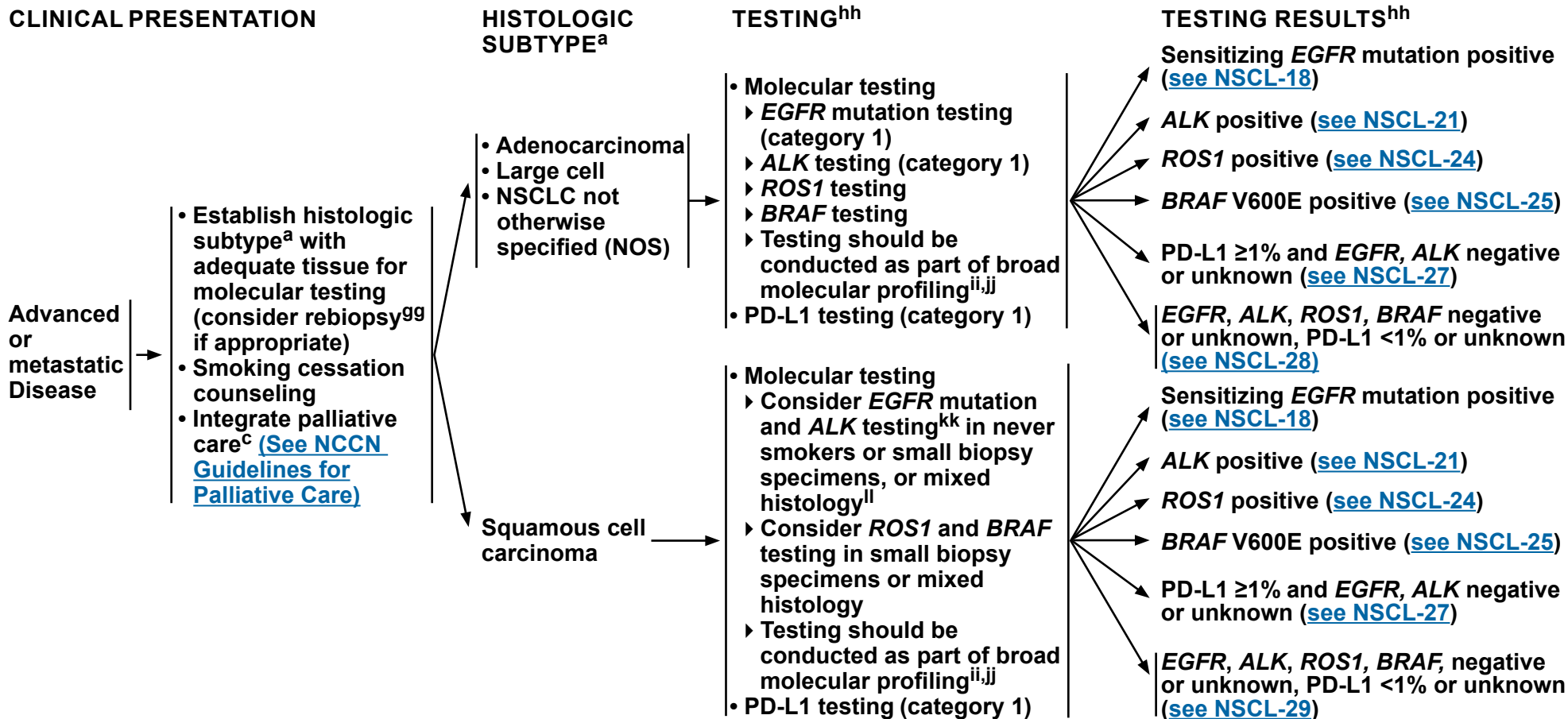
<sup>n</sup>Interventional radiology ablation is an option for selected patients.  
<sup>r</sup>[See Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\)](#).  
<sup>cc</sup>[See NCCN Guidelines for Central Nervous System Cancers](#).

**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.**





# NCCN Guidelines Version 7.2019 Non-Small Cell Lung Cancer



<sup>a</sup>See Principles of Pathologic Review (NSCL-A).

<sup>c</sup>Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733-742.

<sup>gg</sup>If repeat biopsy is not feasible, plasma testing should be considered.

<sup>hh</sup>See Principles of Molecular and Biomarker Analysis (NSCL-G).

<sup>ii</sup>The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See [Emerging Biomarkers to Identify Patients for Therapies \(NSCL-H\)](#).

<sup>jj</sup>Testing should include the neurotrophic receptor tyrosine kinase (NTRK) gene fusion; if positive, see [NSCL-26](#).

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

<sup>ll</sup>Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with EGFR mutant advanced non-small cell lung cancers with a squamous or squamous-like component. *Mol Cancer Ther* 2012;11:2535-2540.

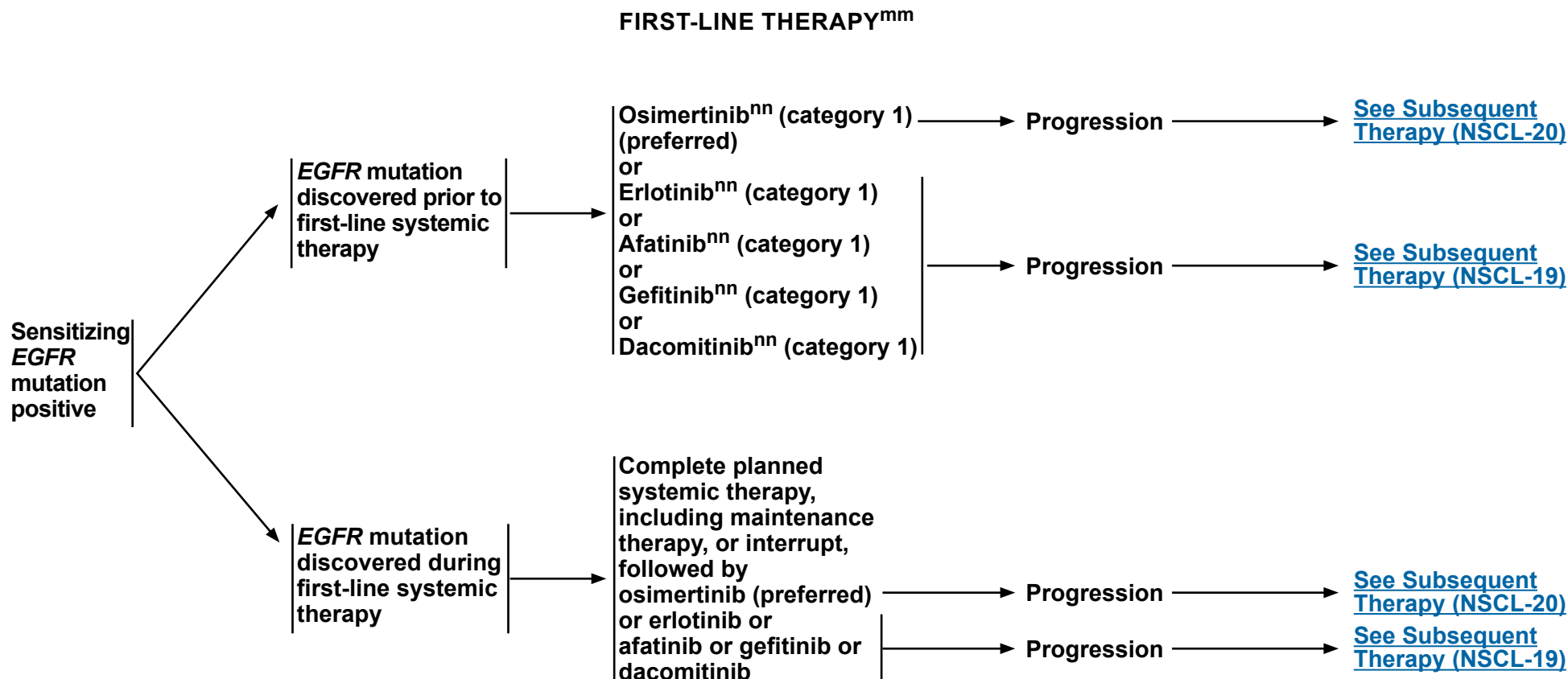
**Note: All recommendations are category 2A unless otherwise indicated.**

**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<sup>hh</sup>



<sup>hh</sup>[See Principles of Molecular and Biomarker Analysis \(NSCL-G\).](#)

<sup>mm</sup>[See Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\).](#)

<sup>nn</sup>For performance status 0-4.

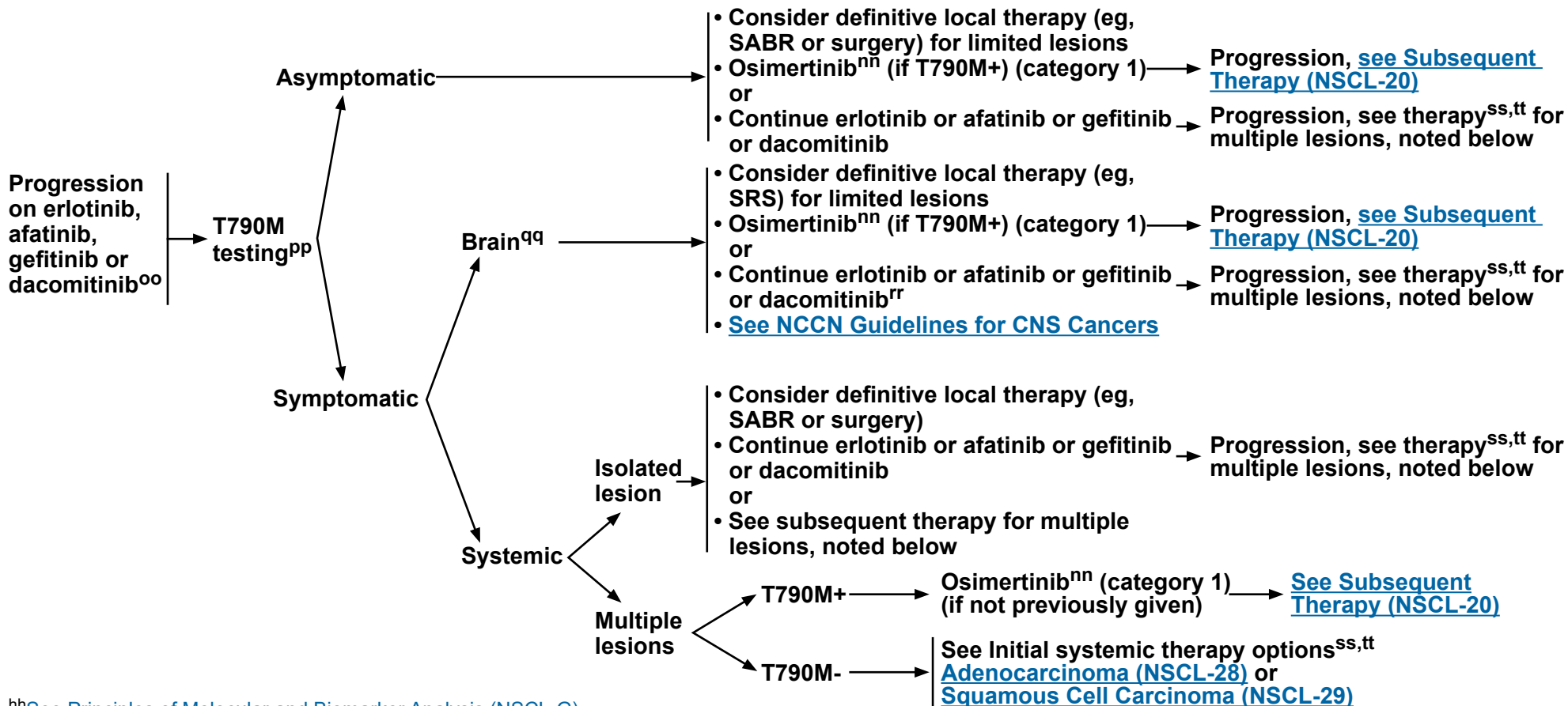
**Note: All recommendations are category 2A unless otherwise indicated.**  
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**





### SENSITIZING EGFR MUTATION POSITIVE<sup>hh</sup>

### SUBSEQUENT THERAPY<sup>mm</sup>



<sup>hh</sup>See Principles of Molecular and Biomarker Analysis (NSCL-G).

<sup>mm</sup>See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).

<sup>nn</sup>For performance status 0-4.

<sup>oo</sup>Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

<sup>pp</sup>Plasma-based testing should be considered at progression on EGFR TKIs for the T790M mutation. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

<sup>qq</sup>Consider osimertinib (regardless of T790M status) or pulse erlotinib for progressive leptomeningeal disease.

<sup>rr</sup>In the randomized phase III trial of dacomitinib, patients with brain metastases were not eligible for enrollment. In the setting of brain metastases, consider other options.

<sup>ss</sup>Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

<sup>tt</sup>The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in EGFR+/ALK+ NSCLC.

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

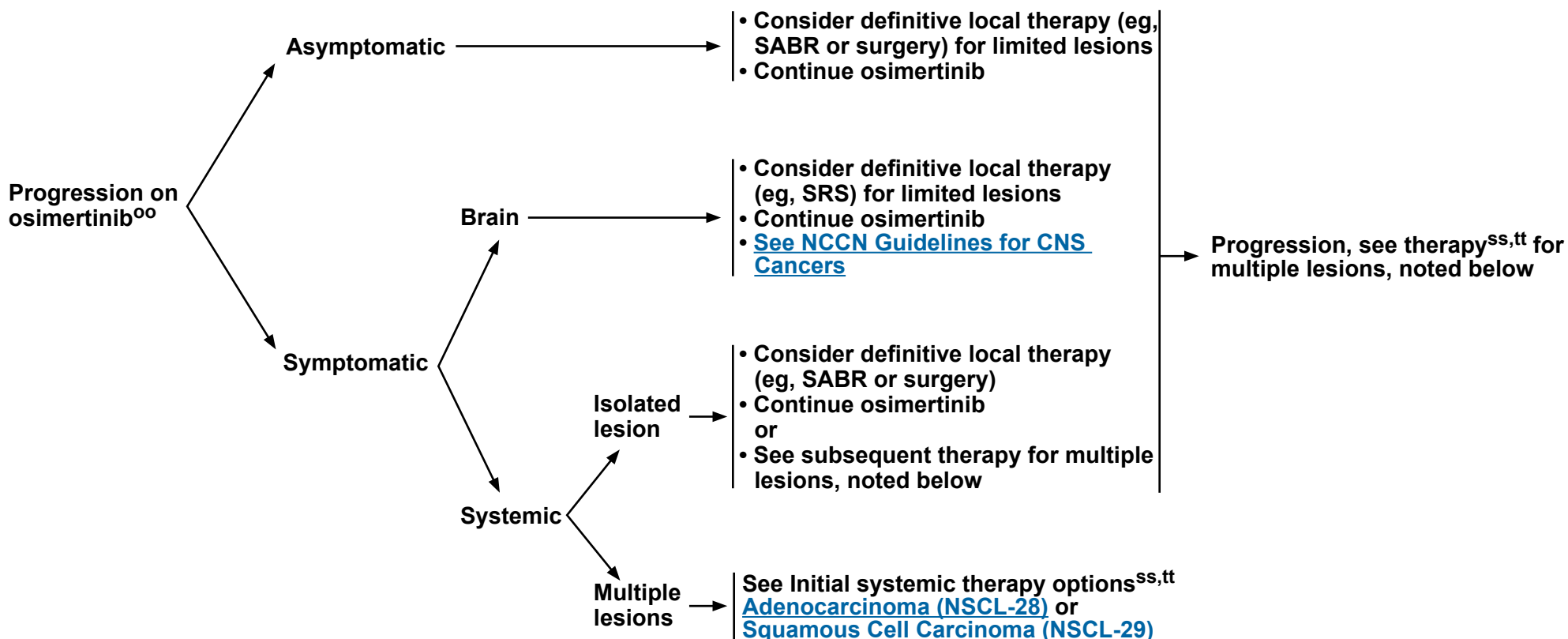
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**





### SENSITIZING EGFR MUTATION POSITIVE<sup>hh</sup>

### SUBSEQUENT THERAPY<sup>mm</sup>



<sup>hh</sup>See [Principles of Molecular and Biomarker Analysis \(NSCL-G\)](#).

<sup>mm</sup>See [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#).

<sup>oo</sup>Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

<sup>ss</sup>Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

<sup>tt</sup>The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR*+/*ALK*+ NSCLC.

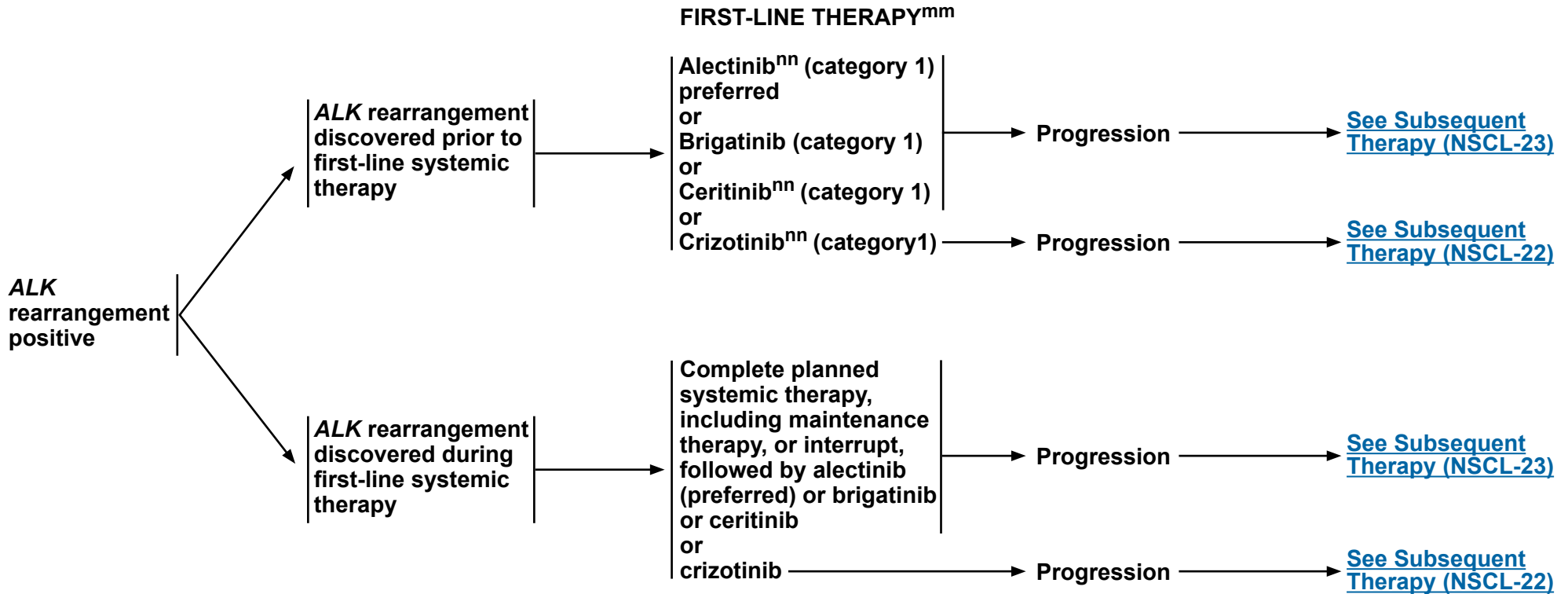
**Note: All recommendations are category 2A unless otherwise indicated.**  
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**







### ALK REARRANGEMENT POSITIVE<sup>hh</sup>



<sup>hh</sup>See [Principles of Molecular and Biomarker Analysis \(NSCL-G\)](#).

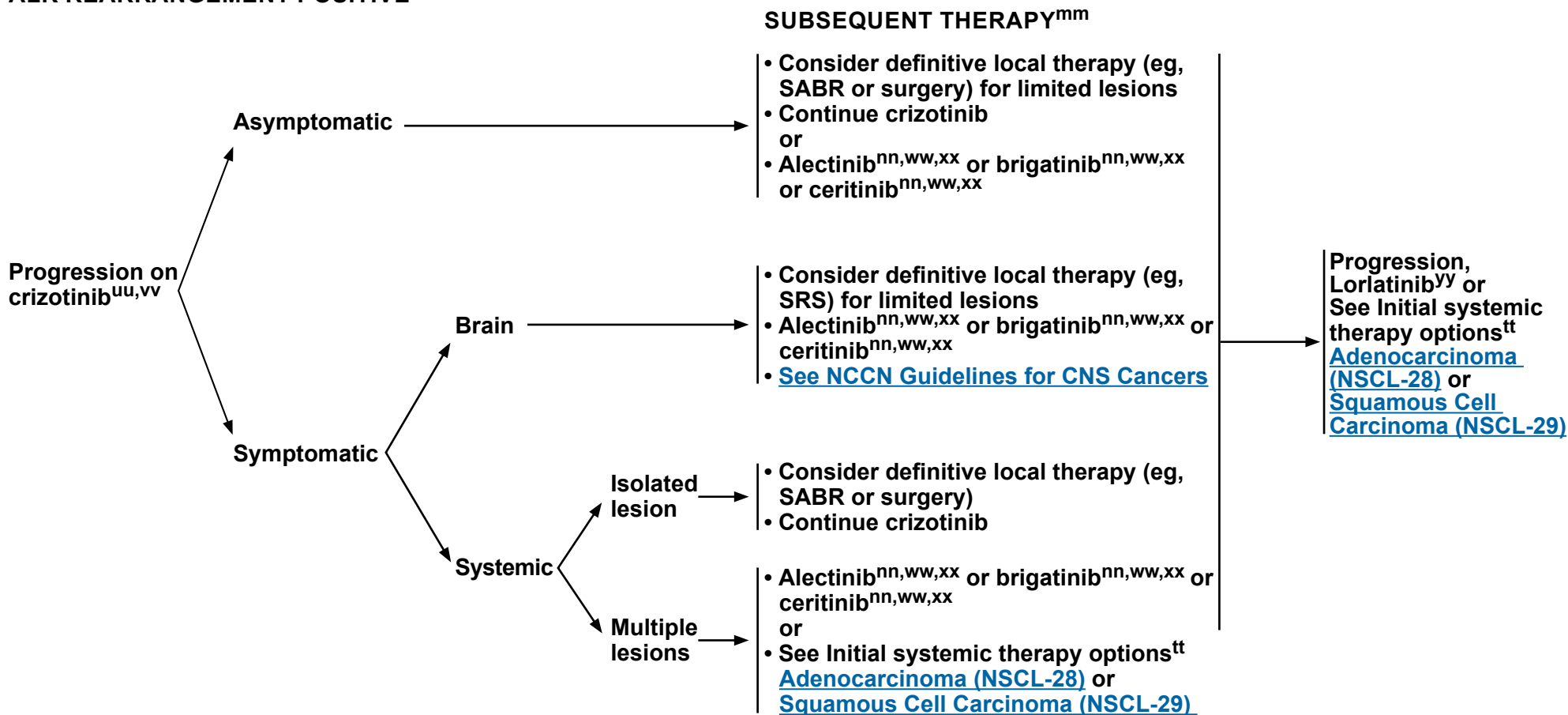
<sup>mm</sup>See [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#).

<sup>nn</sup>For performance status 0-4.

**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.**



### ALK REARRANGEMENT POSITIVE<sup>hh</sup>



<sup>hh</sup>See [Principles of Molecular and Biomarker Analysis \(NSCL-G\)](#).

<sup>mm</sup>See [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#).

<sup>nn</sup>For performance status 0-4.

<sup>tt</sup>The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in EGFR+/ALK+ NSCLC.

<sup>uu</sup>Beware of flare phenomenon in subset of patients who discontinue ALK inhibitor. If disease flare occurs, restart ALK inhibitor.

<sup>vv</sup>Patients who are intolerant to crizotinib may be switched to ceritinib, alectinib, or brigatinib.

<sup>ww</sup>If not previously given.

<sup>xx</sup>Ceritinib, alectinib, or brigatinib are treatment options for patients with ALK-positive metastatic NSCLC that has progressed on crizotinib.

<sup>yy</sup>Lorlatinib is a treatment option after progression on crizotinib and alectinib, brigatinib, or ceritinib.

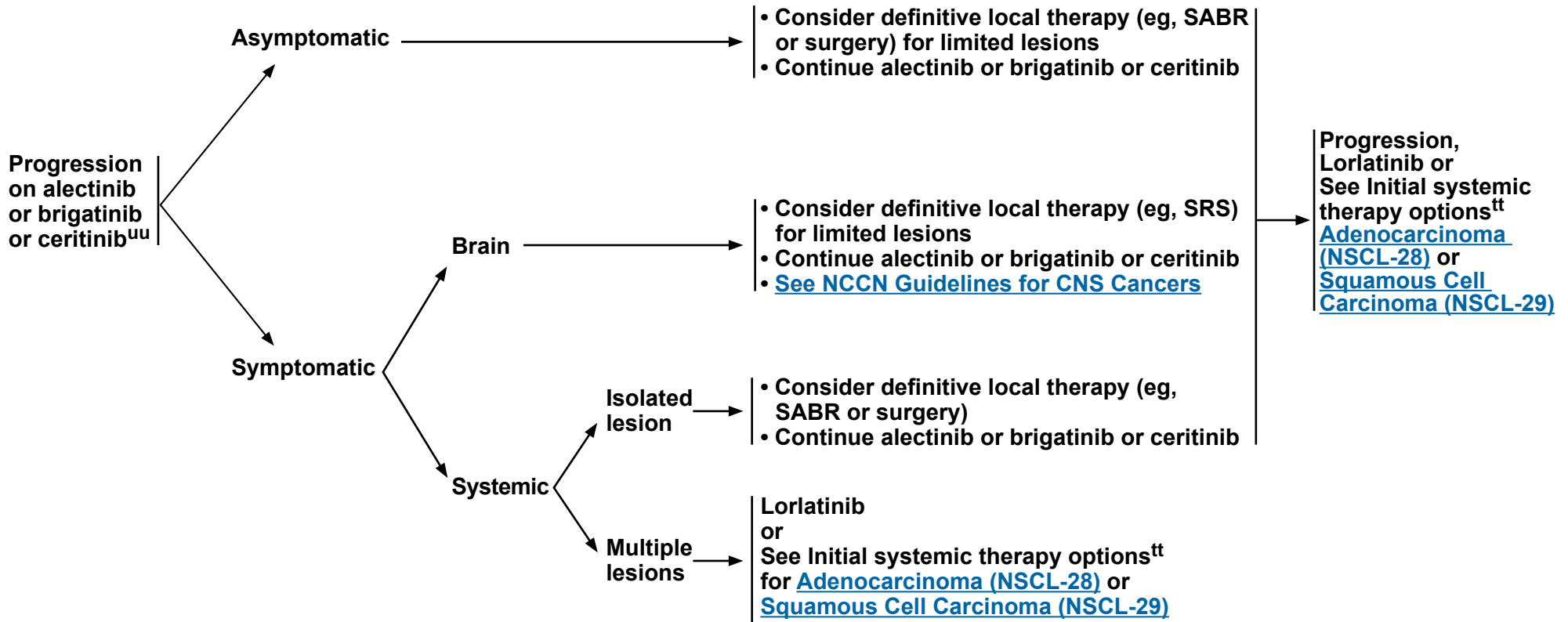
**Note: All recommendations are category 2A unless otherwise indicated.**

**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.**



### ALK REARRANGEMENT POSITIVE<sup>hh</sup>

### SUBSEQUENT THERAPY<sup>mm</sup>



<sup>hh</sup>See [Principles of Molecular and Biomarker Analysis \(NSCL-G\)](#).

<sup>mm</sup>See [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#).

<sup>tt</sup>The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in EGFR+/ALK+ NSCLC.

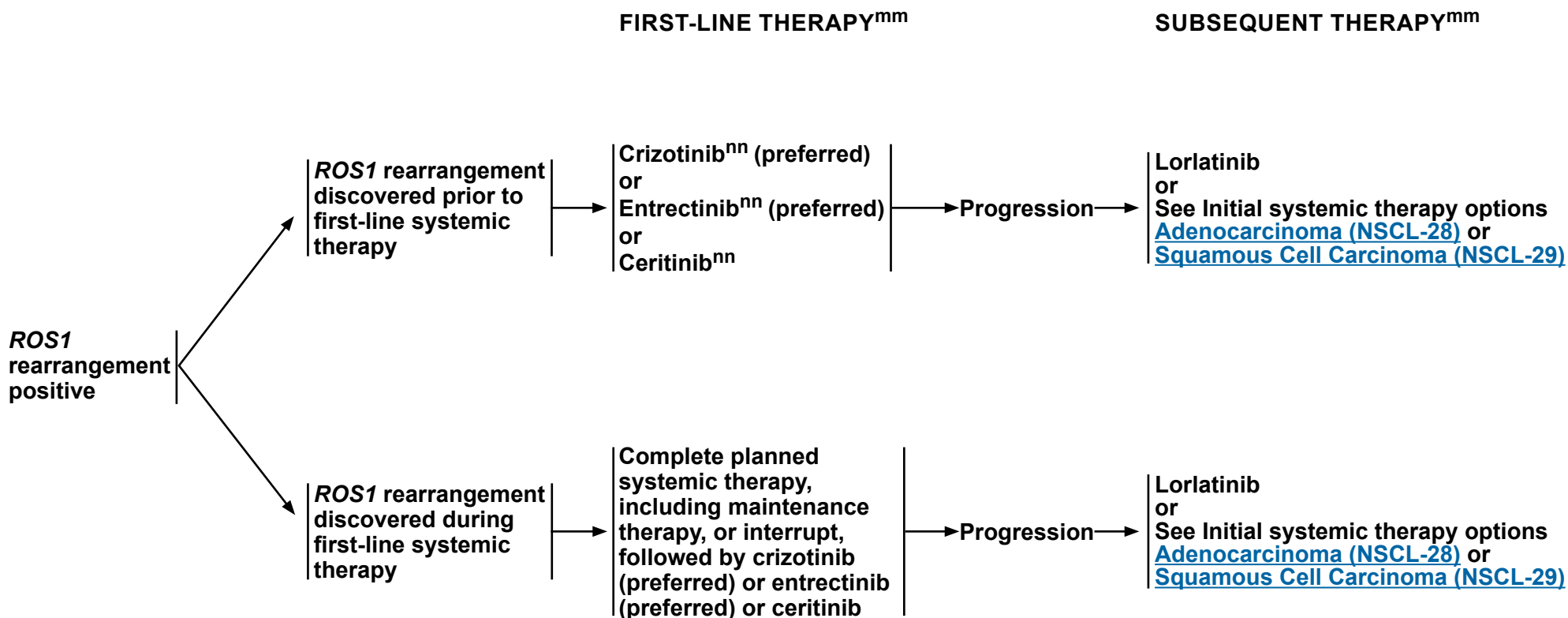
<sup>uu</sup>Beware of flare phenomenon in subset of patients who discontinue ALK inhibitor. If disease flare occurs, restart ALK inhibitor.

**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.**





### ROS1 REARRANGEMENT POSITIVE<sup>hh</sup>



<sup>hh</sup>See [Principles of Molecular and Biomarker Analysis \(NSCL-G\)](#).

<sup>mm</sup>See [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#).

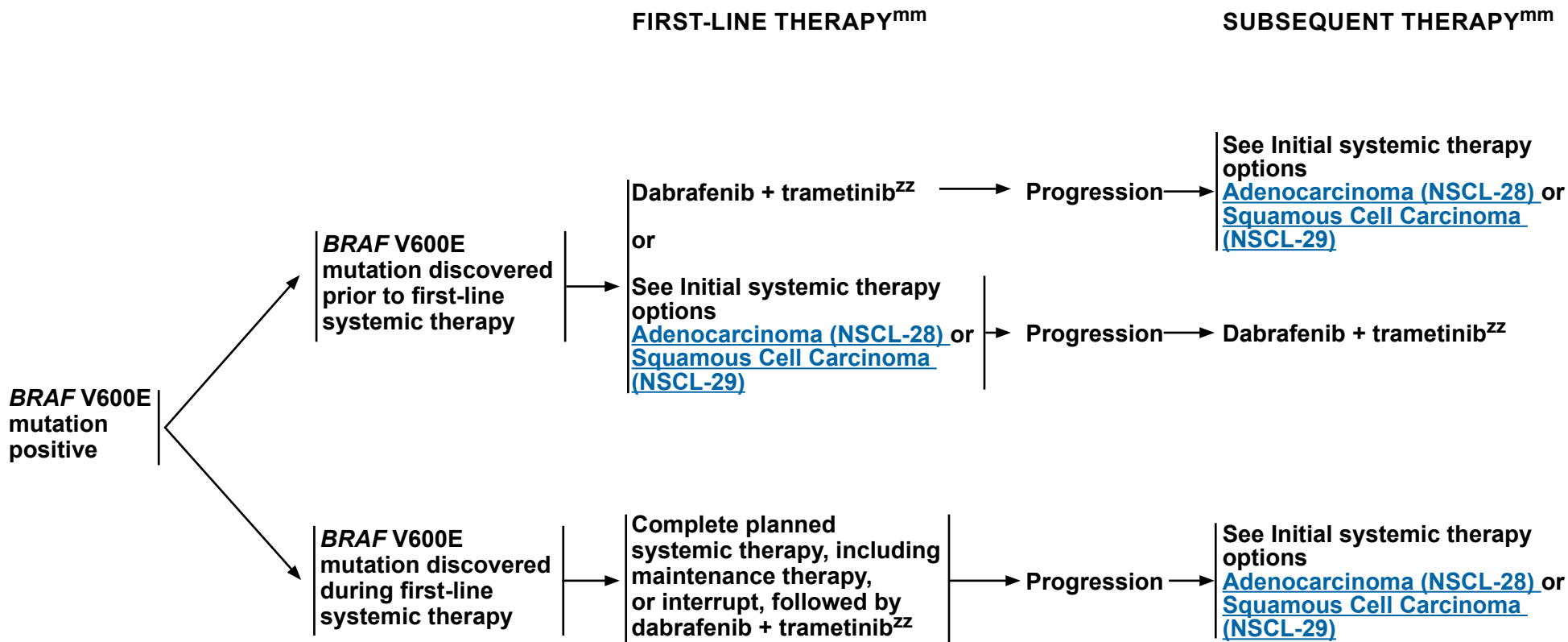
<sup>nn</sup>For performance status 0-4.

**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.**





### BRAF V600E MUTATION POSITIVE<sup>hh</sup>



<sup>hh</sup>See [Principles of Molecular and Biomarker Analysis \(NSCL-G\)](#).

<sup>mm</sup>See [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#).

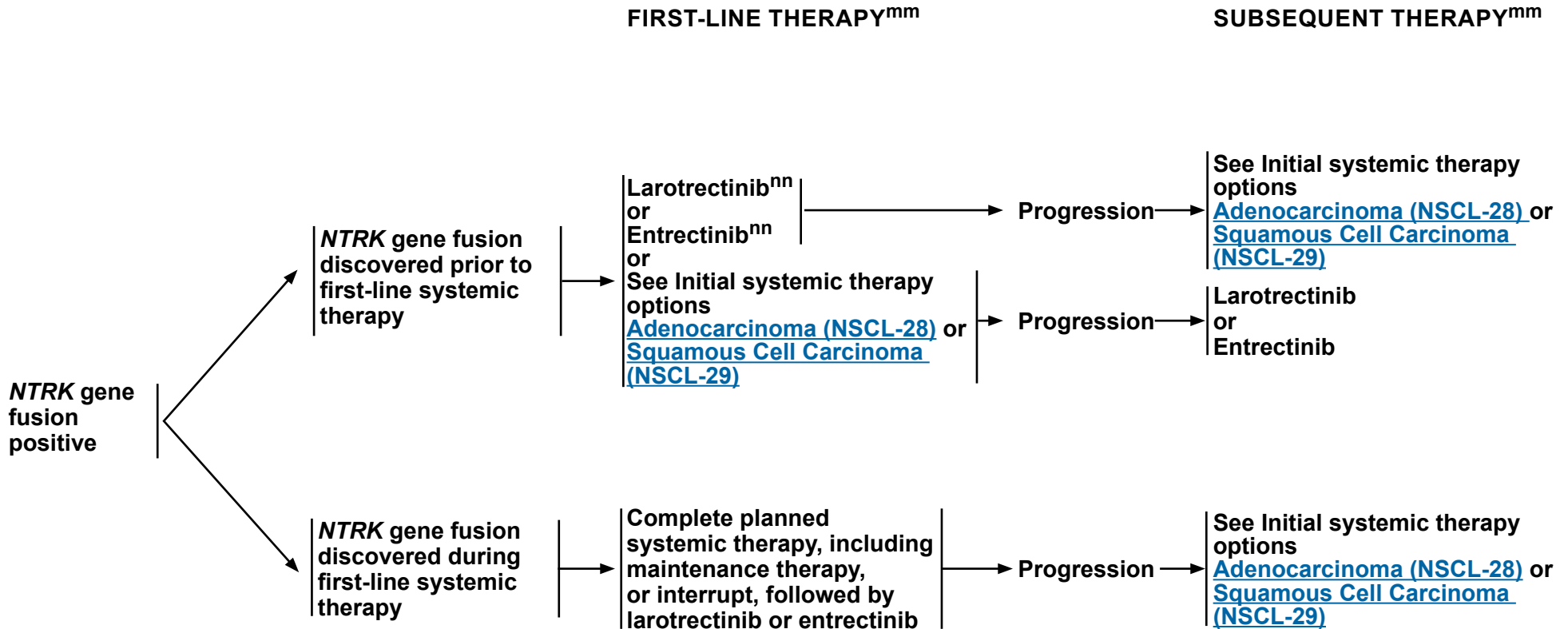
<sup>zz</sup>Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated.

**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.





### NTRK GENE FUSION POSITIVE



<sup>mm</sup>See [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#).

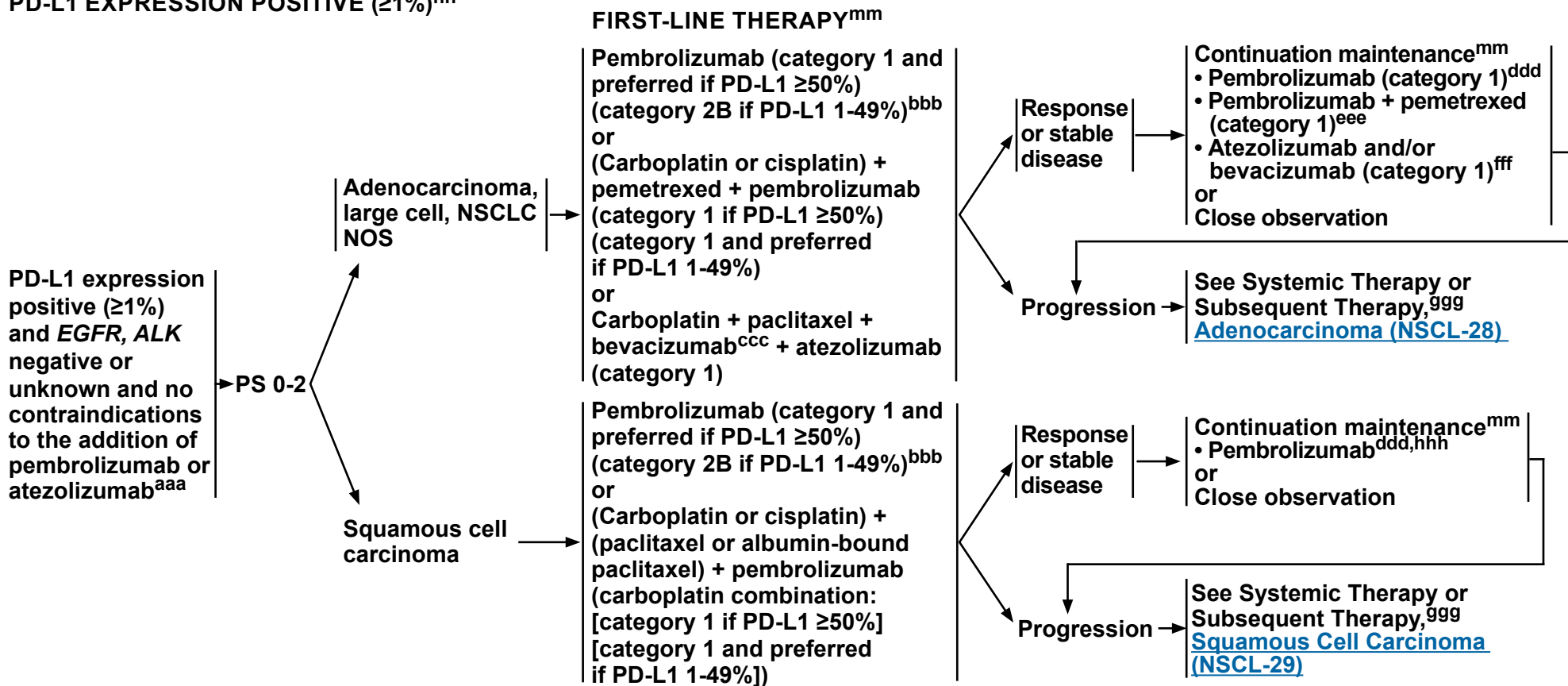
<sup>nn</sup>For performance status 0-4.

**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 (≥1%)<sup>hh</sup>



<sup>hh</sup>See [Principles of Molecular and Biomarker Analysis \(NSCL-G\)](#).

<sup>mm</sup>See [Targeted Therapy for Advanced or Metastatic Disease \(NSCL-I\)](#).

<sup>aaa</sup>Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit. If there are contraindications, refer to [NSCL-28](#) (adenocarcinoma) or [NSCL-29](#) (squamous cell carcinoma).

<sup>bbb</sup>Pembrolizumab monotherapy can be considered in PD-L1 1-49%, in patients with poor PS or other contraindications to combination chemotherapy.

<sup>ccc</sup>An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>ddd</sup>If pembrolizumab monotherapy given.

<sup>eee</sup>If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.

<sup>fff</sup>If atezolizumab/carboplatin/paclitaxel/bevacizumab given.

<sup>ggg</sup>If patient has not received platinum-doublet chemotherapy, refer to "systemic therapy." If patient received platinum chemotherapy and anti-PD-1/PD-L1, refer to "subsequent therapy."

<sup>hhh</sup>If pembrolizumab/(cisplatin or carboplatin)/(paclitaxel or albumin-bound paclitaxel) given.

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

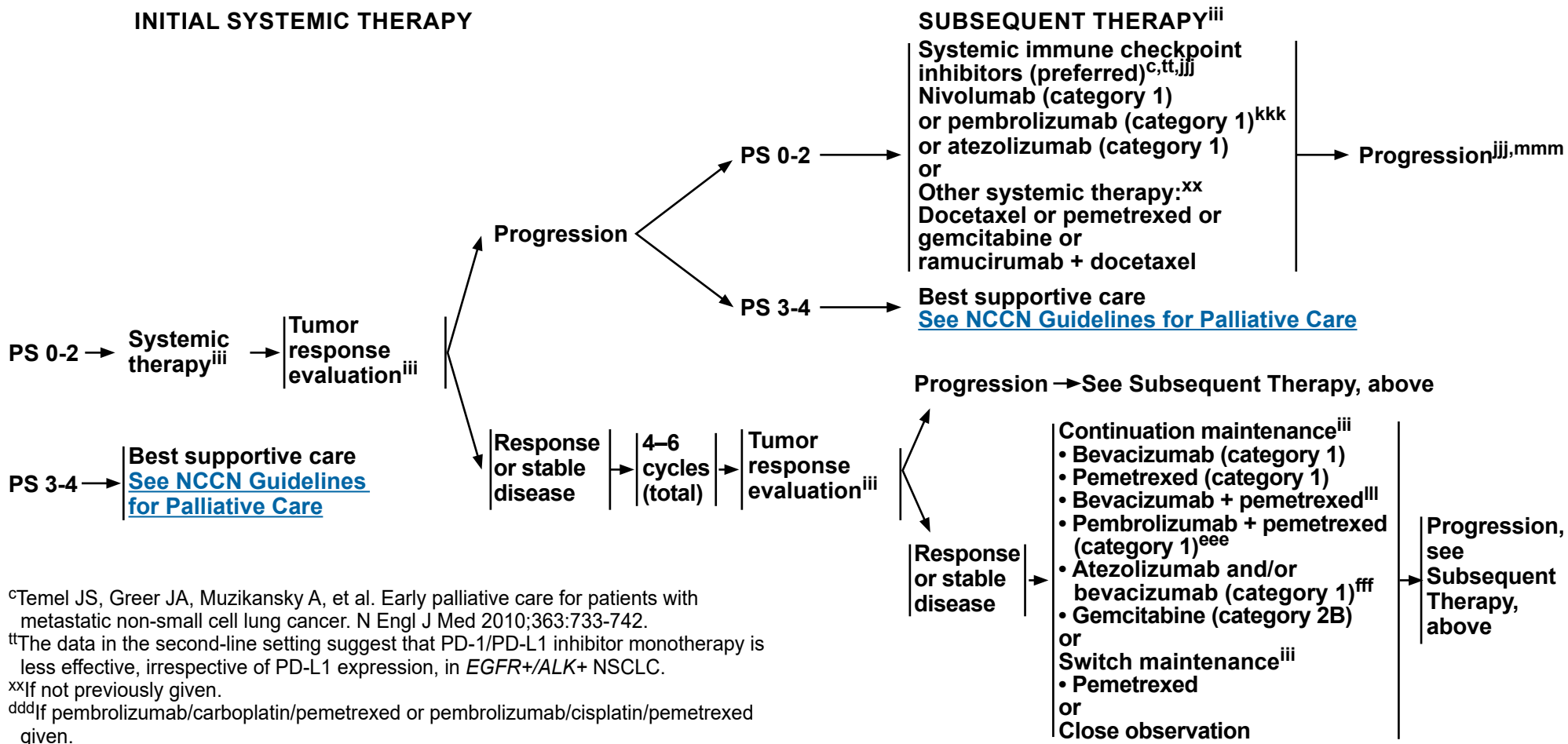
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**





### ADENOCARCINOMA, LARGE CELL, NSCLC NOS

#### INITIAL SYSTEMIC THERAPY



<sup>c</sup>Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. *N Engl J Med* 2010;363:733-742.  
<sup>tt</sup>The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR+/ALK+* NSCLC.  
<sup>xx</sup>If not previously given.  
<sup>ddd</sup>If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.  
<sup>fff</sup>If atezolizumab/carboplatin/paclitaxel/bevacizumab given.  
<sup>iii</sup>See [Systemic Therapy for Advanced or Metastatic Disease \(NSCL-J\)](#).  
<sup>jjj</sup>If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended.  
<sup>kkk</sup>Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels  $\geq 1\%$ , as determined by an FDA-approved test.

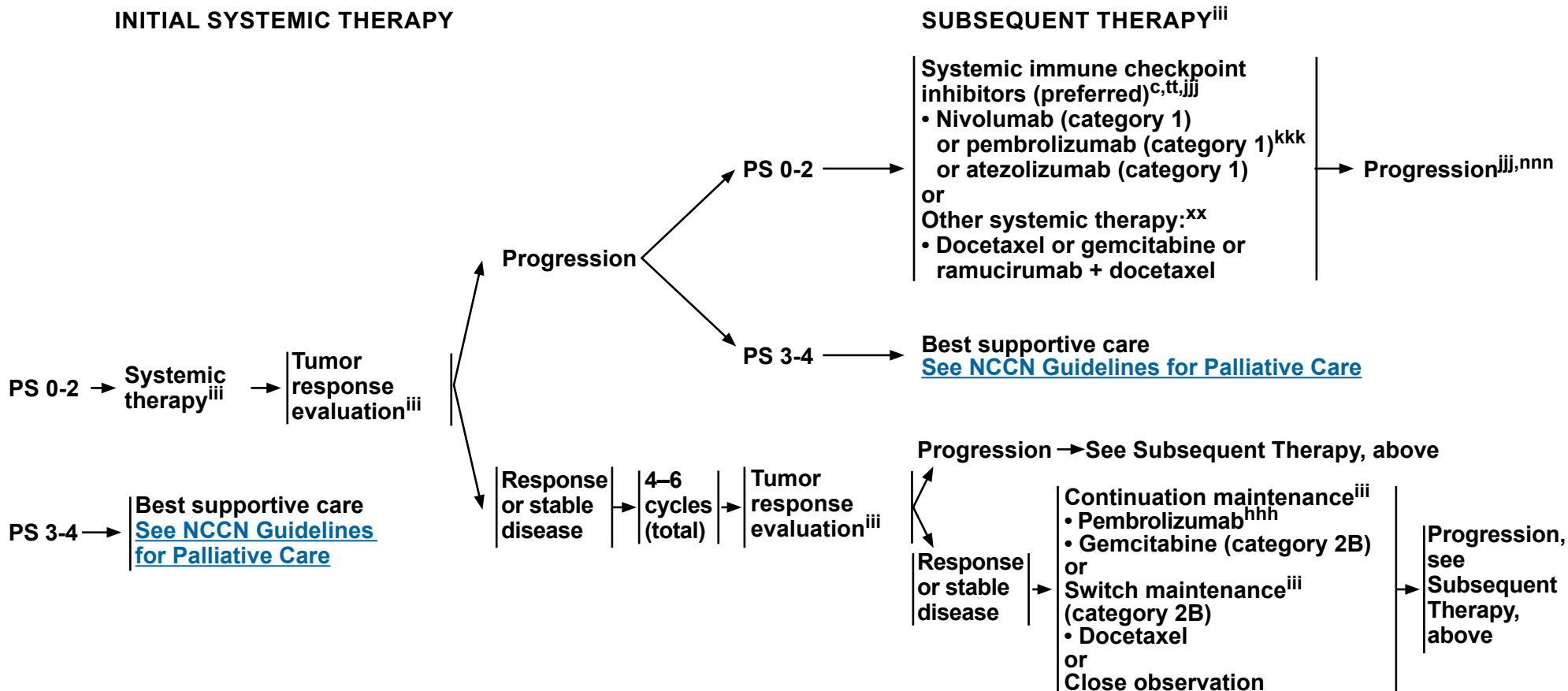
<sup>lll</sup>If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.  
<sup>mmm</sup>If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

**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.**





### SQUAMOUS CELL CARCINOMA



<sup>c</sup>Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. *N Engl J Med* 2010;363:733-742.

<sup>tt</sup>The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR+/ALK+* NSCLC.

<sup>xx</sup>If not previously given.

<sup>hhh</sup>If pembrolizumab/(cisplatin or carboplatin)/(paclitaxel or albumin-bound paclitaxel) given.

<sup>iii</sup>[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-J\).](#)

<sup>jjj</sup>If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended.

<sup>kkk</sup>Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels  $\geq 1\%$ , as determined by an FDA-approved test.

<sup>nnn</sup>If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

**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.**

**PRINCIPLES OF PATHOLOGIC REVIEW****• Pathologic Evaluation**

- ▶ **The purpose of the pathologic evaluation of NSCLC will vary depending on whether the sample 1) is a biopsy or cytology specimen intended for initial diagnosis in a case of suspected NSCLC; 2) is a resection specimen; or 3) is obtained for molecular evaluation in the setting of an established NSCLC diagnosis.**
  - ◊ **In small biopsies or cytology specimens intended for initial diagnosis, the primary purpose is a) to make an accurate diagnosis using the 2015 WHO classification; and b) to preserve the tissue for molecular studies, especially if the patient has advanced-stage disease.**
  - ◊ **In small biopsies of poorly differentiated carcinomas, the terms "non-small cell carcinoma (NSCC)<sup>1</sup>" or "non-small cell carcinoma not otherwise specified (NSCC-NOS)" should be used as little as possible and only when a more specific diagnosis is not possible by morphology and/or special staining.**
  - ◊ **The following terms are acceptable: "NSCC favor adenocarcinoma" and "NSCC favor squamous cell carcinoma." "NSCC-NOS" should be reserved only for cases in which immunohistochemical testing is uninformative or ambiguous (see section on immunohistochemistry).**
  - ◊ **Preservation of material for molecular testing is critical. Efforts should be undertaken to minimize block reorientation and the number of immunohistochemistry stains for cases that cannot be classified on histologic examination alone (see section on immunohistochemistry).**
- ▶ **In resection specimens, the primary purpose is a) to classify the histologic type; and b) to determine all staging parameters, as recommended by the American Joint Committee on Cancer (AJCC), including tumor size, extent of invasion, adequacy of surgical margins, and presence or absence of lymph node metastases.**
  - ◊ **The number of involved lymph node stations should be documented since it has prognostic significance (AJCC 8th ed). Direct extension of the primary tumor into an adjacent lymph node is considered as nodal involvement.**
  - ◊ **The AJCC, Union for International Cancer Control (UICC), and International Association for the Study of Lung Cancer (IASLC) recommend that at least six nodes are removed during surgical resection, three from N1 and three from N2 stations (ie, a representative node from each station) for accurate staging. All lobectomy specimens should be extensively dissected to search for involved lymph nodes.**
- ▶ **In small biopsies or cytology specimens—obtained for molecular testing in the context of an established diagnosis after progression on targeted therapies, the primary purpose is a) to confirm the original pathologic type with minimal use of tissue for immunohistochemistry only in suspected small cell carcinoma transformation or a different histology; and b) to preserve material for molecular analysis.**
- **Formalin-fixed paraffin-embedded (FFPE) material is suitable for most molecular analyses, except bone biopsies that were previously treated with acid decalcifying solutions. Non-acid decalcification approaches may be successful for subsequent molecular testing. While many molecular pathology laboratories currently also accept cytopathology specimens such as cell blocks, direct smears, or touch preparations, laboratories that do not currently do so are strongly encouraged to identify approaches to testing on non-FFPE cytopathology specimens.**

<sup>1</sup>Non-small cell carcinomas (NSCC, without the L for lung) that show no clear adenocarcinoma or squamous cell carcinoma morphology or immunohistochemical markers are regarded as NSCC not otherwise specified (NOS). In this setting, it is recommended that pathologists use the term NSCC rather than NSCLC, because the lack of pneumocyte marker expression in small biopsies or cytology leaves open the possibility of a metastatic carcinoma and the determination of a lung primary must be established clinically after excluding other primary sites.

**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.**

[Continued](#)**NSCL-A**  
**1 OF 4**

**PRINCIPLES OF PATHOLOGIC REVIEW****NSCLC Classification**

- **The types of NSCLC are: adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma, and sarcomatoid carcinoma.**
  - ▶ **Squamous cell carcinoma: A malignant epithelial tumor that either shows keratinization and/or intercellular bridges, or a morphologically undifferentiated NSCC that expresses immunohistochemical markers of squamous cell differentiation.**
  - ▶ **Adenocarcinoma:**
    - ◊ **For small (<3 cm), resected lesions, determining extent of invasion is critical.**
      - **Adenocarcinoma in situ (AIS; formerly BAC): A small (≤3 cm) localized nodule with lepidic growth, mostly non-mucinous, although mucinous types can occur. Multiple synchronous AIS tumors can also occur.**
      - **Minimally invasive adenocarcinoma (MIA): A small (≤3 cm) solitary adenocarcinoma with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension. MIA is usually non-mucinous, but rarely may be mucinous. MIA is, by definition, solitary and discrete.**
      - **Invasive adenocarcinoma: A malignant epithelial tumor with glandular differentiation, mucin production, or pneumocyte marker expression. The tumors show an acinar, papillary, micropapillary, lepidic, or solid growth pattern, with either mucin or pneumocyte marker expression. After comprehensive histologic subtyping in 5%–10% increments, the tumors are classified according to their predominant pattern. The invasive adenocarcinoma component should be present in at least one focus measuring >5 mm in greatest dimension.**
      - **Invasive adenocarcinoma variants: invasive mucinous adenocarcinoma, colloid adenocarcinoma, fetal adenocarcinoma, and enteric adenocarcinoma.**
  - ▶ **Adenosquamous carcinoma: A carcinoma showing components of both squamous cell carcinoma and adenocarcinoma, with each component constituting at least 10% of the tumor. Definitive diagnosis requires a resection specimen, although it may be suggested based on findings in small biopsies, cytology, or excisional biopsies. Presence of any adenocarcinoma component in a biopsy specimen that is otherwise squamous should trigger molecular testing.**
  - ▶ **Large cell carcinoma: Undifferentiated NSCC that lacks the cytologic, architectural, and histochemical features of small cell carcinoma, adenocarcinoma, or squamous cell carcinoma. The diagnosis requires a thoroughly sampled resected tumor and cannot be made on non-resection or cytology specimens.**
  - ▶ **Sarcomatoid carcinoma is a general term that includes pleomorphic carcinoma, carcinosarcoma, and pulmonary blastoma. For this reason, it is best to use the specific term for these entities whenever possible rather than the general term.**
    - ◊ **Pleomorphic carcinoma is a poorly differentiated NSCC that contains at least 10% spindle and/or giant cells or a carcinoma consisting only of spindle and giant cells. Spindle cell carcinoma consists of an almost pure population of epithelial spindle cells, while Giant cell carcinoma consists almost entirely of tumor giant cells.**
    - ◊ **Carcinosarcoma is a malignant tumor that consists of a mixture of NSCC and sarcoma-containing heterologous elements (eg, rhabdomyosarcoma, chondrosarcoma, osteosarcoma).**
    - ◊ **Pulmonary blastoma is a biphasic tumor that consists of fetal adenocarcinoma (typically low grade) and primitive mesenchymal stroma.**

**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.**

[Continued](#)**NSCL-A**  
**2 OF 4**

**PRINCIPLES OF PATHOLOGIC REVIEW****Immunohistochemistry**

- **Judicious use of immunohistochemistry is strongly recommended to preserve tissue for molecular testing, most notably in small specimens. When adenocarcinoma or squamous cell carcinomas are poorly differentiated, the defining morphologic criteria that would allow for specific diagnosis may be inconspicuous or absent. In this case, immunohistochemistry or mucin staining may be necessary to determine a specific diagnosis.**
- **In small specimens, a limited number of immunostains with one lung adenocarcinoma marker (TTF1, napsin A) and one squamous carcinoma marker (p40, p63) should suffice for most diagnostic problems. Virtually all tumors that lack squamous cell morphology and show co-expression of p63 and TTF1 are preferably classified as adenocarcinoma. A simple panel of TTF1 and p40 may be sufficient to classify most NSCC-NOS cases.**
- **Testing for NUT expression by immunohistochemistry should be considered in all poorly differentiated carcinomas that lack glandular differentiation or specific etiology, particularly in non-smokers or in patients presenting at a young age, for consideration of a pulmonary NUT carcinoma.**
- **Immunohistochemistry should be used to differentiate primary lung adenocarcinoma from squamous cell carcinoma, large cell carcinoma, metastatic carcinoma, and primary pleural mesothelioma (particularly for pleural specimens).**
- **Primary pulmonary adenocarcinoma:**
  - ▶ **In patients for whom the primary origin of the carcinoma is uncertain, an appropriate panel of immunohistochemical stains is recommended to assess for metastatic carcinoma to the lung.**
  - ▶ **TTF1 is a homeodomain-containing nuclear transcription protein of the *Nkx2* gene family that is expressed in epithelial cells of the embryonal and mature lung and thyroid. TTF1 immunoreactivity is seen in primary pulmonary adenocarcinoma in the majority (70%–90%) of non-mucinous adenocarcinoma subtypes. Metastatic adenocarcinoma to the lung is nearly always negative for TTF1 except in metastatic thyroid malignancies, in which case thyroglobulin and PAX8 are also positive. Rare cases of TTF1 positivity in tumors of other organs (gynecologic tract, pancreatobiliary) have been noted, and may be dependent on the specific TTF1 clone utilized, stressing the importance of correlation with clinical and radiologic features.**
  - ▶ **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 TTF1.**
  - ▶ **The panel of TTF1 (or alternatively napsin A) and p40 (or alternatively p63) may be useful in refining the diagnosis to either adenocarcinoma or squamous cell carcinoma in small biopsy specimens previously classified as NSCC NOS.**

**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.**

[Continued](#)**NSCL-A**  
**3 OF 4**



### PRINCIPLES OF PATHOLOGIC REVIEW

#### Immunohistochemistry

- Immunohistochemistry should be used to confirm neuroendocrine differentiation when there is morphologic evidence of neuroendocrine morphology (eg, speckled chromatin pattern, nuclear molding, peripheral palisading):
  - ▶ NCAM (CD56), chromogranin, and synaptophysin are used to identify neuroendocrine tumors in cases in which morphologic suspicion of neuroendocrine differentiation exists.
  - ▶ A panel of markers is useful, but one positive marker is enough if the staining is unambiguous in more than 10% of the tumor cells.
- Malignant mesothelioma versus pulmonary adenocarcinoma
  - ▶ The distinction between pulmonary adenocarcinoma and malignant mesothelioma (epithelioid type) can be made by correlation of the histology with the clinical impression, imaging studies, and a panel of immunomarkers.
  - ▶ Immunostains sensitive and specific for mesothelioma include WT-1, calretinin, CK5/6, and D2-40 (usually negative in adenocarcinoma).
  - ▶ Immunostains sensitive and specific for adenocarcinoma include pCEA, Claudin 4, TTF1, and napsin A (negative in mesothelioma). Other potentially useful markers that can be considered include B72.3, Ber-EP4, MOC31, and CD15, but these generally do not have the sensitivity and specificity of the above markers.
  - ▶ A pancytokeratin such as AE1/AE3 is also useful, as a negative result suggests the possibility of other tumors.
  - ▶ Other markers can be helpful in the differential diagnosis between mesothelioma and metastatic carcinoma, and will also help determine the tumor origin. Examples include markers for lung adenocarcinoma (TTF1, napsin A), breast carcinoma (ER $\alpha$ , PR, GCDFP15, mammaglobin), renal cell carcinoma (PAX8), papillary serous carcinoma (PAX8, PAX2, and ER), adenocarcinomas of the gastrointestinal tract (CDX2), and prostate cancer (NKX3.1). Additionally, p40 (or p63) is helpful for distinguishing epithelioid mesotheliomas with pseudosquamous morphology from squamous cell carcinomas.

**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.

**PRINCIPLES OF SURGICAL THERAPY****Evaluation**

- **Determination of resectability, surgical staging, and *pulmonary resection should be performed by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.***
- CT and PET/CT used for staging should be within 60 days before proceeding with surgical evaluation.
- For medically operable disease, resection is the preferred local treatment modality (other modalities include SABR, thermal ablation such as radiofrequency ablation, and cryotherapy). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where SABR is considered for high-risk or borderline operable patients, a multidisciplinary evaluation including a radiation oncologist is recommended.
- The overall plan of treatment as well as needed imaging studies should be determined before any non-emergency treatment is initiated.
- Thoracic surgeons should actively participate in multidisciplinary discussions and meetings regarding lung cancer patients (eg, multidisciplinary clinic and/or tumor board).
- Patients who are active smokers should be provided counseling and smoking cessation support ([NCCN Guidelines for Smoking Cessation](#)). While active smokers have a mildly increased incidence of postoperative pulmonary complications, these should not be considered a prohibitive risk for surgery. Surgeons should not deny surgery to patients solely due to smoking status, as surgery provides the predominant opportunity for prolonged survival in patients with early-stage lung cancer.

**Resection**

- Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.
- Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins  $\geq 2$  cm or  $\geq$  the size of the nodule.
- Sublobar resection should also sample appropriate N1 and N2 lymph node stations unless not technically feasible without substantially increasing the surgical risk.
- Segmentectomy (preferred) or wedge resection is appropriate in selected patients for the following reasons:
  - ▶ Poor pulmonary reserve or other major comorbidity that contraindicates lobectomy
  - ▶ Peripheral nodule<sup>1</sup>  $\leq 2$  cm with at least one of the following:
    - ◊ Pure AIS histology
    - ◊ Nodule has  $\geq 50\%$  ground-glass appearance on CT
    - ◊ Radiologic surveillance confirms a long doubling time ( $\geq 400$  days)
- VATS or minimally invasive surgery (including robotic-assisted approaches) should be strongly considered for patients with no anatomic or surgical contraindications, as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery.
- In high-volume centers with significant VATS experience, VATS lobectomy in selected patients results in improved early outcomes (ie, decreased pain, reduced hospital length of stay, more rapid return to function, fewer complications) without compromise of cancer outcomes.
- Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and margin-negative resection is achieved.
- T3 (invasion) and T4 local extension tumors require en-bloc resection of the involved structure with negative margins. If a surgeon or center is uncertain about potential complete resection, consider obtaining an additional surgical opinion from a high-volume specialized center.

**Margins and Nodal Assessment (see [NSCL-B 2 of 4](#))**

<sup>1</sup>Peripheral is defined as the outer one third of the lung parenchyma.

**The Role of Surgery in Patients with Stage IIIA (N2) NSCLC (see [NSCL-B 2 of 4](#) through [NSCL-B 4 of 4](#))**

**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.



## PRINCIPLES OF SURGICAL THERAPY

### **Margins and Nodal Assessment**

- **Surgical pathologic correlation is critical to assess apparent close or positive margins, as these may not represent true margins or may not truly represent areas of risk for local recurrence (eg, medial surface of mainstem or bronchus intermedius when separate subcarinal lymph node dissection has been performed; pleural margin adjacent to aorta when no attachment to aorta is present).**
- **N1 and N2 node resection and mapping should be a routine component of lung cancer resections—a minimum of three N2 stations sampled or complete lymph node dissection.**
- **Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease.**
- **Complete resection requires free resection margins, systematic node dissection or sampling, and the highest mediastinal node negative for tumor. The resection is defined as incomplete whenever there is involvement of resection margins, unremoved positive lymph nodes, or positive pleural or pericardial effusions. A complete resection is referred to as R0, microscopically positive resection as R1, and macroscopic residual tumor as R2.**
- **Patients with pathologic stage II or greater should be referred to medical oncology for evaluation.**
- **Consider referral to a radiation oncologist for resected stage IIIA.**

### **The Role of Surgery in Patients with Stage IIIA (N2) NSCLC**

The role of surgery in patients with pathologically documented N2 disease remains controversial.<sup>1</sup> Two randomized trials evaluated the role of surgery in this population, but neither showed an overall survival benefit with the use of surgery.<sup>2,3</sup> However, this population is heterogeneous and the panel believes that these trials did not sufficiently evaluate the nuances present with the heterogeneity of N2 disease and the likely oncologic benefit of surgery in specific clinical situations.

- **The presence or absence of N2 disease should be vigorously determined by both radiologic and invasive staging prior to the initiation of therapy since the presence of mediastinal nodal disease has a profound impact on prognosis and treatment decisions. ([NSCL-1](#), [NSCL-2](#), and [NSCL-6](#))**
- **Patients with occult-positive N2 nodes discovered at the time of pulmonary resection should continue with the planned resection along with formal mediastinal lymph node dissection. If N2 disease is noted in patients undergoing VATS, the surgeon may consider stopping the procedure so that induction therapy can be administered before surgery; however, continuing the procedure is also an option.**
- **The determination of the role of surgery in a patient with N2-positive lymph nodes should be made prior to the initiation of any therapy by a multidisciplinary team, including a board-certified thoracic surgeon who has a major part of his/her practice dedicated to thoracic oncology.<sup>4</sup>**
- **The presence of N2-positive lymph nodes substantially increases the likelihood of positive N3 lymph nodes. Pathologic evaluation of the mediastinum must include evaluation of the subcarinal station and contralateral lymph nodes. EBUS +/- EUS are additional techniques for minimally invasive pathologic mediastinal staging that are complementary to mediastinoscopy. Even when these modalities are employed it is important to have an adequate evaluation of the number of stations involved and biopsy and documentation of negative contralateral lymph node involvement prior to a final treatment decision.**

The Role of Surgery in Patients with Stage IIIA (N2) NSCLC is continued on [NSCL-B 3 of 4](#) through [NSCL-B 4 of 4](#)

**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.

**PRINCIPLES OF SURGICAL THERAPY****The Role of Surgery in Patients with Stage IIIA (N2) NSCLC**

- Repeat mediastinoscopy, while possible, is technically difficult and has a lower accuracy compared to primary mediastinoscopy. One possible strategy is to perform EBUS (± EUS) in the initial pretreatment evaluation and reserve mediastinoscopy for nodal restaging after neoadjuvant therapy.<sup>5</sup>
- Patients with a single lymph node smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.<sup>1,6,7</sup>
- Restaging after induction therapy is difficult to interpret, but CT +/- PET should be performed to exclude disease progression or interval development of metastatic disease.
- Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.<sup>7,8</sup>
- Neoadjuvant chemoradiotherapy is used in 50% of the NCCN Member Institutions, while neoadjuvant chemotherapy is used in the other 50%. Overall survival appears similar provided RT is given postoperatively, if not given preoperatively.<sup>5,9</sup> Neoadjuvant chemoradiotherapy is associated with higher rates of pathologic complete response and negative mediastinal lymph nodes.<sup>10</sup> However, that is achieved at the expense of higher rates of acute toxicity and increased cost.
- When neoadjuvant chemoradiotherapy is used with doses lower than those used for standard definitive therapy, all efforts should be made to minimize any possible breaks in radiotherapy for surgical evaluation. Treatment breaks of more than 1 week are considered unacceptable.
- When timely surgical evaluation is not available, the strategy of neoadjuvant chemoradiotherapy should not be used. Another option in individual cases, and with the agreement of the thoracic surgeon, is to complete definitive chemoradiotherapy prior to re-evaluation and consideration for surgery.<sup>11,12</sup> If a surgeon or center is uncertain about the feasibility or safety of resection after definitive doses of radiation, consider obtaining an additional surgical opinion from a high-volume specialized center. These operations may also benefit from additional considerations of soft tissue flap coverage in the radiation field at the time of resection.
- Data from a large multi-institutional trial indicate that pneumonectomy after neoadjuvant chemoradiotherapy has unacceptable morbidity and mortality.<sup>2</sup> However, it is not clear if this is also true with neoadjuvant chemotherapy alone. Further, many groups have challenged that cooperative group finding with single-institution experiences demonstrating safety of pneumonectomy after induction therapy.<sup>13-16</sup> In addition, there is no evidence that adding RT to induction regimens for patients with operable stage IIIA (N2) disease improves outcomes compared to induction chemotherapy.<sup>17</sup>

A questionnaire was submitted to the NCCN Member Institutions in 2010 regarding their approach to patients with N2 disease. Their responses indicate the patterns of practice when approaching this difficult clinical problem.

- Would consider surgery in patients with one N2 lymph node station involved by a lymph node smaller than 3 cm: (90.5%)
- Would consider surgery with more than one N2 lymph node station involved, as long as no lymph node was bigger than 3 cm: (47.6%)
- Uses EBUS (+/- EUS) in the initial evaluation of the mediastinum: (80%)
- Uses pathologic evaluation of the mediastinum, after neoadjuvant therapy, to make a final decision before surgery: (40.5%)
- Would consider neoadjuvant therapy followed by surgery when a patient is likely, based on initial evaluation, to require a pneumonectomy: (54.8%)

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.

**References**



**PRINCIPLES OF SURGICAL THERAPY****The Role of Surgery in Patients with Stage IIIA (N2) NSCLC - References**

- <sup>1</sup>Martins RG, D'Amico TA, Loo BW Jr, et al. The management of patients with stage IIIA non-small cell lung cancer with N2 mediastinal node involvement. *J Natl Compr Canc Netw* 2012;10:599-613.
- <sup>2</sup>Albain K, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomized controlled trial. *Lancet* 2009;374:379-386.
- <sup>3</sup>van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;99:442-450.
- <sup>4</sup>Farjah F, Flum DR, Varghese TK Jr, et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. *Ann Thorac Surg* 2009;87:995-1006.
- <sup>5</sup>Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol* 2008;9:607-608.
- <sup>6</sup>Andre F, Grunenwald D, Pignon J, et al. Survival of patients with resected N2 non-small-cell lung Cancer: Evidence for a subclassification and implications. *J Clin Oncol* 2000;18:2981-2989.
- <sup>7</sup>Decaluwé H, De Leyn P, Vansteenkiste J, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. *Eur J Cardiothorac Surg* 2009;36:433-439.
- <sup>8</sup>Bueno R, Richards WG, Swanson SJ, et al. Nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. *Ann Thorac Surg* 2000;70:1826-1831.
- <sup>9</sup>Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;75:1462-1467.
- <sup>10</sup>de Cabanyes Candela S, Detterbeck FC. A systematic review of restaging after induction therapy for stage IIIa lung cancer: prediction of pathologic stage. *J Thorac Oncol* 2010;5:389-398.
- <sup>11</sup>Bauman JE, Mulligan MS, Martins RG, et al. Salvage Lung Resection After Definitive Radiation (>59 Gy) for Non-Small Cell Lung Cancer: Surgical and Oncologic Outcomes. *Ann Thorac Surg* 2008;86:1632-1639.
- <sup>12</sup>Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary Resection After Curative Intent Radiotherapy (>59 Gy) and Concurrent Chemotherapy in Non-Small-Cell Lung Cancer. *Ann Thorac Surg* 2004;78:1200-1205.
- <sup>13</sup>Evans NR 3rd, Li S, Wright CD, et al. The impact of induction therapy on morbidity and operative mortality after resection of primary lung cancer. *J Thorac Cardiovasc Surg* 2010;139:991-996.
- <sup>14</sup>Gaissert HA, Keum DY, Wright CD, et al. POINT: Operative risk of pneumonectomy—Influence of preoperative induction therapy. *J Thorac Cardiovasc Surg* 2009;138:289-294.
- <sup>15</sup>Mansour Z, Kochetkova EA, Ducrocq X, et al. Induction chemotherapy does not increase the operative risk of pneumonectomy! *Eur J Cardiothorac Surg* 2007;31:181-185.
- <sup>16</sup>Weder W, Collaud S, Eberhardt WEE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 2010;139:1424-1430.
- <sup>17</sup>Shah AA, Berry M, Tzao C, et al. Induction chemoradiotherapy is not superior to induction chemotherapy alone in stage IIIA lung cancer: a systematic review and meta-analysis. *Ann Thorac Surg* 2012;93:1807-1812.

**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.**

**PRINCIPLES OF RADIATION THERAPY****I. General Principles (see Table 1. Commonly Used Abbreviations in Radiation Therapy)**

- Determination of the appropriateness of radiation therapy (RT) should be made by board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice.
- RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with stage III NSCLC, early-stage disease who are medically inoperable, refuse surgery, or are high-risk surgical candidates, and stage IV disease that may benefit from local therapy.
- The critical goals of modern RT are to maximize tumor control and to minimize treatment toxicity. A minimum technologic standard is CT-planned 3D-CRT.<sup>1</sup>
- More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy (<https://www.astro.org/Daily-Practice/Reimbursement/Model-Policies/Model-Policies/>). Nonrandomized comparisons of using advanced technologies demonstrate reduced toxicity and improved survival versus older techniques.<sup>2-4</sup> In a prospective trial of definitive chemo/RT for patients with stage III NSCLC (RTOG 0617), IMRT was associated with a nearly 60% decrease (from 7.9% to 3.5%) in high-grade radiation pneumonitis as well as similar survival and tumor control outcomes despite a higher proportion of stage IIIB and larger treatment volumes compared to 3D-CRT;<sup>5</sup> as such, IMRT is preferred over 3D-CRT in this setting.
- Centers using advanced technologies should implement and document modality-specific quality assurance measures. The ideal is external credentialing of both treatment planning and delivery such as required for participation in RTOG clinical trials employing advanced technologies. Useful references include the ACR Practice Parameters and Technical Standards (<https://www.acr.org/~media/ACR/Documents/PGTS/toc.pdf>).

**II. Radiation Therapy Simulation, Planning, and Delivery**

- Simulation should be performed using CT scans obtained in the RT treatment position with appropriate immobilization devices. IV contrast with or without oral contrast is recommended for better target/organ delineation whenever possible in patients with central tumors or nodal disease. Because IV contrast can affect tissue heterogeneity correction calculations, density masking or use of a pre-contrast scan may be needed when intense enhancement is present.
- PET/CT significantly improves targeting accuracy,<sup>6</sup> especially for patients with significant atelectasis and when IV CT contrast is contraindicated. A randomized trial of PET/CT versus CT-only RT planning demonstrated improved preemption of futile radical RT, decreased recurrences, and a trend toward improved overall survival with PET/CT RT planning.<sup>7</sup> Given the potential for rapid progression of NSCLC,<sup>8,9</sup> PET/CT should be obtained preferably within 4 weeks before treatment. It is ideal to obtain PET/CT in the treatment position.
- Tumor and organ motion, especially owing to breathing, should be assessed or accounted for at simulation. Options include fluoroscopy, inhale/exhale or slow scan CT, or, ideally, 4D-CT.

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.

[Continued](#)NSCL-C  
1 OF 10

**PRINCIPLES OF RADIATION THERAPY****II. Radiation Therapy Simulation, Planning, and Delivery (continued)**

- Photon beam energy should be individualized based on the anatomic location of the tumors and beam paths. In general, photon energies between 4 to 10 MV are recommended for beams passing through low-density lung tissue before entering the tumor. When there is no air gap before the beam enters the tumor (such as for some large mediastinal tumors or tumors attached to the chest wall), higher energies may improve the dose distribution, especially when using a smaller number of fixed beam angles.
- Tissue heterogeneity correction and accurate dose calculation algorithms are recommended that account for buildup and lateral electron scatter effects in heterogeneous density tissues. Heterogeneity correction with simple pencil beam algorithms is not recommended.<sup>10</sup>
- Respiratory motion should be managed when motion is excessive. This includes (but is not limited to) forced shallow breathing with abdominal compression, accelerator beam gating with the respiratory cycle, dynamic tumor tracking, active breathing control (ABC), or coaching/biofeedback techniques. If motion is minimal or the ITV is small, motion-encompassing targeting is appropriate. A useful resource for implementation of respiratory motion management is the report of AAPM Task Group 76.<sup>11</sup>
- IGRT—including (but not limited to) orthogonal pair planar imaging and/or volumetric imaging (such as CBCT or CT on rails)—is recommended when using SABR, 3D-CRT/IMRT, and proton therapy with steep dose gradients around the target, when OARs are in close proximity to high-dose regions, and when using complex motion management techniques.

**III. Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints (See Tables 2–5 on NSCL-C 7 of 10 and NSCL-C 8 of 10)**

- ICRU Reports 62 and 83 detail the current definitions of target volumes for 3D-RT and IMRT. GTV comprises the known extent of disease (primary and nodal) on imaging and pathologic assessment, CTV includes regions of presumed microscopic extent or dissemination, and PTV comprises the ITV (which includes margin for target motion) plus a setup margin for positioning and mechanical variability.  
<https://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx>
- PTV margin can be decreased by immobilization, motion management, and IGRT techniques.
- Consistent delineation of normal structures is critical for evaluating plans for safety. The RTOG consensus lung-contouring atlas is a useful resource. <https://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx>
- Commonly used prescription doses and normal tissue dose constraints are summarized in Tables 2 through 5. These are based on published experience, ongoing trials, historical data, modeling, and empirical judgment.<sup>12,13</sup> Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.<sup>14-18</sup> Because risk of normal organ toxicity increases with dose, doses to normal organs should be kept as low as reasonably achievable rather than simply meeting nominal constraints. This is generally facilitated by more advanced techniques to achieve better dose conformity.

**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.

**PRINCIPLES OF RADIATION THERAPY****IV. General Treatment Information****Early-Stage NSCLC (Stage I, selected node-negative Stage IIA)**

- SABR (also known as SBRT)<sup>19</sup> is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation. SABR has achieved good primary tumor control rates and overall survival, and higher than conventionally fractionated radiotherapy, although not proven equivalent to lobectomy.<sup>20-26</sup>
- SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years], poor lung function).
- For institutions without an established SABR program, more modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are less preferred alternatives.<sup>29-31</sup>
- In patients treated with surgery, postoperative radiotherapy (PORT) is not recommended unless there are positive margins or upstaging to N2 (see *Locally Advanced NSCLC* in this section).

**SABR for Node-Negative Early-Stage NSCLC**

- The high-dose intensity and conformity of SABR require minimizing the PTV.
- Dosing regimen
  - ▶ For SABR, intensive regimens of BED ≥100 Gy are associated with significantly better local control and survival than less intensive regimens.<sup>32</sup> In the United States, only regimens of ≤5 fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are appropriate as well.<sup>32,33</sup> For centrally located tumors (defined variably as within 2 cm of the proximal bronchial tree and/or abutting mediastinal pleura) and even ultra-central tumors (defined as abutting the proximal bronchial tree), 4 to 10 fraction risk-adapted SABR regimens appear to be effective and safe,<sup>34-37</sup> while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.<sup>38</sup> However, particular attention should be paid to tumors abutting the bronchial tree and esophagus to avoid severe toxicity. The maximum tolerated dose for 5-fraction regimens was studied prospectively in RTOG 0813; preliminary results demonstrate no high-grade toxicities at 50 Gy in 5 fractions.<sup>39</sup>
- SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected.<sup>39,40</sup>
- Prescription doses incompletely describe the actual delivered doses, which also strongly depend on how the dose is prescribed (to the isocenter vs. an isodose volume covering a proportion of the PTV), the degree of dose heterogeneity, whether tissue density heterogeneity corrections are used, and the type of dose calculation algorithm.<sup>10,41-42</sup> All of these must be considered when interpreting or emulating regimens from prior studies.

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.

[Continued](#)**NSCL-C**  
**3 OF 10**

**PRINCIPLES OF RADIATION THERAPY****Locally Advanced NSCLC (Stage II-III)**

- Concurrent chemotherapy/RT is recommended for patients with inoperable stage II (node-positive) and stage III NSCLC.<sup>43-46</sup>
- RT interruptions and dose reductions for manageable acute toxicities should be avoided by employing supportive care.
- Sequential chemotherapy/RT or RT alone is appropriate for frail patients unable to tolerate concurrent therapy.<sup>47,48</sup>  
Accelerated RT regimens may be beneficial, particularly if concurrent chemotherapy would not be tolerated (ie, in a sequential or RT-only approach).<sup>49,50</sup>
- Preoperative concurrent chemotherapy/RT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)<sup>51</sup> and is recommended for resectable superior sulcus tumors.<sup>52,53</sup> RT should be planned up front such that it continues to a definitive dose without interruption if the patient does not proceed to surgery as initially planned.
- Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.<sup>54,55</sup> The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and is controversial.<sup>56,57</sup>
- The determination of resectability in trimodality therapy should be made prior to initiation of all treatment. Upfront multidisciplinary consultation is particularly important when considering surgical treatment of patients with stage III NSCLC.
- In patients with clinical stage I/II upstaged surgically to N2+, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.<sup>58,59</sup> Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy and concurrently with chemotherapy for positive resection margins.<sup>60-63</sup>
- PORT is not recommended for patients with pathologic stage N0-1 disease, because it has been associated with increased mortality, at least when using older RT techniques.<sup>64</sup>

**Conventionally Fractionated RT for Locally Advanced NSCLC**

- IFI omitting ENI allows tumor dose escalation and is associated with a low risk of isolated nodal relapse, particularly in a patient staged with PET/CT.<sup>65-69</sup> Two randomized trials found improved survival for IFI versus ENI, possibly because it enabled dose escalation.<sup>70</sup> IFI is reasonable in order to optimize definitive dosing to the tumor.<sup>71</sup> IFI is reasonable in order to optimize definitive dosing to the tumor and/or decrease normal tissue toxicity.
- Dosing Regimens
  - ▶ The most commonly prescribed doses for definitive RT are 60 to 70 Gy in 2 Gy fractions. Doses of at least 60 Gy should be given.<sup>72</sup> Dose escalation is associated with better survival in non-randomized comparisons in RT alone,<sup>73</sup> sequential chemo/RT,<sup>74</sup> or concurrent chemo/RT.<sup>75</sup> While optimal RT dose intensification remains a valid question, higher doses of 74 Gy are not currently recommended for routine use.<sup>76-80</sup> A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens,<sup>81</sup> and individualized accelerated RT dose intensification is now being evaluated in a randomized trial (RTOG 1106).

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.

[Continued](#)**NSCL-C**  
**4 OF 10**

**PRINCIPLES OF RADIATION THERAPY****Conventionally Fractionated RT for Locally Advanced NSCLC (continued)****• Dosing Regimens**

- ▶ Doses of 45 to 54 Gy in 1.8 to 2 Gy fractions are standard preoperative doses.<sup>82</sup> Definitive RT doses delivered as preoperative chemRT can safely be administered and achieve promising nodal clearance and survival rates,<sup>83-86</sup> but require experience in thoracic surgical techniques to minimize the risk of surgical complications after high-dose RT.
- ▶ In PORT, the CTV includes the bronchial stump and high-risk draining lymph node stations.<sup>87</sup> Standard doses after complete resection are 50 to 54 Gy in 1.8 to 2 Gy fractions, but a boost may be administered to high-risk regions including areas of nodal extracapsular extension or microscopic positive margins.<sup>58,59,88</sup> Lung dose constraints should be more conservative, because tolerance appears to be reduced after surgery. The ongoing European LungART trial provides useful guidelines for PORT technique.<sup>89</sup>

**Advanced/Metastatic NSCLC (Stage IV)**

- RT is recommended for local palliation or prevention of symptoms (such as pain, bleeding, or obstruction).
- Definitive local therapy to isolated or limited metastatic sites (oligometastases) (including but not limited to brain, lung, and adrenal gland) achieves prolonged survival in a small proportion of well-selected patients with good performance status who have also received radical therapy to the intrathoracic disease.<sup>90</sup> Definitive RT to oligometastases (limited number is not universally defined but clinical trials have included up to 3–5 metastases), particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.<sup>91,92</sup> In 2 randomized phase II trials, significantly improved progression-free survival was found for local consolidative therapy (RT or surgery) to oligometastatic lesions versus maintenance systemic therapy or observation for patients not progressing on systemic therapy.<sup>93,94</sup>
- In the setting of progression at a limited number of sites on a given line of systemic therapy (oligoprogression), local ablative therapy to the oligoprogressive sites may extend the duration of benefit of the current line of systemic therapy.
- When treating oligometastatic/oligoprogressive lesions, if SABR is not feasible, other dose-intensive accelerated/hypofractionated conformal radiation therapy regimens may be used.
- See the [NCCN Guidelines for Central Nervous System Cancers](#) regarding RT for brain metastases.

**Palliative RT for Advanced/Metastatic NSCLC**

- The dose and fractionation of palliative RT should be individualized based on goals of care, symptoms, performance status, and logistical considerations. Shorter courses of RT are preferred for patients with poor performance status and/or shorter life expectancy because they provide similar pain relief as longer courses, although there is a higher potential need for retreatment.<sup>95-98</sup> For palliation of thoracic symptoms, higher dose/longer-course thoracic RT (eg, ≥30 Gy in 10 fractions) is associated with modestly improved survival and symptoms, particularly in patients with good performance status.<sup>99,100</sup> When higher doses (>30 Gy) are warranted, technologies to reduce normal tissue irradiation (at least 3D-CRT and including IMRT or proton therapy as appropriate) may be used.

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.

[Continued](#)**NSCL-C**  
**5 OF 10**

**PRINCIPLES OF RADIATION THERAPY****Table 1. Commonly Used Abbreviations in Radiation Therapy**

RT	Radiation Therapy or Radiotherapy	ICRU	International Commission on Radiation Units and Measurements
2D-RT	2-Dimensional RT	IFI	Involved Field Irradiation
3D-CRT	3-Dimensional Conformal RT	IGRT	Image-Guided RT
4D-CT	4-Dimensional Computed Tomography	IMRT	Intensity-Modulated RT
AAPM	American Association of Physicists in Medicine	ITV*	Internal Target Volume
ABC	Active Breathing Control	OAR	Organ at Risk
ACR	American College of Radiology	OBI	On-Board Imaging
ASTRO	American Society for Radiation Oncology	PORT	Postoperative RT
BED	Biologically Effective Dose	PTV*	Planning Target Volume
CBCT	Cone-Beam CT	QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
CTV*	Clinical Target Volume	RTOG	Radiation Therapy Oncology Group now part of NRG Oncology
ENI	Elective Nodal Irradiation	SABR	Stereotactic Ablative RT, also known as Stereotactic Body RT (SBRT)
GTV*	Gross Tumor Volume	VMAT	Volumetric Modulated Arc Therapy

\*Refer to ICRU Report 83 for detailed definitions.

**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.**[Continued](#)**NSCL-C**  
**6 OF 10**



### PRINCIPLES OF RADIATION THERAPY

**Table 2. Commonly Used Doses for SABR**

Total Dose	# Fractions	Example Indications
25–34 Gy	1	Peripheral, small (<2 cm) tumors, esp. >1 cm from chest wall
45–60 Gy	3	Peripheral tumors and >1 cm from chest wall
48–50 Gy	4	Central or peripheral tumors <4–5 cm, especially <1 cm from chest wall
50–55 Gy	5	Central or peripheral tumors, especially <1 cm from chest wall
60–70 Gy	8–10	Central tumors

**Table 3. Maximum Dose Constraints for SABR\***

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	105% of PTV prescription <sup>^</sup>
Brachial plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32 Gy (6.4 Gy/fx)
Heart/pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	105% of PTV prescription <sup>^</sup>
Great vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription <sup>^</sup>
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription <sup>^</sup>
Rib	30 Gy	30 Gy (10 Gy/fx)	40 Gy (10 Gy/fx)	NS
Skin	26 Gy	24 Gy (8 Gy/fx)	36 Gy (9 Gy/fx)	32 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

\*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).

<sup>^</sup>for central tumor location. NS = not specified

**Please note - Tables 2–4 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.**

**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.**

[Continued](#)





## PRINCIPLES OF RADIATION THERAPY

**Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT**

Treatment Type	Total Dose	Fraction Size	Treatment Duration
Definitive RT with or without chemotherapy	60–70 Gy	2 Gy	6–7 weeks
Preoperative RT	45–54 Gy	1.8–2 Gy	5 weeks
Postoperative RT • Negative margins • Extracapsular nodal extension or microscopic positive margins • Gross residual tumor	50–54 Gy	1.8–2 Gy	5–6 weeks
	54–60 Gy	1.8–2 Gy	6 weeks
	60–70 Gy	2 Gy	6–7 weeks
Palliative RT • Obstructive disease (SVC syndrome or obstructive pneumonia) • Bone metastases with soft tissue mass • Bone metastases without soft tissue mass • Brain metastases • Symptomatic chest disease in patients with poor PS • Any metastasis in patients with poor PS	30–45 Gy	3 Gy	2–3 weeks
	20–30 Gy	4–3 Gy	1–2 weeks
	8–30 Gy	8–3 Gy	1 day–2 weeks
	<a href="#">CNS GLs*</a> 17 Gy	<a href="#">CNS GLs*</a> 8.5 Gy	<a href="#">CNS GLs*</a> 1–2 weeks
	8–20 Gy	8–4 Gy	1 day–1 week

**Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT with Concurrent Chemotherapy\***

OAR	Constraints in 30–35 fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%–40% <sup>†</sup> ; MLD ≤20 Gy
Heart	V50 ≤25%; Mean ≤20 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose; V60 ≤17%; contralateral sparing is desirable
Brachial plexus	Median dose ≤69 Gy

V<sub>xx</sub> = % of the whole OAR receiving ≥xx Gy.

\*These constraints represent doses that generally should not be exceeded. Because the risk of toxicity increases progressively with dose to normal tissues, a key principle of radiation treatment planning is to keep normal tissue doses "as low as reasonably achievable" while adequately covering the target. The doses to any given organ at risk should typically be lower than these constraints, approaching them only when there is close proximity to the target volume.

<sup>†</sup>Use V20 <35%, especially for the following: elderly ≥70 years, taxane chemotherapy, and poor PFTs (such as FEV1 or DLCO <50% normal). Use more conservative limits with a diagnosis or radiologic evidence of idiopathic pulmonary fibrosis (IDP)/usual interstitial pneumonia (UIP) (the tolerance of these patients is lower though not well characterized).

**[\\*NCCN Guidelines for Central Nervous System Cancers](#)**

Please note: Tables 2–5 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

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.

**[References](#)**





- <sup>1</sup>Chen AB, et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. *J Clin Oncol* 2011;29:2305-2311.
- <sup>2</sup>Liao ZX, et al. Influence of Technologic Advances on Outcomes in Patients With Unresectable, Locally Advanced Non-Small-Cell Lung Cancer Receiving Concomitant Chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2010;76:775-781.
- <sup>3</sup>Sejpal S, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer. *Cancer* 2011;117:3004-3013.
- <sup>4</sup>Chang JY, et al. Proton beam radiotherapy and concurrent chemotherapy for unresectable stage III non-small cell lung cancer: final results of a phase 2 study. *JAMA Oncol* 2017;3:e172032.
- <sup>5</sup>Chun SG, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small cell lung cancer: a secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. *J Clin Oncol* 2017;35:56-62.
- <sup>6</sup>MacManus M, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. *Radiother Oncol* 2009;91:85-94.
- <sup>7</sup>Ung YC, et al. An Ontario Clinical Oncology Group (OCOG) randomized trial (PET START) of FDG PET/CT in patients with stage 3 non-small cell lung cancer (NSCLC): impact of PET on radiation treatment volumes [Abstract]. *J Thorac Oncol* 2011;6:S428.
- <sup>8</sup>Everitt S, et al. High rates of tumor growth and disease progression detected on serial pretreatment positrooxyglucose-positron emission tomography/computed tomography scans in radical radiotherapy candidates with nonsmall cell lung cancer. *Cancer* 2010;116:5030-5037.
- <sup>9</sup>Mohammed N, et al. Rapid disease progression with delay in treatment of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;79:466-472.
- <sup>10</sup>Liu MB, et al. Clinical impact of dose overestimation by effective path length calculation in stereotactic ablative radiation therapy of lung tumors. *Practical Radiation Oncology* 2013;3:294-300.
- <sup>11</sup>Keall PJ, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. *Med Phys* 2006;33:3874-3900.
- <sup>12</sup>Kong FM, et al. Physical models and simpler dosimetric descriptors of radiation late toxicity. *Semin Radiat Oncol* 2007;17:108-120.
- <sup>13</sup>Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol* 2008;18:215-222.
- <sup>14</sup>Marks LB, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010;76:S10-19.
- <sup>15</sup>Marks LB, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010; 76:S70-76.
- <sup>16</sup>Werner-Wasik M, et al. Radiation dose-volume effects in the esophagus. *Int J Radiat Oncol Biol Phys* 2010;76:S86-93.
- <sup>17</sup>Gagliardi G, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys* 2010;76:S77-85.
- <sup>18</sup>Kirkpatrick JP, et al. Radiation dose-volume effects in the spinal cord. *Int J Radiat Oncol Biol Phys* 2010;76:S42-49.
- <sup>19</sup>Videtic GMM, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: executive summary of an ASTRO evidence-based guideline. *Pract Radiat Oncol* 2017;7:295-301.
- <sup>20</sup>Timmerman R, et al. Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer. *JAMA* 2010;303:1070-1076.
- <sup>21</sup>Baumann P, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;27:3290-3296.
- <sup>22</sup>Onishi H, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011;81:1352-1358.
- <sup>23</sup>Grutters JPC, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol* 2010;95:32-40.
- <sup>24</sup>Palma D, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 2010;28:5153-5159.
- <sup>25</sup>Shrivani SM, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys* 2012;84:1060-1070.
- <sup>26</sup>Sun B, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. *Cancer* 2017;123:3031-3039.
- <sup>27</sup>Grills IS, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol* 2010;28:928-935.
- <sup>28</sup>Crabtree TD, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2010;140:377-386.
- <sup>29</sup>Bogart JA, et al. Phase I study of accelerated conformal radiotherapy for stage I non-small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904. *J Clin Oncol* 2010;28:202-206.
- <sup>30</sup>Zhao L, et al. High radiation dose may reduce the negative effect of large gross tumor volume in patients with medically inoperable early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2007;68:103-110.
- <sup>31</sup>Cheung P, et al. Phase II study of accelerated hypofractionated three-dimensional conformal radiotherapy for stage T1-3 N0 M0 non-small cell lung cancer: NCIC CTG BR.25. *J Natl Cancer Inst* 2014;106:1-8.
- <sup>32</sup>Onishi H, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007; 2:S94-100.
- <sup>33</sup>Lagerwaard FJ, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;70:685-692.
- <sup>34</sup>Chang JY, et al. Stereotactic body radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small-cell lung cancer: how to fly in a "no fly zone". *Int J Radiat Oncol Biol Phys* 2014;88:1120-1128.
- <sup>35</sup>Timmerman R, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; 24:4833-4839.
- <sup>36</sup>Chaudhuri AA, et al. Stereotactic ablative radiotherapy for treatment of central and ultra-central lung tumors. *Lung Cancer* 2015;89:50-56.
- <sup>37</sup>Haseltine JM, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. *Pract Radiat Oncol* 2016;6:e27-33.
- <sup>38</sup>Woody NM, et al. Stereotactic body radiation therapy for non-small cell lung cancer tumors greater than 5 cm: safety and efficacy. *Int J Radiat Oncol Biol Phys* 2015;92:325-331.
- <sup>39</sup>Bezjak A, et al. Primary study endpoint analysis for NRG Oncology/RTOG 0813 trial of stereotactic body radiation therapy for centrally located non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2016;94:5-6.
- <sup>40</sup>Fakiris AJ, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677-682.
- <sup>41</sup>Xiao Y, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;73:1235-1242.
- <sup>42</sup>Zhao L, et al. Planning target volume D95 and mean dose should be considered for optimal local control for stereotactic ablative radiation therapy. *Int J Radiat Oncol Biol Phys* 2016;95:1226-35.
- <sup>43</sup>Aupérin A, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181-2190.
- <sup>44</sup>O'Rourke N, et al. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev* 2010:CD002140.
- <sup>45</sup>Curran WJ Jr, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 2011;103:1452-1460.
- <sup>46</sup>Sause W, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest* 2000;117:358-364.
- <sup>47</sup>Dillman RO, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;88:1210-1215.
- <sup>48</sup>Baumann M, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). *Radiother Oncol* 2011;100:76-85.
- <sup>49</sup>Maugen A, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:2788-2797.
- <sup>50</sup>Albain KS, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009;374:379-386.
- <sup>51</sup>Kunitoh H, et al. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical Oncology Group trial 9806. *J Clin Oncol* 2008;26:644-649.
- <sup>52</sup>Rusch VW, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol* 2007;25:313-318.
- <sup>53</sup>Thomas M, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomized trial in stage III non-small-cell lung cancer. *Lancet Oncol* 2008;9:607-608.
- <sup>54</sup>Higgins K, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;75:1462-1467.
- <sup>55</sup>Sher DJ, et al. Comparative effectiveness of neoadjuvant chemoradiotherapy versus chemotherapy alone followed by surgery for patients with stage IIIA non-small cell lung cancer. *Lancet Oncol* 2015;88:267-274.

[Continued](#)**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.**



- <sup>56</sup>Shah AA, et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. *Ann Thorac Surg* 2012;93:1807-1812.
- <sup>57</sup>Douillard J-Y, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys* 2008;72:695-701.
- <sup>58</sup>Lally BE, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006;24:2998-3006.
- <sup>59</sup>Feigenberg SJ, et al. A phase II study of concurrent carboplatin and paclitaxel and thoracic radiotherapy for completely resected stage II and IIIA non-small cell lung cancer. *J Thorac Oncol* 2007;2:287-292.
- <sup>60</sup>Bradley JD, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group--RTOG 9705. *J Clin Oncol* 2005;23:3480-3487.
- <sup>61</sup>Keller SM, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. *N Engl J Med* 2000; 343:1217-1222.
- <sup>62</sup>Hancock JG, et al. Impact of adjuvant treatment for microscopic residual disease after non-small cell lung cancer surgery. *Ann Thorac Surg* 2015;99:406-416.
- <sup>63</sup>Burdett S, Stewart L, Group PM-a. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. *Lung Cancer* 2005;47:81-83.
- <sup>64</sup>Francis S, et al. Sequencing of postoperative radiotherapy and chemotherapy for locally advanced or incompletely resected non-small-cell lung cancer. *J Clin Oncol* 2018;36:333-341.
- <sup>65</sup>Belderbos JS, et al. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2008;72:335-342.
- <sup>66</sup>Bradley J, et al. A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of radiation therapy oncology group (RTOG) 0515. *Int J Radiat Oncol Biol Phys* 2012;82:435-441.
- <sup>67</sup>Sanuki-Fujimoto N, et al. Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. *Radiation Oncol* 2009; 91:433-437.
- <sup>68</sup>Sulman EP, et al. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. *Radiat Oncol* 2009;4:5-11.
- <sup>69</sup>Rosenzweig KE, Sura S, Jackson A, Yorke E. Involved-field radiation therapy for inoperable non small-cell lung cancer. *J Clin Oncol* 2007;25:5557-5561.
- <sup>70</sup>Yuan S, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III non-small cell lung cancer. *Am J Clin Oncol* 2007;30:239-244.
- <sup>71</sup>Chen M, et al. Involved-field radiotherapy versus elective nodal irradiation in combination with concurrent chemotherapy for locally advanced non-small cell lung cancer: a prospective randomized study. *Biomed Res Int* 2013;37:11819.
- <sup>72</sup>Perez CA, et al. Long-term observations of the patterns of failure in patients with unresectable non-small cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987; 59:1874-1881.
- <sup>73</sup>Kong FM, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005;63:324-333.
- <sup>74</sup>Rengan R, et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;60:741-747.
- <sup>75</sup>Machtay M, et al. Higher biologically effective dose of radiotherapy is associated with improved Outcomes for Locally Advanced Non-Small Cell Lung Carcinoma Treated with Chemoradiation: An Analysis of the radiation therapy oncology group. *Int J Radiat Oncol Biol Phys* 2012;82:425-434.
- <sup>76</sup>Schild SE, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; 65:1106-1111.
- <sup>77</sup>Socinski MA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. *J Clin Oncol* 2008;26:2457-2463.
- <sup>78</sup>Stinchcombe TE, et al. Long-term follow-up of a phase I/II trial of dose escalating three-dimensional conformal thoracic radiation therapy with induction and concurrent carboplatin and paclitaxel in unresectable stage IIIA/B non-small cell lung cancer. *J Thorac Oncol* 2008; 3:1279-1285.
- <sup>79</sup>Bradley JD, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. *J Clin Oncol* 2010;28:2475-2480.
- <sup>80</sup>Bradley JD, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015;16:187-199.
- <sup>81</sup>Maugen A, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:2788-2797.
- <sup>82</sup>Sher DJ, et al. Relationship between radiation therapy dose and outcome in patients treated with neoadjuvant chemoradiation therapy and surgery for stage IIIA non-small cell lung cancer: a population-based, comparative effectiveness analysis. *Int J Radiat Oncol Biol Phys* 2015;92:307-316.
- <sup>83</sup>Cerfolio RJ, Bryant AS, Jones VL, Cerfolio RM. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. *Eur J Cardiothorac Surg* 2009; 35:718-723; discussion 723.
- <sup>84</sup>Kwong KF, et al. High-dose radiotherapy in trimodality treatment of Pancoast tumors results in high pathologic complete response rates and excellent long-term survival. *J Thorac Cardiovasc Surg* 2005;129:1250-1257.
- <sup>85</sup>Sonett JR, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. *Ann Thorac Surg* 2004;78:1200-1205.
- <sup>86</sup>Suntharalingam M, et al. Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 2012;84:456-463.
- <sup>87</sup>Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. *Int J Radiat Oncol Biol Phys* 2006;65:1097-1105.
- <sup>88</sup>Corso CD, et al. Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the National Cancer Database. *J Thorac Oncol* 2015;10:148-155.
- <sup>89</sup>Spoelstra FOB, et al. Variations in target volume definition for postoperative radiotherapy in stage III non-small-cell lung cancer: analysis of an international contouring study. *Int J Radiat Oncol Biol Phys* 2010; 76:1106-1113.
- <sup>90</sup>Ashworth AB, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014;15:346-355.
- <sup>91</sup>Milano MT, Katz AW, Okunieff P. Patterns of recurrence after curative-intent radiation for oligometastases confined to one organ. *Am J Clin Oncol* 2010;33:157-163.
- <sup>92</sup>Salama JK, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. *Clin Cancer Res* 2008;14:5255-5259.
- <sup>93</sup>Gomez DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016;17:1672-1682.
- <sup>94</sup>Iyengar P, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. *JAMA Oncol* 2018;4:e173501.
- <sup>95</sup>Chow E, et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007;25:1423-1436.
- <sup>96</sup>Lutz S, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79:965-976.
- <sup>97</sup>Cross CK, et al. Prospective study of palliative hypofractionated radiotherapy (8.5 Gy x 2) for patients with symptomatic non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004; 58:1098-1105.
- <sup>98</sup>Medical Research Council Lung Cancer Working Party. A Medical Research Council (MRC) randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Medical Research Council Lung Cancer Working Party. *Br J Canc* 1992; 65:934-941.
- <sup>99</sup>Rodrigues G, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol* 2011;1:60-71.
- <sup>100</sup>Koshy M, et al. Comparative effectiveness of aggressive thoracic radiation therapy and concurrent chemoradiation therapy in metastatic lung cancer. *Pract Radiat Oncol* 2015;5:374-382.

**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.**

**CHEMOTHERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY**

- Cisplatin 50 mg/m<sup>2</sup> days 1 and 8; vinorelbine 25 mg/m<sup>2</sup> days 1, 8, 15, 22, every 28 days for 4 cycles<sup>1</sup>
- Cisplatin 100 mg/m<sup>2</sup> day 1; vinorelbine 30 mg/m<sup>2</sup> days 1, 8, 15, 22, every 28 days for 4 cycles<sup>2,3</sup>
- Cisplatin 75–80 mg/m<sup>2</sup> day 1; vinorelbine 25–30 mg/m<sup>2</sup> days 1 + 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m<sup>2</sup> day 1; etoposide 100 mg/m<sup>2</sup> days 1–3, every 28 days for 4 cycles<sup>2</sup>
- Cisplatin 75 mg/m<sup>2</sup> day 1; gemcitabine 1250 mg/m<sup>2</sup> days 1, 8, every 21 days for 4 cycles<sup>4</sup>
- Cisplatin 75 mg/m<sup>2</sup> day 1; docetaxel 75 mg/m<sup>2</sup> day 1 every 21 days for 4 cycles<sup>5</sup>
- Cisplatin 75 mg/m<sup>2</sup> day 1, pemetrexed 500 mg/m<sup>2</sup> day 1 for nonsquamous every 21 days for 4 cycles<sup>6</sup>

**Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin**

- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m<sup>2</sup> day 1, every 21 days for 4 cycles<sup>7</sup>
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m<sup>2</sup> days 1, 8, every 21 days for 4 cycles<sup>8</sup>
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m<sup>2</sup> day 1 for nonsquamous every 21 days for 4 cycles<sup>9</sup>

**All regimens can be used for sequential chemotherapy/RT.**

<sup>1</sup>Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-lung cancer. *N Engl J Med* 2005;352:2589-2597.

<sup>2</sup>Arriagada R, Bergman B, Dunant A, et al. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. *N Engl J Med* 2004;350:351-360.

<sup>3</sup>Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006;7:719-727.

<sup>4</sup>Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2012;30:3516-3524.

<sup>5</sup>Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;21:3016-3024.

<sup>6</sup>Kreuter M, Vansteenkiste J, Fishcer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. *Ann Oncol* 2013;24:986-992.

<sup>7</sup>Strauss GM, Herndon III JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;26:5043-5051.

<sup>8</sup>Usami N, Yokoi K, Hasegawa Y, et al. Phase II study of carboplatin and gemcitabine as adjuvant chemotherapy in patients with completely resected non-small cell lung cancer: a report from the Central Japan Lung Study Group, CJLSG 0503 trial. *Int J Clin Oncol* 2010;15:583-587.

<sup>9</sup>Zhang L, Ou W, Liu Q, et al. Pemetrexed plus carboplatin as adjuvant chemotherapy in patients with curative resected non-squamous non-small cell lung cancer. *Thorac Cancer* 2014;5:50-56.

**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.**

**CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY****Concurrent Chemotherapy/RT Regimens**

- Cisplatin 50 mg/m<sup>2</sup> on days 1, 8, 29, and 36; etoposide 50 mg/m<sup>2</sup> days 1–5, 29–33; concurrent thoracic RT<sup>1,2,\*,†</sup>
- Cisplatin 100 mg/m<sup>2</sup> days 1 and 29; vinblastine 5 mg/m<sup>2</sup>/weekly x 5; concurrent thoracic RT<sup>2,\*,†</sup>
- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m<sup>2</sup> on day 1 every 21 days for 4 cycles; concurrent thoracic RT<sup>3</sup> (nonsquamous)\*,†
- Cisplatin 75 mg/m<sup>2</sup> on day 1, pemetrexed 500 mg/m<sup>2</sup> on day 1 every 21 days for 3 cycles; concurrent thoracic RT<sup>4,5</sup> (nonsquamous)\*,† ± additional 4 cycles of pemetrexed 500 mg/m<sup>2</sup>†
- Paclitaxel 45–50 mg/m<sup>2</sup> weekly; carboplatin AUC 2, concurrent thoracic RT<sup>6,\*,†</sup> ± additional 2 cycles every 21 days of paclitaxel 200 mg/m<sup>2</sup> and carboplatin AUC 6†

**Consolidation Therapy for Patients with Unresectable Stage III NSCLC, PS 0-1, and No Disease Progression After 2 or More Cycles of Definitive Chemoradiation****Durvalumab 10 mg/kg IV every 2 weeks for up to 12 months<sup>7</sup> (category 1)**

\*Regimens can be used as preoperative/adjuvant chemotherapy/RT.

†Regimens can be used as definitive concurrent chemotherapy/RT.

‡Durvalumab may be used after any of the concurrent chemo/RT regimens listed above for eligible patients.

<sup>1</sup>Albain KS, Crowley JJ, Turrisi AT III, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: A Southwest Oncology Group Phase II Study, SWOG 9019. *J Clin Oncol* 2002;20:3454-3460.

<sup>2</sup>Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst.* 2011;103:1452-1460.

<sup>3</sup>Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol* 2011;29:3120-3125.

<sup>4</sup>Choy H, Gerber DE, Bradley JD, et al. Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a systematic review of completed and ongoing studies. *Lung Cancer* 2015;87:232-240.

<sup>5</sup>Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2016;34:953-962.

<sup>6</sup>Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015;16:187-199.

<sup>7</sup>Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018;379:2342-2530.

**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.**



### CANCER SURVIVORSHIP CARE

#### **NSCLC Long-term Follow-up Care**

- Cancer Surveillance (See [NSCL-15](#))
- Immunizations
  - ▶ Annual influenza vaccination
  - ▶ Herpes zoster vaccine
  - ▶ Pneumococcal vaccination with revaccination as appropriate
- [See NCCN Guidelines for Survivorship Counseling Regarding Health Promotion and Wellness](#)<sup>1</sup>
- Maintain a healthy weight
- Adopt a physically active lifestyle (Regular physical activity: 30 minutes of moderate-intensity physical activity on most days of the week)
- Consume a healthy diet with emphasis on plant sources
- Limit consumption of alcohol if one consumes alcoholic beverages

#### **Additional Health Monitoring**

- Routine blood pressure, cholesterol, and glucose monitoring
- Bone health: Bone density testing as appropriate
- Dental health: Routine dental examinations
- Routine sun protection

#### **Resources**

- National Cancer Institute Facing Forward: Life After Cancer Treatment <http://www.cancer.gov/cancertopics/life-after-treatment/allpages>

#### **Cancer Screening Recommendations**<sup>2,3</sup>

These recommendations are for average-risk individuals and high-risk patients should be individualized.

- Colorectal Cancer:  
[See NCCN Guidelines for Colorectal Cancer Screening](#)
- Prostate Cancer:  
[See NCCN Guidelines for Prostate Cancer Early Detection](#)
- Breast Cancer:  
[See NCCN Guidelines for Breast Cancer Screening](#)

<sup>1</sup>ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention:

<http://www.cancer.org/healthy/eathealthygetactive/acsguidelinesonnutritionphysicalactivityforcancerprevention/index?sitearea=PED>.

<sup>2</sup>Memorial Sloan Kettering Cancer Center Screening Guidelines: <https://www.mskcc.org/cancer-care/risk-assessment-screening/screening-guidelines>.

<sup>3</sup>American Cancer Society Guidelines for Early Detection of Cancer:

<http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer?sitearea=PED>.

**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.**

**PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS****Molecular Diagnostic Studies in Non-Small Cell Lung Cancer**

- Numerous gene alterations have been identified that impact therapy selection. Testing of lung cancer specimens for these alterations is important for identification of potentially efficacious targeted therapies, as well as avoidance of therapies unlikely to provide clinical benefit.
- Some selection approaches for targeted therapy include predictive immunohistochemical analyses, which are distinct from immunohistochemical studies utilized to identify tumor type and lineage.
- Major elements of molecular testing that are critical for utilization and interpretation of molecular results include:
  - ▶ Use of a laboratory that is properly accredited, with a minimum of CLIA accreditation
  - ▶ Understanding the methodologies that are utilized and the major limitations of those methodologies
  - ▶ Understanding the spectrum of alterations tested (and those not tested) by a specific assay
  - ▶ Knowledge of whether a tumor sample is subjected to pathologic review and tumor enrichment (ie, microdissection, macrodissection) prior to testing
  - ▶ The types of samples accepted by the testing laboratory
- Specimen Acquisition and Management:
  - ▶ Although tumor testing has been primarily focused on use of formalin-fixed paraffin-embedded (FFPE) tissues, increasingly, laboratories accept other specimen types, notably cytopathology preparations not processed by FFPE methods. Although testing on cell blocks is not included in the FDA approval for multiple companion diagnostic assays, testing on these specimen types is highly recommended when it is the only or best material.
  - ▶ A major limitation in obtaining molecular testing results for NSCLC occurs when minimally invasive techniques are used to obtain samples; the yield may be insufficient for molecular, biomarker, and histologic testing. Therefore, bronchoscopists and interventional radiologists should procure sufficient tissue to enable all appropriate testing.
  - ▶ When tissue is minimal, laboratories should deploy techniques to maximize tissue for molecular and ancillary testing, including dedicated histology protocols for small biopsies, including “up-front” slide sectioning for diagnostic and predictive testing.
- Testing Methodologies
  - ▶ Appropriate possible testing methodologies are indicated below for each analyte separately; however, several methodologies are generally considerations for use:
    - ◊ Next-generation sequencing (NGS) is used in clinical laboratories. Not all types of alterations are detected by individual NGS assays and it is important to be familiar with the types of alterations identifiable in individual assays or combination(s) of assays.
    - ◊ Real-time polymerase chain reaction (PCR) can be used in a highly targeted fashion (specific mutations targeted). When this technology is deployed, only those specific alterations that are targeted by the assay are assessed.
    - ◊ Sanger sequencing requires the greatest degree of tumor enrichment. Unmodified Sanger sequencing is not appropriate for detection of mutations in tumor samples with less than 25% to 30% tumor after enrichment and is not appropriate for assays in which identification of subclonal events (eg, resistance mutations) is important. If Sanger sequencing is utilized, tumor enrichment methodologies are nearly always recommended.
    - ◊ Other methodologies may be utilized, including multiplex approaches not listed above (ie, SNaPshot, MassARRAY).
    - ◊ Fluorescence in situ hybridization (FISH) analysis is utilized for many assays examining copy number, amplification, and structural alterations such as gene rearrangements.
    - ◊ Immunohistochemistry (IHC) is specifically utilized for some specific analytes, and can be a useful surrogate or screening assay for others.

[Continued](#)**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.

**PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS****• Molecular Targets for Analysis**

- ▶ **In general, the mutations/alterations described below are seen in a non-overlapping fashion, although between 1%–3% of NSCLC may harbor concurrent alterations.**
- ▶ ***EGFR* (Epidermal Growth Factor Receptor) Gene Mutations:** *EGFR* is a receptor tyrosine kinase normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies.
  - ◊ **The most commonly described mutations in *EGFR* (exon 19 deletions, p.L858R point mutation in exon 21) are associated with responsiveness to *EGFR* tyrosine kinase inhibitor (TKI) therapy; most recent data indicate that tumors that do not harbor a sensitizing *EGFR* mutation should not be treated with *EGFR* TKI in any line of therapy.**
  - ◊ **Many of the less commonly observed alterations in *EGFR*, which cumulatively account for ~10% of *EGFR*-mutated NSCLC (ie, exon 19 insertions, p.L861Q, p.G719X, p.S768I) are also associated with responsiveness to *EGFR* TKI therapy, although the number of studied patients is lower.**
  - ◊ **Some mutations in *EGFR* are associated with lack of responsiveness to *EGFR* TKI therapy, including most *EGFR* exon 20 insertions, and p.T790M.**
    - **Most *EGFR* exon 20 insertion mutations predict resistance to clinically achievable levels of TKIs.**
    - **The exception is a rare *EGFR* exon 20 insertion variant, p.A763\_Y764insFQEA, which is associated with responsiveness to *EGFR* TKI therapy. Therefore, knowledge of an *EGFR* exon 20 insertion must be included in the specific sequence alteration.**
    - **The finding of p.T790M is most commonly associated with relapse following initial therapy with *EGFR* TKI, which is a known mechanism of resistance. If identified prior to TKI exposure, genetic counseling should be considered, because germline p.T790M is associated with familial lung cancer predisposition and additional testing is warranted.**
  - ◊ **As use of NGS testing increases, additional *EGFR* variants are increasingly identified; however, the clinical implications of individual alterations are unlikely to be well established.**
  - ◊ **Some clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with the presence of an *EGFR* mutation; however, these features should not be utilized in selecting patients for testing.**
  - ◊ **Testing Methodologies:** Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS are the most commonly deployed methodologies for examining *EGFR* mutation status.
- ▶ ***ALK* (Anaplastic Lymphoma Kinase) Gene Rearrangements:** *ALK* is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the *ALK* kinase domain.
  - ◊ **The most common fusion partner seen with *ALK* is echinoderm microtubule-associated protein-like 4 (EML4), although a variety of other fusion partners have been identified.**
  - ◊ **The presence of an *ALK* rearrangement is associated with responsiveness to *ALK* TKIs, with recent studies demonstrating improved efficacy of alectinib over crizotinib in the first-line setting.**
  - ◊ **Some clinicopathologic features—such as smoking status and histology have been associated with the presence of an *ALK* rearrangement; however, these features should not be utilized in selecting patients for testing.**
  - ◊ **Testing Methodologies:** FISH break-apart probe methodology was the first methodology deployed widely. IHC can be deployed as an effective screening strategy. FDA-approved IHC (*ALK* [D5F3] CDx Assay) can be utilized as a stand-alone test, not requiring confirmation by FISH, although secondary confirmation is encouraged. Numerous NGS methodologies can detect *ALK* fusions, and targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners.

[Continued](#)**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.



**PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS**

- ▶ ***ROS1* (ROS proto-oncogene 1) Gene Rearrangements:** *ROS1* is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the *ROS1* kinase domain.
  - ◊ Numerous fusion partners are seen with *ROS1*, and common fusion partners include: CD74, SLC34A2, CCDC6, and FIG.
  - ◊ The presence of a *ROS1* rearrangement is associated with responsiveness to oral *ROS1* TKIs.
  - ◊ Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of a *ROS1* rearrangement; however, these features should not be utilized in selecting patients for testing.
  - ◊ **Testing Methodologies:** FISH break-apart probe methodology can be deployed; however, it may under-detect the FIG-*ROS1* variant. IHC approaches can be deployed; however, IHC for *ROS1* fusions has low specificity, and follow-up confirmatory testing is a necessary component of utilizing *ROS1* IHC as a screening modality. Numerous NGS methodologies can detect *ROS1* fusions, and targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners (which may lead to under-detection of *ROS1* fusion events).
- ▶ ***BRAF* (B-Raf proto-oncogene) point mutations:** *BRAF* is a serine/threonine kinase that is part of the canonical MAP/ERK signaling pathway. Activating mutations in *BRAF* result in unregulated signaling through the MAP/ERK pathway.
  - ◊ Mutations in *BRAF* can be seen in NSCLC. The presence of a specific mutation resulting in a change in amino acid position 600 (p.V600E) has been associated with responsiveness to combined therapy with oral inhibitors of *BRAF* and MEK.
  - ◊ Note that other mutations in *BRAF* are observed in NSCLC, and the impact of those mutations on therapy selection is not well understood at this time.
  - ◊ **Testing Methodologies:** Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS are the most commonly deployed methodologies for examining *BRAF* mutation status. While an anti-*BRAF* p.V600E-specific monoclonal antibody is commercially available, and some studies have examined utilizing this approach, it should only be deployed after extensive validation.
- ▶ ***KRAS* (*KRAS* proto-oncogene) point mutations:** *KRAS* is a G-protein with intrinsic GTPase activity, and activating mutations result in unregulated signaling through the MAP/ERK pathway.
  - ◊ Mutations in *KRAS* are most commonly seen at codon 12, although other mutations can be seen in NSCLC.
  - ◊ The presence of a *KRAS* mutation is prognostic of poor survival when compared to patients with tumors without *KRAS* mutation.
  - ◊ Mutations in *KRAS* have been associated with reduced responsiveness to EGFR TKI therapy.
  - ◊ Owing to the low probability of overlapping targetable alterations, the presence of a mutation in *KRAS* may identify patients who will not benefit from further molecular testing.
- **Testing in the Setting of Progression on Targeted Therapy:**
  - ▶ For many of the above listed analytes, there is growing recognition of the molecular mechanisms of resistance to therapy. Re-testing of a sample that is actively progressing while exposed to targeted therapy can shed light on appropriate next therapeutic steps:
    - ◊ For patients with an underlying *EGFR* sensitizing mutation who have been treated with EGFR TKI, minimum appropriate testing includes high-sensitivity evaluation for p.T790M; when there is no evidence of p.T790M, testing for alternate mechanisms of resistance (*MET* amplification, *ERBB2* amplification) may be used to direct patients for additional therapies. The presence of p.T790M can direct patients to third-generation EGFR TKI therapy.

**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.

[Continued](#)

**NSCL-G**  
**3 OF 5**

**PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS**

- **Testing in the Setting of Progression on Targeted Therapy (continued)**
  - Assays for the detection of *EGFR* p.T790M should be designed to have an analytic sensitivity of a minimum of 5% allelic fraction. The original sensitizing mutation can be utilized as an internal control in many assays to determine whether a p.T790M is within the range of detection if present as a sub-clonal event.
  - ◊ For patients with underlying *ALK* rearrangement who have been treated with ALK TKI, it is unclear whether identification of specific tyrosine kinase domain mutation can identify appropriate next steps in therapy, although some preliminary data suggest that specific kinase domain mutations can impact next line of therapy.
- **IHC for Biomarker Selection in NSCLC:**
  - ▶ **PD-L1 (Programmed Death Ligand 1):** PD-L1 is a co-regulatory molecule that can be expressed on tumor cells and inhibit T-cell-mediated cell death. T-cells express PD-1, a negative regulator, which binds to ligands including PD-L1 (CD274) or PD-L2 (CD273). In the presence of PD-L1, T-cell activity is suppressed.
    - ◊ Checkpoint inhibitor antibodies block the PD-1 and PD-L1 interaction, thereby improving the antitumor effects of endogenous T cells.
    - ◊ IHC for PD-L1 can be utilized to identify disease most likely to respond to first-line anti PD-1/PD-L1.
      - Various antibody clones have been developed for IHC analysis of PD-L1 expression, and while several show relative equivalence, some do not.
      - Interpretation of PD-L1 IHC is typically focused on the proportion of tumor cells expressing membranous staining at any level and therefore is a linear variable.
      - The FDA-approved IHC assay for PD-L1 utilizes a cutoff of  $\geq 1\%$  tumor proportion score for first-line and 1% tumor proportion score for second-line therapy with pembrolizumab.
      - The definition of positive and negative testing is dependent on the individual antibody and platform deployed, which may be unique to each checkpoint inhibitor therapy. The potential for multiple different assays for PD-L1 has raised concern among both pathologists and oncologists.
  - ▶ **ALK fusions:** IHC assays for ALK can serve as a screening modality for further ALK testing, and can alternatively be used as a stand-alone test to determine eligibility for ALK TKI. An FDA-approved IHC assay for ALK is available.
  - ▶ **ROS1 fusions:** IHC assays for ROS1 should only be deployed as a screening modality for further ROS1 testing, because the specificity of a positive result is low. Positive ROS1 IHC should not be utilized to select patients for TKI therapy without additional confirmatory testing. Currently there is not an FDA-approved IHC assay for ROS1.
  - ▶ **BRAF p.V600E mutations:** An antibody specific to the p.V600E mutation is available. Some studies have examined utilization of this antibody in cases of NSCLC; however, optimization of this antibody may be tumor-specific and care should be exercised when using this approach.

**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.

[Continued](#)**NSCL-G**  
**4 OF 5**



### PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Plasma Cell-Free/Circulating Tumor DNA Testing:**
  - ▶ **Cell-free/circulating tumor DNA testing should not be used in lieu of a tissue diagnosis .**
  - ▶ **Some laboratories offer testing for molecular alterations examining nucleic acids in peripheral circulation, most commonly in processed plasma (sometimes referred to as "liquid biopsy").**
  - ▶ **Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to 30% false-negative rate.**
  - ▶ **Standards for analytical performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.**
  - ▶ **Cell-free tumor DNA testing can identify alterations that are unrelated to a lesion of interest, for example, clonal hematopoiesis of indeterminate potential (CHIP).**
  - ▶ **The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably:**
    - ◊ **If a patient is medically unfit for invasive tissue sampling**
    - ◊ **In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified**

**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.**

**EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC**

<b>Genetic Alteration (ie, Driver event)</b>	<b>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</b>
High-level <i>MET</i> amplification or <i>MET</i> exon 14 skipping mutation	Crizotinib <sup>1-5</sup>
<i>RET</i> rearrangements	Cabozantinib <sup>6,7</sup> Vandetanib <sup>8</sup>
<i>ERBB2</i> ( <i>HER2</i> ) mutations	Ado-trastuzumab emtansine <sup>9</sup>
Tumor mutational burden (TMB)*	Nivolumab + ipilimumab <sup>10</sup> Nivolumab <sup>11</sup>

\*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.

<sup>1</sup>Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. *J Thorac Oncol* 2011;6:942-946.

<sup>2</sup>Camidge RD, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer. *J Clin Oncol* 2014;32(Suppl 5): Abstract 8001.

<sup>3</sup>Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov* 2015;5:850-859.

<sup>4</sup>Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. *Cancer Discov* 2015;5:842-849.

<sup>5</sup>Awad MM, Oxnard GR, Jackman DM, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and cMET overexpression. *J Clin Oncol* 2016;34:721-730.

<sup>6</sup>Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov* 2013; 3:630-635.

<sup>7</sup>Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol* 2016;17:1653-1660.

<sup>8</sup>Lee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. *Ann Oncol* 2017;28:292-297.

<sup>9</sup>Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: Results from a phase II basket trial. *J Clin Oncol* 2018;36:2532-2537.

<sup>10</sup>Hellmann MD, Ciuleanu TE, Pluzanski A et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018; 378:2093-2104.

<sup>11</sup>Carbone DP, Reck M, Paz-Ares L et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med* 2017;376:2415–2426.

**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.**

**TARGETED THERAPY FOR ADVANCED OR METASTATIC DISEASE****Monitoring During Initial Therapy**

- 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.

**Monitoring During Subsequent 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.

**Sensitizing EGFR Mutation Positive**

- First-line therapy
  - ▶ Afatinib<sup>1</sup>
  - ▶ Erlotinib<sup>2</sup>
  - ▶ Dacomitinib<sup>3</sup>
  - ▶ Gefitinib<sup>4,5</sup>
  - ▶ Osimertinib<sup>6</sup>
- Subsequent therapy
  - ▶ Osimertinib<sup>7</sup>

**ALK Rearrangement Positive**

- First-line therapy
  - ▶ Alectinib<sup>8,9</sup>
  - ▶ Brigatinib<sup>10</sup>
  - ▶ Ceritinib<sup>11</sup>
  - ▶ Crizotinib<sup>8,12</sup>
- Subsequent therapy
  - ▶ Alectinib<sup>13,14</sup>
  - ▶ Brigatinib<sup>15</sup>
  - ▶ Ceritinib<sup>16</sup>
  - ▶ Lorlatinib<sup>17</sup>

**ROS1 Rearrangement Positive**

- First-line therapy
  - ▶ Ceritinib<sup>18</sup>
  - ▶ Crizotinib<sup>19</sup>
  - ▶ Entrectinib<sup>20</sup>

**BRAF V600E Mutation Positive**

- First-line therapy
  - ▶ Dabrafenib/trametinib<sup>21</sup>
- Subsequent therapy
  - ▶ Dabrafenib/trametinib<sup>22,23</sup>

**NTRK Gene Fusion Positive**

- First-line/Subsequent therapy
  - ▶ Larotrectinib<sup>24</sup>
  - ▶ Entrectinib<sup>20</sup>

**PD-L1 ≥1%**

- First-line therapy\*
  - ▶ Pembrolizumab<sup>25-27</sup>
  - ▶ (Carboplatin or cisplatin)/pemetrexed/pembrolizumab (non-squamous)<sup>28</sup>
  - ▶ Carboplatin/paclitaxel/bevacizumab\*\*/atezolizumab (nonsquamous)<sup>29</sup>
  - ▶ (Carboplatin or cisplatin)/(paclitaxel or albumin-bound paclitaxel)/pembrolizumab (squamous)<sup>30</sup>

\*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.

\*\*An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

**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.**

**References**

### TARGETED THERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES

- 1 Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin based chemotherapy for EGFR mutation positive lung adenocarcinoma (LUX Lung 3 and LUX Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015;16:141-151.
- 2 Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first line treatment for European patients with advanced EGFR mutation positive non small cell lung cancer (EURTAC): a multicentre, open label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239-246.
- 3 Wu Y-L, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomized, open-label, phase 3 trial. *Lancet Oncol* 2017;18:1454-1466.
- 4 Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-957.
- 5 Douillard JY, Ostoros G, Cobo M, et al. First line gefitinib in Caucasian EGFR mutation positive NSCLC patients: a phase IV, open label, single arm study. *Br J Cancer* 2014;110:55-62.
- 6 Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018;378:113-125.
- 7 Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum pemetrexed in EGFR T790M positive lung cancer. *N Engl J Med* 2017;376:629-640.
- 8 Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 2017;377:829-838.
- 9 Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* 2017;390(10089):29-39.
- 10 Camidge DR, Kim HR, Ahn JC-H, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med* 2018;379:2027-2039.
- 11 Soria JC, Tan DS, Chiari R, et al. First line ceritinib versus platinum based chemotherapy in advanced ALK rearranged non small cell lung cancer (ASCEND 4): a randomised, open label, phase 3 study. *Lancet* 2017;389:917-929.
- 12 Solomon BJ, Mok T, Kim DW, et al. First line crizotinib versus chemotherapy in ALK positive lung cancer. *N Engl J Med* 2014;371:2167-2177.
- 13 Ou SI, Ahn JS, De Petris L, et al. Alectinib in crizotinib refractory ALK rearranged non small cell lung cancer: a phase II global study. *J Clin Oncol* 2016;34:661-668.
- 14 Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK positive, crizotinib resistant, non small cell lung cancer: a single group, multicentre, phase 2 trial. *Lancet Oncol* 2016;17:234-242.
- 15 Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib refractory anaplastic lymphoma kinase positive non small cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol* 2017;35:2490-2498.
- 16 Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 2017;18:874-886.
- 17 Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol* 2018;19:1654-1667.
- 18 Lim SM, Kim HR, Lee JS, et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. *J Clin Oncol* 2017;35:2613-2618.
- 19 Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;371:1963-1971.
- 20 Drilon A, Siena S, Ou SI, et al. Safety and antitumor activity of the multitargeted Pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). *Cancer Discov*. 2017;7:400-409.
- 21 Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol* 2017;18:1307-1316.
- 22 Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E) mutant metastatic non small cell lung cancer: an open label, multicentre phase 2 trial. *Lancet Oncol* 2016;17:984-993.
- 23 Planchard D, Besse B, Kim TM, et al. Updated survival of patients (pts) with previously treated BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC) who received dabrafenib (D) or D + trametinib (T) in the phase II BRF113928 study [abstract]. *J Clin Oncol* 2017;35: Abstract 9075.
- 24 Drilon A, Laetsch TW, Kummar W et al. Efficacy of Larotrectinib in TRK fusion-positive cancers in adults and Children. *N Engl J Med* 2018;378:731-739.
- 25 Reck M, Rodriguez Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD L1 positive non small cell lung cancer. *N Engl J Med* 2016;375:1823-1833.
- 26 Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non squamous non small cell lung cancer: a randomised, phase 2 cohort of the open label KEYNOTE 021 study. *Lancet Oncol* 2016;17:1497-1508.
- 27 Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (Keynote-042): a randomized open-label, controlled, phase 3 trial. *Lancet* 2019. Published online April 4, 2019.
- 28 Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018;378:2078-2092.
- 29 Socinski M, Jotte R, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018;378:2288-2301.
- 30 Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018;379:2040-2051.

**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

#### Monitoring During Initial Therapy

- 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.

#### Monitoring During Subsequent 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 Systemic Therapy Options for Adenocarcinoma, Large cell, NSCLC NOS on NSCL-J \(2 of 4\)](#)

[See Initial Systemic Therapy Options for Squamous Cell Carcinoma on NSCL-J \(3 of 4\)](#)

**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<sup>a,b</sup>****Initial Systemic Therapy Options****Adenocarcinoma, Large Cell, NSCLC NOS (PS 0-1)****No contraindications to the addition of pembrolizumab or atezolizumab<sup>c</sup>**

- Pembrolizumab/carboplatin/pemetrexed (category 1)<sup>1,2,d</sup> (preferred)
- Pembrolizumab/cisplatin/pemetrexed (category 1)<sup>2,d</sup> (preferred)
- Atezolizumab/carboplatin/paclitaxel/bevacizumab<sup>e</sup> (category 1)<sup>3,d,f,g,h</sup>

**Contraindications to the addition of pembrolizumab or atezolizumab<sup>c</sup>**

- Bevacizumab<sup>e</sup>/carboplatin/paclitaxel (category 1)<sup>4,f,g,h</sup>
- Bevacizumab<sup>e</sup>/carboplatin/pemetrexed<sup>4,f,g,h</sup>
- Bevacizumab<sup>e</sup>/cisplatin/pemetrexed<sup>6,f,g,h</sup>
- Carboplatin/albumin-bound paclitaxel (category 1)<sup>7</sup>
- Carboplatin/docetaxel (category 1)<sup>8</sup>
- Carboplatin/etoposide (category 1)<sup>9,10</sup>
- Carboplatin/gemcitabine (category 1)<sup>11</sup>
- Carboplatin/paclitaxel (category 1)<sup>12</sup>
- Carboplatin/pemetrexed (category 1)<sup>13</sup>
- Cisplatin/docetaxel (category 1)<sup>8</sup>
- Cisplatin/etoposide (category 1)<sup>14</sup>
- Cisplatin/gemcitabine (category 1)<sup>12,15</sup>
- Cisplatin/paclitaxel (category 1)<sup>16</sup>
- Cisplatin/pemetrexed (category 1)<sup>15</sup>
- Gemcitabine/docetaxel (category 1)<sup>17</sup>
- Gemcitabine/vinorelbine (category 1)<sup>18</sup>

**Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)**

- Albumin-bound paclitaxel<sup>19</sup>
- Carboplatin/albumin-bound paclitaxel<sup>20,21</sup>
- Carboplatin/docetaxel<sup>8</sup>
- Carboplatin/etoposide<sup>9,10</sup>
- Carboplatin/gemcitabine<sup>11</sup>
- Carboplatin/paclitaxel<sup>12</sup>
- Carboplatin/pemetrexed<sup>13</sup>
- Docetaxel<sup>22,23</sup>
- Gemcitabine<sup>24-26</sup>
- Gemcitabine/docetaxel<sup>17</sup>
- Gemcitabine/vinorelbine<sup>18</sup>
- Paclitaxel<sup>27-29</sup>
- Pemetrexed<sup>30</sup>

<sup>a</sup> 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.

<sup>b</sup> Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.

<sup>c</sup> Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit.

<sup>d</sup> If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended.

<sup>e</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

<sup>f</sup> Bevacizumab should be given until progression.

<sup>g</sup> Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.

<sup>h</sup> 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.

**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<sup>a,b,i</sup>****Initial Systemic Therapy Options****Squamous Cell Carcinoma (PS 0-1)****No contraindications to the addition of pembrolizumab<sup>c</sup>**

- Pembrolizumab/carboplatin/paclitaxel<sup>31,d</sup> (category 1) (preferred)
- Pembrolizumab/carboplatin/albumin-bound paclitaxel<sup>31,d</sup> (category 1) (preferred)
- Pembrolizumab/cisplatin/paclitaxel<sup>d</sup>
- Pembrolizumab/cisplatin/albumin-bound paclitaxel<sup>d</sup>

**Contraindications to the addition of pembrolizumab<sup>c</sup>**

- Carboplatin/albumin-bound paclitaxel (category 1)<sup>7</sup>
- Carboplatin/docetaxel (category 1)<sup>8</sup>
- Carboplatin/gemcitabine (category 1)<sup>11</sup>
- Carboplatin/paclitaxel (category 1)<sup>12</sup>
- Cisplatin/docetaxel (category 1)<sup>8</sup>
- Cisplatin/etoposide (category 1)<sup>14</sup>
- Cisplatin/gemcitabine (category 1)<sup>12,15</sup>
- Cisplatin/paclitaxel (category 1)<sup>16</sup>
- Gemcitabine/docetaxel (category 1)<sup>17</sup>
- Gemcitabine/vinorelbine (category 1)<sup>18</sup>

**Squamous Cell Carcinoma (PS 2)**

- Albumin-bound paclitaxel<sup>19</sup>
- Carboplatin/albumin-bound paclitaxel<sup>20,21</sup>
- Carboplatin/docetaxel<sup>8</sup>
- Carboplatin/etoposide<sup>9,10</sup>
- Carboplatin/gemcitabine<sup>11</sup>
- Carboplatin/paclitaxel<sup>12</sup>
- Docetaxel<sup>22,23</sup>
- Gemcitabine<sup>24-26</sup>
- Gemcitabine/docetaxel<sup>17</sup>
- Gemcitabine/vinorelbine<sup>18</sup>
- Paclitaxel<sup>27-29</sup>

<sup>a</sup> 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.

<sup>b</sup> Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.

<sup>c</sup> Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit.

<sup>d</sup> If progression on PD-1/PD-L1 inhibitor, switching to another PD-1/PD-L1 inhibitor is not routinely recommended.

<sup>i</sup> 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.**

**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE**

- <sup>1</sup>Langer CJ, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *The Lancet Oncology*. 2016;17:1497-1508.
- <sup>2</sup>Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018;378:2078-2092.
- <sup>3</sup>Socinski M, Jotte R, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018;378:2288-2301.
- <sup>4</sup>Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. *N Engl J Med* 2006;355:2542-2550.
- <sup>5</sup>Patel JD, Socinski MA, Garon EB, et al. Pointbreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small cell lung cancer. *J Clin Oncol* 2013;31:4349-4357.
- <sup>6</sup>Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small cell lung cancer: AVAPERL. *J Clin Oncol* 2013;31:3004-3011.
- <sup>7</sup>Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012;30:2055-2062.
- <sup>8</sup>Fossella F, Periera JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;21(16):3016-3024.
- <sup>9</sup>Klastersky J, Sculier JP, Lacroix H, et al. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small cell lung cancer: European Organization for Research and Treatment of Cancer Protocol 07861. *J Clin Oncol* 1990;8:1556-1562.
- <sup>10</sup>Frasci G, Comella P, Panza N, et al. Carboplatin-oral etoposide personalized dosing in elderly non-small cell lung cancer patients. Gruppo Oncologico Cooperativo Sud-Italia. *Eur J Cancer* 1998;34:1710-1714.
- <sup>11</sup>Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced non-small cell lung carcinoma. *Cancer* 2003;98:542-553.
- <sup>12</sup>Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007;18:317-323.
- <sup>13</sup>Scagliotti GV, Kortsik C, Dark GG, et al. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter, randomized, phase II trial. *Clin Cancer Res* 2005;11:690-696.
- <sup>14</sup>Cardenal F, Lopez-Cabrerizo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol* 1999;17:12-18.
- <sup>15</sup>Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage NSCLC. *J Clin Oncol* 2008;26:3543-3551.
- <sup>16</sup>Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med* 2002;346:92-98.
- <sup>17</sup>Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. *Ann Oncol* 2005;16:602-610.
- <sup>18</sup>Tan EH, Szczesna A, Krzakowski M, et al. Randomized study of vinorelbine--gemcitabine versus vinorelbine--carboplatin in patients with advanced non-small cell lung cancer. *Lung Cancer* 2005;49:233-240.
- <sup>19</sup>Green M, Manikhas G, Orlov S, et al. Abraxane®, a novel Cremophor®-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann Oncol* 2006;17:1263-1268.
- <sup>20</sup>Rizvi N, Riely G, Azzoli C, et al. Phase I/II Trial of Weekly Intravenous 130-nm Albumin-Bound Paclitaxel As Initial Chemotherapy in Patients With Stage IV Non-Small-Cell Lung Cancer. *J Clin Oncol* 2008;26:639-643.
- <sup>21</sup>Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012;30:2055-2062.
- <sup>22</sup>Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354-2362.
- <sup>23</sup>Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small cell lung cancer. *J Clin Oncol* 2009;27:591-598.
- <sup>24</sup>Zatloukal P, Kanitz E, Magyar P, et al. Gemcitabine in locally advanced and metastatic non-small cell lung cancer: the Central European phase II study. *Lung Cancer* 1998;22:243-250.
- <sup>25</sup>Sederholm C, Hillerdal G, Lamberg K, et al. Phase III trial of gemcitabine plus carboplatin versus single agent gemcitabine in the treatment of locally advanced or metastatic non-small cell lung cancer: the Swedish Lung Cancer Study group. *J Clin Oncol* 2005;23:8380-8288.
- <sup>26</sup>Perol M, Chouaid C, Perol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small cell lung cancer. *J Clin Oncol* 2012;30:3516-3524.
- <sup>27</sup>Lilenbaum RC, Herndon JE, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small cell lung cancer: the cancer and leukemia group B (study 9730). *J Clin Oncol* 2005;23:190-196.
- <sup>28</sup>Ceresoli GL, Gregorc V, Cordio S, et al. Phase II study of weekly paclitaxel as second-line therapy in patients with advanced non-small cell lung cancer. *Lung Cancer* 2004;44:231-239.
- <sup>29</sup>Yasuda K, Igishi T, Kawasaki Y, et al. Phase II study of weekly paclitaxel in patients with non-small cell lung cancer who have failed previous treatments. *Oncology* 2004;66:347-352.
- <sup>30</sup>Hanna NH, Sheperd FA, Fossella FV, et al. Randomized phase III study of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589-1597.
- <sup>31</sup>Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018;379:2040-2051.

**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.**

**Table 1. Definitions for T, N, M**

<b>T</b>	<b>Primary Tumor</b>
<b>TX</b>	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
<b>T0</b>	No evidence of primary tumor
<b>Tis</b>	Carcinoma in situ Squamous cell carcinoma in situ (SCIS) Adenocarcinoma in situ (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
<b>T1</b>	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
<b>T2</b>	Tumor >3 cm but ≤5 cm or having any of the following features: (1) Involves the main bronchus, regardless of distance to the carina, but without involvement of the carina; (2) Invades visceral pleura (PL1 or PL2); (3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T2a	Tumor >3 cm but ≤4 cm in greatest dimension
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
<b>T3</b>	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
<b>T4</b>	Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a ipsilateral lobe different from that of the primary

<sup>a</sup>Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

**Table 1. Definitions for T, N, M (continued)**

<b>N</b>	<b>Regional Lymph Nodes</b>
<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
<b>N2</b>	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
<b>N3</b>	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
<b>M</b>	<b>Distant Metastasis</b>
<b>MX</b>	Distant metastasis cannot be assessed
<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion <sup>a</sup>
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

**Table 2. AJCC Prognostic Groups**

	<b>T</b>	<b>N</b>	<b>M</b>		<b>T</b>	<b>N</b>	<b>M</b>
<b>Occult Carcinoma</b>	TX	N0	M0	<b>Stage IIIB</b>	T1a	N3	M0
<b>Stage 0</b>	Tis	N0	M0		T1b	N3	M0
<b>Stage IA1</b>	T1mi	N0	M0		T1c	N3	M0
	T1a	N0	M0		T2a	N3	M0
<b>Stage IA2</b>	T1b	N0	M0		T2b	N3	M0
<b>Stage IA3</b>	T1c	N0	M0		T3	N2	M0
<b>Stage IB</b>	T2a	N0	M0	<b>Stage IIIC</b>	T4	N2	M0
<b>Stage IIA</b>	T2b	N0	M0		T3	N3	M0
<b>Stage IIB</b>	T1a	N1	M0		T4	N3	M0
	T1b	N1	M0	<b>Stage IVA</b>	Any T	Any N	M1a
	T1c	N1	M0		Any T	Any N	M1b
	T2a	N1	M0	<b>Stage IVB</b>	Any T	Any N	M1c
	T2b	N1	M0				
	T3	N0	M0				
<b>Stage IIIA</b>	T1a	N2	M0				
	T1b	N2	M0				
	T1c	N2	M0				
	T2a	N2	M0				
	T2b	N2	M0				
	T3	N1	M0				
	T4	N0	M0				
	T4	N1	M0				

<sup>a</sup>Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

**Table 3. Comparison of the Descriptors in the Eighth Edition of the TNM Classification of Lung Cancer Compared with the Seventh Edition\***

Descriptor	7th Edition T/N/M	8th Edition T/N/M
<b>T component</b>		
0 cm (pure lepidic adenocarcinoma ≤3 cm in total size)	T1a if ≤2 cm; T1b if >2-3 cm	Tis (AIS)
≤0.5 cm invasive size (lepidic predominant adenocarcinoma ≤3 cm total size)	T1a if ≤2 cm; T1b if >2-3 cm	T1mi
≤1 cm	T1a	T1a
>1-2 cm	T1a	T1b
>2-3 cm	T1b	T1c
>3-4 cm	T2a	T2a
>4-5 cm	T2a	T2b
>5-7 cm	T2b	T3
>7 cm	T3	T4
Bronchus <2 cm from carina	T3	T2
Total atelectasis/pneumonitis	T3	T2
Invasion of diaphragm	T3	T4
Invasion of mediastinal pleura	T3	—
<b>N component</b>		
No assessment, no involvement, or involvement of regional lymph nodes	NX, N0, N1, N2, N3	No change
<b>M component</b>		
Metastasis within the thoracic cavity	M1a	M1a
Single extrathoracic metastasis	M1b	M1b
Multiple extrathoracic metastasis	M1b	M1c

\*Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:138-155.



# NCCN Guidelines Version 7.2019 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

## Discussion

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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

## Table of Contents

<a href="#">Overview</a>	MS-3
Literature Search Criteria and Guidelines Update Methodology	MS-3
Risk Factors	MS-3
Smoking Cessation	MS-4
Lung Cancer Screening	MS-5
Classification and Prognostic Factors	MS-5
<a href="#">Diagnostic Evaluation</a>	MS-5
Incidental Lung Nodules	MS-5
Larger Tumors	MS-6

<a href="#">Pathologic Evaluation of Lung Cancer</a>	MS-7
Adenocarcinoma	MS-8
Immunohistochemical Staining	MS-9
<a href="#">Staging</a>	MS-10
<a href="#">Predictive and Prognostic Biomarkers</a>	MS-11
Molecular Testing for Biomarkers	MS-13
<i>EGFR</i> Mutations	MS-14
<i>BRAF</i> V600E Mutations	MS-15
<i>ALK</i> Gene Rearrangements	MS-16
<i>ROS1</i> Rearrangements	MS-18
<i>NTRK</i> Gene Fusions	MS-19
<i>KRAS</i> Mutations	MS-19
PD-L1 Expression Levels	MS-19
<a href="#">Treatment Approaches</a>	MS-21
Surgery	MS-21
Lymph Node Dissection	MS-21
Stage IIIA N2 Disease	MS-22
Thorascopic Lobectomy	MS-22
Radiation Therapy	MS-23
General Principles	MS-23
Radiation Simulation, Planning, and Delivery	MS-23
Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints	MS-24
General Treatment Information	MS-25





# NCCN Guidelines Version 7.2019 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

Stereotactic Ablative Radiotherapy.....	MS-26	Trial Data.....	MS-68
Whole Brain RT and Stereotactic Radiosurgery.....	MS-28	Number of Cycles of First-Line Systemic Therapy.....	MS-69
Combined Modality Therapy.....	MS-28	Maintenance Therapy.....	MS-70
Surgery Followed by Chemotherapy: Trial Data.....	MS-29	Continuation of Targeted Therapy After Progression on Initial Therapy.....	MS-70
Preoperative Chemotherapy Followed by Surgery: Trial Data.....	MS-30	Second-Line and Beyond (Subsequent) Systemic Therapy.....	MS-71
Chemoradiation: Trial Data.....	MS-31	<b>Summary.....</b>	<b>MS-75</b>
Chemotherapy: Trial Data.....	MS-33	<b>References.....</b>	<b>MS-77</b>
Targeted Therapies.....	MS-35		
EGFR Inhibitor.....	MS-46		
Immune Checkpoint Inhibitors.....	MS-46		
Maintenance Therapy.....	MS-53		
<b>Clinical Evaluation.....</b>	<b>MS-55</b>		
Additional Pretreatment Evaluation.....	MS-56		
<b>Initial Therapy.....</b>	<b>MS-57</b>		
Stage I, Stage II, and Stage IIIA Disease.....	MS-58		
Multiple Lung Cancers.....	MS-59		
Stage IIIB Disease.....	MS-60		
Stage IV Disease.....	MS-60		
<b>Postoperative Treatment.....</b>	<b>MS-61</b>		
Chemotherapy or Chemoradiation.....	MS-61		
Radiation Therapy.....	MS-63		
<b>Surveillance.....</b>	<b>MS-64</b>		
<b>Treatment of Recurrences and Distant Metastases.....</b>	<b>MS-64</b>		



### Overview

Lung cancer is the leading cause of cancer death in the United States.<sup>1</sup> In 2019, an estimated 228,150 new cases (116,440 in men and 111,710 in women) of lung and bronchial cancer will be diagnosed, and 142,670 deaths (76,650 in men and 66,020 in women) are estimated to occur because of the disease.<sup>2</sup> Only 18% of all patients with lung cancer are alive 5 years or more after diagnosis.<sup>3</sup> However, much progress has been made recently for lung cancer such as screening, minimally invasive techniques for diagnosis and treatment, and advances in radiation therapy (RT) including stereotactic ablative radiotherapy (SABR), targeted therapies, and immunotherapies.<sup>4-9</sup> Patients with metastatic lung cancer who are eligible for targeted therapies or immunotherapies are now surviving longer.<sup>9-11</sup> Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; patients with symptoms are more likely to have chronic obstructive pulmonary disease (COPD).<sup>12</sup>

These NCCN Guidelines® for Non-Small Cell Lung Cancer (NSCLC) were first published in 1996.<sup>13</sup> Subsequently, the NCCN Guidelines® have been updated at least once a year by the NCCN NSCLC Panel; there have been 7 updates for the 2019 guidelines. The *Summary of the Guidelines Updates* describes the most recent revisions to the algorithms, which have been incorporated into this updated Discussion text (see the NCCN Guidelines for NSCLC and *Summary* in this Discussion). It is important to note that all recommendations are category 2A in the NCCN Guidelines unless otherwise indicated. Category 2A recommendations are based on lower level evidence (such as phase 2 trials) and uniform NCCN consensus (at least 85% of panel members) that the intervention is appropriate. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.

### Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature in NSCLC using the following search term: non-small cell lung cancer. The PubMed database was chosen because it is the most widely used resource for medical literature and indexes peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles selected by the NCCN NSCLC Panel for review during the NCCN Guidelines update meeting, as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel, have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). If high-level evidence is lacking, recommendations are based on the panel's review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available at [www.NCCN.org](http://www.NCCN.org).

### Risk Factors

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths.<sup>1,14-18</sup> Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).<sup>17,19</sup> The risk for lung cancer increases with the number of packs of cigarettes smoked per day and with the number of years spent smoking (ie, pack-years of smoking history). Exposed nonsmokers also have an increased relative risk (RR = 1.24) of developing lung cancer from secondhand smoke; other studies have reported a modest risk (hazard ratio [HR], 1.05).<sup>15,19-22</sup>



Other possible risk factors for lung cancer include disease history (eg, COPD), cancer history, family history of lung cancer, and exposure to other carcinogens (see the NCCN Guidelines for Lung Cancer Screening, available at [www.NCCN.org](http://www.NCCN.org)).<sup>23,24</sup> The International Agency for Research on Cancer lists several agents known to cause lung cancer, including arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, and diesel fumes.<sup>25-27</sup> Asbestos is a known carcinogen that increases the risk for lung cancer in people exposed to airborne fibers, especially in individuals who smoke. It is estimated that about 3% to 4% of lung cancers are caused by asbestos exposure.<sup>28</sup> Asbestos also causes malignant pleural mesothelioma (see the NCCN Guidelines for Malignant Pleural Mesothelioma, available at [www.NCCN.org](http://www.NCCN.org)). Radon gas, a radioactive gas that is produced by the decay of radium 226, also seems to cause lung cancer.

It is not clear whether hormone replacement therapy (HRT) affects the risk for lung cancer in women. More than 20 studies have been published, but the results have been inconsistent. In a large randomized controlled study,<sup>29</sup> no increase in the incidence of lung cancer was found among postmenopausal women treated with estrogen plus progestin HRT; however, the risk of death from NSCLC increased.<sup>29</sup> In women who received estrogen alone, the incidence or risk of death from lung cancer did not increase.<sup>30</sup>

### Smoking Cessation

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.<sup>16</sup> Active smoking and secondhand smoke both cause lung cancer. There is a causal relationship between active smoking and lung cancer and also between other cancers (eg, esophageal, oral cavity, laryngeal, pharyngeal, bladder, pancreatic, gastric, kidney, ovarian cancer, colorectal, and cervical cancers) and other diseases and conditions.<sup>16</sup> Smoking harms nearly every organ in the body; smokers have increased

mortality compared with nonsmokers.<sup>31</sup> Those who live with someone who smokes have an increased risk for lung cancer.<sup>20</sup> Further complicating this problem, cigarettes also contain nicotine, which is a highly addictive substance.

Oncologists should encourage smoking cessation, especially in patients with cancer (see the NCCN Guidelines for Smoking Cessation, available at [www.NCCN.org](http://www.NCCN.org)).<sup>32-35</sup> The 5 A's framework is a useful tool (that is, Ask, Advise, Assess, Assist, Arrange).<sup>36</sup> It is in the best interest of patients to quit smoking. Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival.<sup>37</sup> Some surgeons will not operate on a current smoker, because active smoking may increase postoperative pulmonary complications.<sup>38</sup> However, active smoking should not be used to exclude patients with early-stage lung cancer from surgical treatment that will prolong survival. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful.<sup>39</sup> The American Cancer Society (ACS) has a *Guide to Quitting Smoking*.

Agents that can be used to promote smoking cessation include nicotine replacement (eg, gum, inhaler, lozenge, nasal spray, patch), bupropion sustained release, and varenicline.<sup>40,41</sup> A study suggests that cytosine is more efficacious than nicotine replacement therapy, although more side effects were reported with cytosine such as nausea, vomiting, and sleep disorders.<sup>42</sup> Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.<sup>43-45</sup> The effectiveness of varenicline for preventing relapse has not been clearly established.<sup>46</sup> The FDA has issued an alert for varenicline regarding neuropsychiatric symptoms. Varenicline has also been associated with visual disturbances, movement disorders, unconsciousness, and cardiovascular disorders; therefore, it is banned in truck and bus drivers, pilots, and air traffic controllers.<sup>47-50</sup> Other side effects with varenicline include nausea,

abnormal dreams, insomnia, and headache.<sup>45,51,52</sup> Bupropion may also be associated with similar serious neuropsychiatric symptoms. Nicotine replacement has fewer adverse effects than varenicline or bupropion.<sup>53</sup> In spite of the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.<sup>53</sup>

### Lung Cancer Screening

Lung cancer is the leading cause of cancer death worldwide in men, and late diagnosis is a major obstacle to improving lung cancer outcomes.<sup>1,54,55</sup> Because localized cancer can be managed with curative intent and because the mortality rate in other solid tumors (eg, cervix, colon) seems to be decreased by screening and early detection, lung cancer is an appropriate candidate for a population-based screening approach.

The National Lung Screening Trial (NLST) (ACRIN Protocol A6654) was a randomized controlled study involving more than 53,000 current or former heavy smokers that assessed the risks and benefits of low-dose CT scans compared with chest radiographs for detecting lung cancer.<sup>56</sup> Data from the NLST showed that screening individuals with high-risk factors using low-dose CT decreased the mortality rate from lung cancer by 20%.<sup>57</sup> Individuals with high-risk factors were either current or former smokers with a 30 or more pack-year smoking history (former smokers had quit up to 15 years before enrollment), were 55 to 74 years of age, and had no evidence of lung cancer.<sup>56,58</sup> The NCCN, ACS, U.S. Preventive Services Task Force (USPSTF), American College of Chest Physicians, European Society for Medical Oncology (ESMO), and other organizations recommend lung cancer screening using low-dose CT for select high-risk current and former smokers (see the NCCN Guidelines for Lung Cancer Screening, available at [www.NCCN.org](http://www.NCCN.org)).<sup>59-62</sup> Low-dose CT screening and follow-up are not a substitute for smoking cessation; patients should be offered smoking cessation counseling (see NCCN Guidelines for Smoking Cessation, available at [www.NCCN.org](http://www.NCCN.org)).

### Classification and Prognostic Factors

WHO divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: NSCLC (discussed in these guidelines) and small cell lung cancer (SCLC) (see the NCCN Guidelines for Small Cell Lung Cancer, available at [www.NCCN.org](http://www.NCCN.org)).<sup>63,64</sup> NSCLC accounts for more than 80% of all lung cancer cases, and it includes 2 major types: 1) nonsquamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other subtypes); and 2) squamous cell (epidermoid) carcinoma.<sup>3</sup> Adenocarcinoma is the most common subtype of lung cancer seen in the United States and is also the most frequently occurring histology in nonsmokers. In 2011, an international panel revised the classification of lung adenocarcinoma (see the *Pathologic Evaluation of Lung Cancer* in this Discussion), which has been adopted by WHO.<sup>63-65</sup> All NSCLC should be classified according to subtype using the WHO Guidelines.<sup>64</sup> Recently, the NCCN NSCLC Panel extensively revised the pathology section (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC and *Pathologic Evaluation of Lung Cancer* in this Discussion). Some of the recent changes include the addition of information about adenosquamous carcinomas, large cell carcinomas, and carcinoid tumors. Certain prognostic factors are predictive of survival in patients with NSCLC. Good prognostic factors include early-stage disease at diagnosis, good performance status (PS) (ECOG 0, 1), no significant weight loss (<5%), and female gender.<sup>66</sup>

### Diagnostic Evaluation

#### Incidental Lung Nodules

Lung cancer screening is recommended for early diagnosis in asymptomatic patients at high risk. Risk assessment is used to determine which individuals are at high risk for lung cancer and thus are candidates for screening with low-dose CT.<sup>67</sup> Clinicians are referred to the NCCN Guidelines for Lung Cancer Screening for risk assessment criteria to

determine which patients are eligible for screening and for how to evaluate and follow up on low-dose CT screening findings.<sup>68</sup> The NCCN Guidelines for Lung Cancer Screening were recently revised to harmonize with the LungRADs system developed by the American College of Radiology with the goal of decreasing the false-positive low-dose CT screening results reported in the NLST.<sup>69</sup>

The diagnostic algorithm for pulmonary nodules in the NCCN Guidelines for NSCLC incorporates information from the NCCN Guidelines for Lung Cancer Screening. Recently, the NCCN NSCLC Panel revised the diagnostic algorithms for incidental solid and subsolid lung nodules detected on chest CT based on the updated Fleischner criteria (see the NCCN Guidelines for NSCLC).<sup>70-74</sup> The cutoff thresholds were increased to 6 mm for a positive scan result. Note that the Fleischner Society Guidelines do not specify whether a CT with contrast is necessary for follow-up or whether a low-dose CT is sufficient. Low-dose CT is preferred unless contrast enhancement is needed for better diagnostic resolution.

Solid and subsolid nodules are the 2 main types of pulmonary nodules that may be seen on chest CT scans. The Fleischner Society has recommendations for patients with solid and subsolid nodules.<sup>71,72</sup>

Subsolid nodules include: 1) nonsolid nodules also known as ground-glass opacities (GGOs) or ground-glass nodules (GGNs); and 2) part-solid nodules, which contain both ground-glass and solid components.<sup>72,75-77</sup>

Nonsolid nodules are mainly adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), formerly known as bronchioloalveolar carcinoma (BAC) (see *Adenocarcinoma* in this Discussion); patients have 5-year disease-free survival of 100% if these nonsolid nodules are completely resected.<sup>65,72,75,76,78-80</sup> Data suggest that many nonsolid nodules discovered incidentally on CT imaging will resolve and many of those that persist may not progress to clinically significant cancer.<sup>78,81,82</sup> Solid and part-solid nodules are more likely to be invasive, faster-growing cancers,

factors that are reflected in the increased suspicion and follow-up of these nodules (see the NCCN Guidelines for Lung Cancer Screening, available at [www.NCCN.org](http://www.NCCN.org)).<sup>68,71,72</sup>

All findings and factors for a patient need to be carefully evaluated in a multidisciplinary diagnostic team before establishing a diagnosis of lung cancer and before starting treatment. The NCCN Guidelines recommend biopsy or surgical excision for highly suspicious nodules seen on low-dose CT scans or further surveillance for nodules with a low suspicion of cancer depending on the type of nodule and a multidisciplinary evaluation of other patient factors (see the NCCN Guidelines for Lung Cancer Screening, available at [www.NCCN.org](http://www.NCCN.org)). For patients having repeat scans, the most important radiologic factor is change or stability of a nodule when compared with a previous imaging study. False-positive results (eg, benign intrapulmonary lymph nodes, noncalcified granulomas) frequently occurred with low-dose CT when using the original cutoffs for nodule size deemed suspicious for malignancy from the NLST.<sup>57</sup> The revised cutoff values for suspicious nodules recommended by the American College of Radiology and incorporated into the LungRADs system have been reported to decrease the false-positive rate from low-dose CT.<sup>83-85</sup>

### Larger Tumors

The NCCN Guidelines recommend that the diagnostic strategy should be individualized for each patient depending on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (eg, comorbidities), and local expertise. The diagnostic strategy needs to be decided in a multidisciplinary setting. Decisions regarding whether a biopsy (including what type of biopsy) or surgical excision is appropriate depend on several factors as outlined in the NSCLC algorithm (see *Principles of Diagnostic Evaluation* in the NCCN Guidelines for NSCLC). For example, a preoperative biopsy may be appropriate if an intraoperative diagnosis seems to be difficult or very risky

(such as a small and central lesion, where it is difficult to wedge or do intraoperative core needle biopsy). The preferred biopsy technique depends on the disease site and is described in the NSCLC algorithm (see *Principles of Diagnostic Evaluation*). For example, radial endobronchial ultrasound (EBUS; also known as endosonography), navigational bronchoscopy, or transthoracic needle aspiration (TTNA) are recommended for patients with suspected peripheral nodules.<sup>86</sup>

PET/CT imaging is useful before selecting a biopsy site, because it is better to biopsy the site that will confer the highest stage. For patients with suspected nodal disease, pathologic mediastinal lymph node evaluation is recommended with either noninvasive or invasive staging methods, including endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA), EBUS–guided transbronchial needle aspiration (EBUS-TBNA), navigational bronchoscopy, or mediastinoscopy (see *Mediastinal Lymph Node Evaluation* in this Discussion and *Principles of Diagnostic Evaluation* in the NCCN Guidelines for NSCLC). Clinicians use both noninvasive and invasive methods when staging patients.<sup>87</sup> EBUS provides access to nodal stations 2R/2L, 4R/4L, 7, 10R/10L, and other hilar nodal stations. EUS provides access to nodal stations 5, 7, 8, and 9.

If pathology results from biopsy or surgical excision indicate a diagnosis of NSCLC, then further evaluation and staging need to be done so that the patient's health care team can determine the most appropriate and effective treatment plan (see *Pathologic Evaluation of Lung Cancer and Staging* in this Discussion and the NCCN Guidelines for NSCLC). Diagnosis, staging, and planned resection (eg, lobectomy) are ideally one operative procedure for patients with early-stage disease (see the *Principles of Diagnostic Evaluation* in the NCCN Guidelines for NSCLC). A preoperative or intraoperative tissue diagnosis of lung cancer should be established before doing a lobectomy.

## Pathologic Evaluation of Lung Cancer

Pathologic evaluation is performed to classify the histologic subtype of the lung cancer, determine the extent of invasion, determine whether it is primary lung cancer or metastatic cancer, establish the cancer involvement status of the surgical margins (ie, positive or negative margins), and do molecular diagnostic studies to determine whether certain gene alterations are present (eg, epidermal growth factor receptor [*EGFR*] mutations) (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).<sup>88</sup> Data show that targeted therapy is potentially very effective in patients with specific gene mutations or rearrangements; therefore, tissue needs to be conserved for molecular testing (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).<sup>7,89-95</sup>

Preoperative evaluations include examination of the following: bronchial brushings, bronchial washings, sputum, FNA biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy.<sup>86,96</sup> Minimally invasive techniques can be used to obtain specimens in patients with advanced unresectable NSCLC;<sup>97,98</sup> however, diagnosis may be more difficult when using small biopsies and cytology.<sup>79</sup> The mediastinal lymph nodes are systematically sampled to determine the staging and therapeutic options. Other lung diseases also need to be ruled out (eg, tuberculosis, sarcoidosis, coccidioidomycosis).<sup>99-101</sup> Lobectomy or pneumonectomy specimens are evaluated intraoperatively to determine the surgical resection margin status, diagnose incidental nodules discovered at the time of surgery, or evaluate the regional lymph nodes.

Postoperative evaluation provides the pathology characteristics necessary for the classification of tumor type, staging, and prognostic factors. The surgical pathology report should include the WHO histologic classification for carcinomas of the lung.<sup>63,64,102</sup> In 2011, the classification for lung adenocarcinoma was revised by an international panel, which has been

adopted by the WHO (see *Adenocarcinoma* in this Discussion).<sup>63-65</sup> The revised classification recommends immunohistochemical (IHC) and molecular studies (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).<sup>103</sup> In addition, the revised classification recommends that use of general categories (eg, non-small cell carcinoma [NSCC], NSCC not otherwise specified [NOS]) should be minimized, because more effective treatment can be selected when the histology is known.

Recently, the NCCN NSCLC Panel extensively revised the pathology section in the algorithm, including new information about adenosquamous carcinomas, large cell carcinomas, and carcinoid tumors (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC). The purpose of the pathologic evaluation of NSCLC varies depending on whether the sample is 1) intended for initial diagnosis in a case of suspected NSCLC; 2) a definitive resection sample; or 3) obtained for molecular evaluation in the setting of an established NSCLC diagnosis. Further details are provided in the algorithm. All NSCLC should be classified according to subtype using the WHO Guidelines.<sup>64</sup> Major subtypes of NSCLC include adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma, carcinoid tumor, and less common subtypes that are not discussed here. Ideally, the subtype should be obtained. The general terms NSCC or NSCC NOS should be used infrequently and only when a more specific diagnosis cannot be obtained by morphology and/or special staining.

Adenocarcinomas include AIS, MIA, invasive adenocarcinomas, and invasive adenocarcinoma variants (see *Adenocarcinoma* in this Discussion and the NCCN Guidelines for NSCLC). Squamous cell carcinoma is a malignant epithelial tumor that 1) shows either keratinization and/or intercellular bridges; or 2) is an undifferentiated NSCC that demonstrates positivity for squamous cell carcinoma markers

by IHC. Adenosquamous carcinomas are tumors with mixed adenocarcinoma and squamous cell carcinoma components; each component comprises at least 10% of the tumor. The presence of any adenocarcinoma component in a biopsy specimen that is otherwise squamous should trigger molecular testing. Large cell carcinomas are tumors lacking morphologic or IHC evidence of clear lineage, with negative or uninformative stains for squamous cell carcinoma and adenocarcinoma. The diagnosis of large cell carcinoma requires a thoroughly sampled resected tumor and cannot be made on non-resected or cytology specimens. Staining for large cell carcinomas should include mucin stain to look for occult glandular differentiation. Although carcinoid tumors are not treated like other types of NSCLC, they are staged in the same manner and are part of the differential diagnosis of pulmonary lesions. Care should be taken to properly distinguish typical carcinoid from atypical carcinoid by assessing for necrosis and using a morphologic mitotic count.

### Adenocarcinoma

As previously mentioned, most lung carcinomas are adenocarcinomas. In 2011, the classification for lung adenocarcinoma was revised by an international panel and adopted by WHO.<sup>63-65</sup> The revised classification recommends that use of general categories—NSCC and NSCC NOS—should be minimized, because more effective treatment can be selected when the specific subtype is known; IHC and molecular studies are also recommended (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).<sup>103</sup>

The categories of BAC or mixed subtype adenocarcinoma are no longer used to classify adenocarcinoma.<sup>65</sup> The categories for adenocarcinoma include: 1) AIS, which is a preinvasive, typically solitary lesion that is usually non-mucinous; 2) MIA, which is a solitary and discrete non-mucinous lesion with a maximum area of invasion no greater than 0.5

cm; and 3) invasive adenocarcinoma (see the NCCN Guidelines for NSCLC). Both AIS and MIA are associated with excellent survival if they are resected. The terms *AIS*, *MIA*, and *large cell carcinoma* should not be used for small samples because of challenges with complete assessment of the lesion.<sup>65</sup>

The international panel and the NCCN NSCLC Panel recommend that all patients with adenocarcinoma be tested for *EGFR* mutations; the NCCN NSCLC Panel also recommends that patients receive routine testing for anaplastic lymphoma kinase (*ALK*) gene rearrangements, *ROS1* rearrangements, *BRAF* mutations, and programmed death (PD-1) receptor expression levels by IHC, because FDA-approved agents for lung cancer are available for these biomarkers. For the 2019 update (Version 1), the NCCN NSCLC Panel revised the recommendation for PD-L1 IHC testing to category 1 (from category 2A) in patients with metastatic NSCLC based on phase 3 randomized trial data.<sup>104</sup> The panel also advises consideration of testing for other genetic alterations, such as *NTRK* gene fusions, *RET* rearrangements, *MET* genetic alterations, and *ERBB2* (*HER2*) mutations, to identify rare oncogenic driver alterations for which effective therapy may be available (see *Emerging Biomarkers to Identify Novel Therapies for Patients With Metastatic NSCLC* in the NCCN Guidelines for NSCLC).<sup>105-107</sup>

### Immunohistochemical Staining

Judicious use of IHC in small tissue samples is strongly recommended to conserve tumor tissue for molecular studies, especially in patients with advanced disease (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).<sup>98,108</sup> Note that IHC analyses used to identify tumor type and lineage (eg, adenocarcinoma vs. squamous cell carcinoma) are distinct from IHC analyses used to determine whether patients are candidates for ALK inhibitor therapy or PD-1 ligand (PD-L1) inhibitor therapy. Before using IHC to determine histologic subtype, all material

should be assessed morphologically, including routine staining approaches such as hematoxylin and eosin (H&E) histology (or relevant stains for cytology specimens), clinical findings, imaging studies, and the patient's history. Cytology may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.<sup>109</sup> If necessary, IHC should be used to distinguish adenocarcinoma, squamous cell carcinoma, metastatic malignancy, and primary pleural mesothelioma (particularly for pleural samplings). IHC is useful for poorly differentiated NSCLC in small biopsy and/or cytology specimens.<sup>65,110</sup> Squamous cell carcinomas are often TTF-1 negative and p40 (or alternatively p63) positive, whereas adenocarcinomas are usually TTF-1 positive.<sup>65</sup> These 2 markers may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.<sup>65,110</sup> Other markers (eg, p40, Napsin A) may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.<sup>111,112</sup> Napsin A positivity occurs in more than 80% of lung adenocarcinomas. In small biopsy specimens previously classified as NSCC NOS, a panel of TTF-1 (or alternatively Napsin A) and p40 (or alternatively p63) may be sufficient to refine the diagnosis to either adenocarcinoma or squamous cell carcinoma. Note that p63 can co-stain with TTF-1 or Napsin A in adenocarcinoma.

An appropriate panel of IHC stains should include those relevant for evaluation of metastatic carcinomas to the lung if the primary origin of the carcinoma is uncertain. It is appropriate to first perform a limited panel of IHC to evaluate for NSCLC and, if negative, then proceed to additional IHC for evaluation of possible metastasis from a distant site. TTF-1 is very important for distinguishing primary lung adenocarcinoma from metastatic adenocarcinoma, because most (70%–90%) non-mucinous primary adenocarcinomas are TTF-1 positive. TTF-1 is typically negative in squamous cell carcinoma.<sup>110</sup> However, TTF-1 is also positive in tumors such as thyroid cancer and rarely in a few other organ systems.<sup>113</sup> In addition, thyroglobulin and PAX8 are positive in tumors from patients with

thyroid cancer, while they are negative in lung cancer tumors. Immunomarkers that may be useful to assess for metastatic carcinoma to the lung include breast carcinoma (GCDFFP-15, mammaglobin), renal cell carcinoma (PAX8), papillary serous carcinoma (PAX8, PAX2, ER), and adenocarcinomas of the gastrointestinal tract (CDX2) or prostate gland (NKX3.1). All typical and atypical carcinoid tumors are positive for chromogranin and synaptophysin, whereas SCLC is negative in 25% of cases.

Malignant pleural mesothelioma is a rare disease.<sup>114,115</sup> The NCCN NSCLC Panel feels that malignant mesothelioma and lung adenocarcinoma can be distinguished using clinical impression, imaging, and a limited panel of immunomarkers (if needed) to preserve tissue for molecular testing. Commonly used immunostains sensitive and specific for adenocarcinoma include pCEA, Claudin4, TTF-1, and Napsin A (negative in mesothelioma). Other potentially useful markers include B72.3, Ber-EP4, MOC31, and CD15; however, these markers generally do not have the sensitivity and specificity of the commonly used markers. Immunostains sensitive and specific for mesothelioma include WT-1, calretinin, cytokeratin 5/6, and D2-40 (podoplanin antibody) (negative in adenocarcinoma).<sup>114-116</sup> Broad epithelial markers such as keratin(s), as well as other lineage-specific markers, should be used when the differential diagnosis includes non-pulmonary and non-mesothelial lesions. Other markers can be useful in the differential diagnosis between mesothelioma and metastatic carcinoma to the lung (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).

Although the cytologic diagnosis of NSCLC is generally reliable, it is more difficult to diagnose SCLC.<sup>86,110,117</sup> Many patients with SCLC have characteristic CT and clinical findings (eg, massive lymphadenopathy, mediastinal invasion). Most SCLCs are immunoreactive for TTF-1; they are typically negative for CK34βE12 and p63.<sup>118,119</sup> Many SCLCs also

stain positively for markers of neuroendocrine differentiation, including chromogranin and synaptophysin. IHC should be used to confirm neuroendocrine differentiation only when appropriate morphologic features—speckled chromatin pattern, nuclear molding, and peripheral palisading—are present. NCAM (CD56), chromogranin, and synaptophysin are used to identify neuroendocrine tumors if morphologic suspicion of neuroendocrine differentiation exists. One positive marker is sufficient if the staining is not ambiguous in more than 10% of the tumor cells.

### Staging

A revised edition of the AJCC Cancer Staging Manual (8th edition) was published in late 2016 and is effective for all cancer cases recorded on or after January 1, 2018.<sup>120</sup> The NCCN Guidelines used the AJCC (7<sup>th</sup> edition) staging system for lung cancer until January 1, 2018.<sup>121</sup> The definitions for TNM and the stage grouping for the eighth edition are summarized in Tables 1 and 2 of the staging tables (see *Definitions for T,N,M* and *Staging* in the NCCN Guidelines for NSCLC). The descriptors of the TNM classification scheme are summarized in Table 3 of the staging tables, which shows the differences between the seventh and eighth editions (see *Staging*).<sup>122</sup> The lung cancer staging system was revised by the International Association for the Study of Lung Cancer (IASLC)<sup>123-125</sup> and was adopted by the AJCC.<sup>126,127</sup> Early-stage disease is stages I and II with negative nodes (N0), whereas locally advanced disease is stages II and III with positive nodes (N+);<sup>128</sup> advanced or metastatic disease is stage IV. Pathologic staging uses both clinical staging information (which is noninvasive and includes medical history, physical examination, and imaging) and other invasive staging procedures (eg, thoracotomy, examination of lymph nodes using mediastinoscopy).<sup>121</sup>

From 2008 to 2014, the overall 5-year relative survival rate for NSCLC was 22.7% in the United States.<sup>3</sup> Of NSCLC and bronchial cancer cases,

19% were diagnosed while the cancer was still confined to the primary site; 24% were diagnosed after the cancer had spread to regional lymph nodes or directly beyond the primary site; 55% were diagnosed after the cancer had already metastasized; and for the remaining 2% the staging information was unknown. The corresponding 5-year relative survival rates were 60.1% for localized, 33.4% for regional, 5.5% for distant, and 13.8% for unstaged.<sup>3</sup>

Five-year survival after lobectomy for pathologic stage I NSCLC ranges from 45% to 65%, depending on whether the patient has stage 1A or 1B disease and on the location of the tumor.<sup>129</sup> Another study in patients with stage I disease (n = 19,702) found that 82% had surgical resection and their 5-year overall survival was 54%; for untreated stage I NSCLC, 5-year overall survival was only 6%.<sup>130</sup> Of patients with stage I disease who refused surgery (although it was recommended), 78% died of lung cancer within 5 years.

### Predictive and Prognostic Biomarkers

Several biomarkers have emerged as predictive and prognostic markers for NSCLC. A *predictive* biomarker is indicative of therapeutic efficacy, because there is an interaction between the biomarker and therapy on patient outcome. A *prognostic* biomarker is indicative of patient survival independent of the treatment received, because the biomarker is an indicator of the innate tumor behavior (see *KRAS Mutations* at the end of this section). A section on biomarkers was recently added to the algorithm and the content was revised for the 2019 update (Version 1) (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). For example, new information about plasma cell-free/circulating tumor DNA testing (so-called “liquid biopsy”) for genetic alterations was added to the section on biomarkers. Briefly, the panel feels that cell-free/circulating tumor DNA testing should not be used in lieu of tissue diagnosis. Standards and guidelines for cell-free DNA

(cfDNA)/circulating tumor DNA testing for genetic alterations have not been established, there is up to a 30% false-negative rate, and alterations can be detected that are not related to the tumor (eg, clonal hematopoiesis of indeterminate potential [CHIP]).<sup>131,132</sup> For example, an IDH1 mutation identified by cfDNA testing is likely unrelated to NSCLC, given exceptionally low incidence, and is more likely to represent CHIP. Rare examples of CHIP with *KRAS* mutations have been described, suggesting caution in the interpretation of cfDNA findings.<sup>133</sup> In addition, CHIP can be identified following prior chemotherapy or radiotherapy, further confounding interpretation of alterations such as in *TP53*.<sup>134</sup> However, cfDNA testing can be used in specific circumstances if 1) the patient is not medically fit for invasive tissue sampling, or 2) there is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified. Given the previous caveats, careful consideration is required to determine whether cfDNA findings reflect a true driver mutation or an unrelated finding.

Predictive biomarkers include the *ALK* fusion oncogene (fusion between *ALK* and other genes [eg, echinoderm microtubule-associated protein-like 4]), *ROS1* gene rearrangements, sensitizing *EGFR* gene mutations, *BRAF* V600E point mutations, and PD-L1 expression (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). Emerging predictive biomarkers include *ERBB2* (also known as *HER2*) mutations, *RET* gene rearrangements, high-level *MET* amplifications or *MET* exon 14 skipping mutations (METex14), and tumor mutational burden (TMB) (see *Emerging Biomarkers to Identify Novel Therapies for Patients With Metastatic NSCLC* in the NCCN Guidelines for NSCLC). The presence of *EGFR* exon 19 deletions or exon 21 L858R mutations is predictive of treatment benefit from EGFR tyrosine kinase inhibitor (EGFR TKI) therapy (eg, erlotinib); therefore, these mutations are referred to as *sensitizing EGFR* mutations (see *EGFR Mutations* in this Discussion).<sup>135,136</sup> The presence of *EGFR* exon 19 deletions (LREA) or



exon 21 L858R mutations does not appear to be prognostic of survival for patients with NSCLC, independent of therapy.<sup>137</sup>

*ALK* fusion oncogenes (ie, *ALK* gene rearrangements) and *ROS1* rearrangements are predictive biomarkers that have been identified in a small subset of patients with NSCLC; both predict for benefit from targeted therapy such as crizotinib or ceritinib (see *ALK Gene Rearrangements* and *ROS1 Rearrangements* in this Discussion and *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). Other gene rearrangements (ie, gene fusions) have recently been identified (such as *RET*) that are susceptible to targeted therapies, particularly therapies currently under investigation in clinical trials (see *Emerging Biomarkers to Identify Novel Therapies for Patients With Metastatic NSCLC* in the NCCN Guidelines for NSCLC).<sup>138-143</sup>

Testing for *ALK* gene rearrangements and *EGFR* gene mutations is recommended (category 1 for both) in the NSCLC algorithm for patients with metastatic nonsquamous NSCLC or NSCLC NOS so that patients with these genetic abnormalities can receive effective treatment with targeted agents (see *Targeted Therapies* in this Discussion and the NCCN Guidelines for NSCLC).<sup>144-148</sup> Testing for *ROS1* rearrangements and *BRAF* mutations (both are category 2A) is also recommended in the NCCN Guidelines for nonsquamous NSCLC or NSCLC NOS. Although rare, patients with *ALK* rearrangements or *EGFR* mutations can have mixed squamous cell histology.<sup>149,150</sup> Therefore, testing for *ALK* rearrangements and *EGFR* mutations can be considered in select patients with metastatic squamous cell carcinoma if they are never smokers, small biopsy specimens were used for testing, or mixed histology was reported. Data suggest that *EGFR* mutations occur in patients with adenosquamous carcinoma at a rate similar to adenocarcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.<sup>149</sup> Thus, testing for *EGFR* mutations and *ALK* rearrangements is recommended in

mixed squamous cell lung specimens that contain an adenocarcinoma component, such as adenosquamous NSCLC or in samples in which an adenocarcinoma component cannot be excluded.<sup>148</sup> The incidence of *EGFR* mutations is very low in patients with pure squamous cell histology (<4%).<sup>151</sup> Testing for *ROS1* rearrangements or *BRAF* mutations is also recommended (category 2A) in patients with squamous cell carcinoma who have small biopsy specimens or mixed histology.

*EGFR*, *KRAS*, *ROS1*, and *ALK* genetic alterations do not usually overlap; thus, testing for *KRAS* mutations may identify patients who will not benefit from further molecular testing.<sup>138,152,153</sup> *BRAF* mutations typically do not overlap with *EGFR* mutations or *ALK* rearrangements.<sup>154,155</sup> For patients with metastatic nonsquamous NSCLC, the NCCN NSCLC Panel currently recommends that a minimum of the following biomarkers should be tested, including *EGFR* mutations, *BRAF* mutations, *ALK* rearrangements, *ROS1* rearrangements, and PD-L1 expression levels. This list of recommended biomarkers may be revised as new oncogenic driver alterations are identified and new agents are approved. Patients with NSCLC may have other genetic alterations (see *Emerging Biomarkers to Identify Novel Therapies for Patients With Metastatic NSCLC* in the NCCN Guidelines for NSCLC).<sup>90,156,157</sup> The NCCN Guidelines do not endorse specific testing modalities or techniques for biomarker tests.<sup>158</sup> Biomarker testing should be done at properly accredited laboratories (minimum of Clinical Laboratory Improvement Amendments [CLIA] accreditation) (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).

Other driver mutations and gene rearrangements (ie, driver events) are being identified such as *RET* gene rearrangements, high-level *MET* amplification or *MET* exon 14 mutations, *ERBB2* mutations, and TMB.<sup>138,139,141,143,154,159-169</sup> For the 2019 update (Version 1), the NCCN NSCLC Panel added TMB as a new emerging biomarker that may be

helpful for identifying patients with metastatic NSCLC who are eligible for first-line therapy with nivolumab with or without ipilimumab (see *Nivolumab* in this Discussion).<sup>170,171</sup> However, there is no consensus on how to measure TMB. Targeted agents are available for patients with NSCLC who have these other genetic alterations, although they are FDA approved for other indications (see *Emerging Biomarkers to Identify Novel Therapies for Patients With Metastatic NSCLC* in the NCCN Guidelines for NSCLC).<sup>172,173</sup> Thus, the NCCN NSCLC Panel strongly advises broader molecular profiling to identify rare driver mutations to ensure that patients receive the most appropriate treatment; patients may be eligible for clinical trials for some of these targeted agents.<sup>147</sup> Several online resources are available that describe NSCLC driver events such as *My Cancer Genome*.<sup>174,175</sup>

The *KRAS* oncogene is a prognostic biomarker. The presence of *KRAS* mutations is prognostic of poor survival for patients with NSCLC when compared to the absence of *KRAS* mutations, independent of therapy (see *KRAS Mutations* in this Discussion).<sup>176</sup> *KRAS* mutations are also predictive of lack of benefit from EGFR TKI therapy.<sup>135,177,178</sup> *EGFR*, *KRAS*, *ROS1*, and *ALK* genetic alterations do not usually overlap.<sup>152,153,179</sup> *BRAF* mutations typically do not overlap with *EGFR* mutations or *ALK* rearrangements.<sup>154</sup> EGFR TKI therapy is not effective in patients with *KRAS* mutations, *BRAF* V600E mutations, *ALK* gene rearrangements, or *ROS1* rearrangements.

### Molecular Testing for Biomarkers

Molecular testing is used to test for genomic alterations associated with oncogenic driver events if targeted therapies are available; these genomic alterations (also known as biomarkers) include mutations and gene rearrangements. The various molecular testing methods that may be used to assess for the different biomarkers are described in the algorithm (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines

for NSCLC). Broad molecular profiling systems may be used to simultaneously test for multiple biomarkers.

Next-generation sequencing (NGS) (also known as massively parallel sequencing) is a type of broad molecular profiling system that can detect panels of mutations and gene rearrangements if the NGS platforms have been designed and validated to detect these genetic alterations.<sup>172,180-187</sup> It is important to recognize that NGS requires quality control as much as any other diagnostic technique; because it is primer dependent, the panel of genes and abnormalities detected with NGS will vary depending on the design of the NGS platform. For example, some NGS platforms can detect both mutations and gene rearrangements, as well as copy number variation, but they are not uniformly present in all NGS assays being conducted either commercially or in institutional laboratories.

Other mutation screening assays are available for detecting multiple biomarkers simultaneously—such as Sequenom's MassARRAY® system and SNaPshot® Multiplex System—which can detect more than 50 point mutations; NGS platforms can detect even more biomarkers.<sup>174,188</sup> However, these multiplex polymerase chain reaction (PCR) systems do not typically detect gene rearrangements. *ROS1* and *ALK* gene rearrangements can be detected using fluorescence in situ hybridization (FISH), NGS, and other methods (see *ALK Gene Rearrangements* and *ROS1 Rearrangements* in this Discussion and *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).

To minimize tissue use and potential wastage, the NCCN NSCLC Panel recommends that biomarker testing be done as part of broad molecular profiling using a validated test(s) that assesses a minimum of the following potential genetic alterations: *EGFR* mutations, *BRAF* mutations, *ALK* rearrangements, and *ROS1* rearrangements. Both FDA and laboratory-developed test platforms are available that address the need to evaluate these and other analytes. Broad molecular profiling is

also recommended to identify rare driver mutations for which effective therapy may be available, such as neurotrophic receptor tyrosine kinase (*NTRK*) gene fusions, high-level *MET* amplification, *MET* exon 14 skipping mutation, *RET* rearrangements, *ERBB2* (*HER2*) mutations, and TMB. Although clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with specific genetic alterations (eg, *EGFR* mutations), these features should not be used to select patients for testing.

### EGFR Mutations

In patients with NSCLC, the most commonly found *EGFR* gene mutations are deletions in exon 19 (Exon19del [with conserved deletion of the LREA sequence] in 45% of patients with *EGFR* mutations) and a point mutation in exon 21 (L858R in 40%). Both mutations result in activation of the tyrosine kinase domain, and both are associated with sensitivity to the small molecule EGFR TKIs, such as erlotinib, gefitinib, afatinib, osimertinib, and dacomitinib (see *Targeted Therapies* in this Discussion).<sup>189</sup> Thus, these mutations are referred to as sensitizing *EGFR* mutations. Other less common mutations (10%) that are also sensitive to EGFR TKIs include exon 19 insertions, p.L861Q, p.G719X, and p.S768I (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).<sup>190,191</sup> Data suggest that patients harboring tumors without sensitizing *EGFR* mutations should not be treated with EGFR TKIs in any line of therapy. These sensitizing *EGFR* mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients.<sup>192</sup>

Most patients with sensitizing *EGFR* mutations are nonsmokers or former light smokers with adenocarcinoma histology. However, smoking status, ethnicity, and histology should not be used in selecting patients for testing. *EGFR* mutation testing is not usually recommended in patients with pure squamous cell carcinoma unless they are a former light or never-smoker,

if only a small biopsy specimen (ie, not a surgical resection) was used to assess histology, or if the histology is mixed.<sup>149</sup> Data suggest that *EGFR* mutations can occur in patients with adenosquamous carcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.<sup>149</sup>

The predictive effects of the drug-sensitive *EGFR* mutations are well defined. Patients with these mutations have a significantly better response to erlotinib, gefitinib, afatinib, osimertinib, or dacomitinib.<sup>189</sup>

Non-responsiveness to EGFR TKI therapy is associated with *KRAS* and *BRAF* mutations and *ALK* or *ROS1* gene rearrangements. Patients with *EGFR* exon 20 insertion mutations are usually resistant to TKIs, although there are rare exceptions (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).<sup>193-197</sup> *EGFR* p.Thr790Met (T790M) is a mutation associated with acquired resistance to EGFR TKI therapy and has been reported in about 60% of patients with disease progression after initial response to erlotinib, gefitinib, or afatinib.<sup>185,198-204</sup> Most patients with sensitizing *EGFR* mutations become resistant to erlotinib, gefitinib, or afatinib; progression-free survival (PFS) is about 9.7 to 13 months.<sup>199,205-208</sup> Studies suggest T790M may also occur in patients who have not previously received erlotinib, gefitinib, or afatinib, although this is a rare event.<sup>209</sup> Genetic counseling is recommended for patients with pre-treatment p.T790M, because this suggests the possibility of germline mutation and is associated with predisposition to familial lung cancer.<sup>210,211</sup> Osimertinib is recommended (category 1) as second-line and beyond (subsequent) therapy for patients with *EGFR* T790M who have progressed on erlotinib, gefitinib, afatinib, or dacomitinib (see *Osimertinib* in this Discussion).<sup>208,212</sup> For the 2019 update (Version 1), the NCCN NSCLC Panel voted that osimertinib is a preferred first-line therapy option (category 1) regardless of pre-treatment T790M status. Acquired resistance may also be associated with histologic transformation from NSCLC to SCLC and with epithelial to mesenchymal transition.<sup>213-215</sup>

Acquired resistance can also be mediated by other molecular events, such as acquisition of *ALK* rearrangement, *MET*, or *ERBB2* amplification.<sup>216</sup>

DNA mutational analysis is the preferred method to assess for *EGFR* status; IHC is not recommended for detecting *EGFR* mutations.<sup>217-220</sup> Real-time PCR, Sanger sequencing (paired with tumor enrichment), and NGS are the most commonly used methods to assess *EGFR* mutation status (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).<sup>148,217</sup> 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.<sup>192,219,221-223</sup> Mutation screening assays using multiplex PCR (eg, Sequenom's MassARRAY® system, SNaPshot® Multiplex System) can simultaneously detect more than 50 point mutations.<sup>188</sup> NGS can also be used to detect *EGFR* mutations.<sup>186</sup>

The predictive effects of the drug-sensitive *EGFR* mutations—Exon19del (LREA deletion) and L858R—are well defined. Patients with these mutations have a significantly better response to erlotinib, gefitinib, afatinib, osimertinib, or dacomitinib.<sup>189</sup> Data show that *EGFR* TKI therapy should be used as first-line systemic therapy in patients with advanced NSCLC and sensitizing *EGFR* mutations documented before first-line therapy (see *Targeted Therapies* in this Discussion).<sup>206,224-228</sup> PFS is improved with use of *EGFR* TKI in patients with sensitizing *EGFR* mutations when compared with cytotoxic systemic therapy, although overall survival is not statistically different.<sup>206,207,224</sup> Patients receiving erlotinib have fewer treatment-related severe side effects and deaths when compared with those receiving chemotherapy.<sup>206,229</sup> A phase 4 trial showed that gefitinib is safe and effective in patients with sensitizing *EGFR* mutations.<sup>145</sup>

Based on these data and the FDA approvals, erlotinib and gefitinib are recommended (category 1) as first-line systemic therapy in patients with sensitizing *EGFR* mutations including the less common mutations.<sup>145,206</sup> In a phase 3 randomized trial, patients receiving afatinib had decreased cough, decreased dyspnea, and improved health-related quality of life when compared with those receiving cisplatin/pemetrexed.<sup>229</sup> Based on these data and the FDA approval, afatinib is also recommended (category 1) as first-line systemic therapy in patients with sensitizing *EGFR* mutations.<sup>224</sup> Afatinib was potentially associated with 4 treatment-related deaths, whereas there were none in the chemotherapy group.<sup>224</sup> A combined analysis (LUX 3 and LUX 6) reported a survival advantage in patients with exon 19 deletions who received afatinib when compared with chemotherapy.<sup>230</sup>

### ***BRAF* V600E Mutations**

*BRAF* (v-Raf murine sarcoma viral oncogene homolog B) is a serine/threonine kinase that is part of the MAP/ERK signaling pathway. *BRAF* V600E is the most common of the *BRAF* point mutations when considered across all tumor types; it occurs in 1% to 2% of patients with lung adenocarcinoma.<sup>154,231</sup> Although other *BRAF* mutations occur in patients with NSCLC at a rate approximately equal to p.V600E (unlike many other tumor types), specific targeted therapy is not available for these other mutations. Patients with *BRAF* V600E mutations are typically current or former smokers in contrast to those with *EGFR* mutations or *ALK* rearrangements who are typically nonsmokers.<sup>167</sup> Mutations in *BRAF* typically do not overlap with *EGFR* mutations, *ALK* rearrangements, or *ROS1* rearrangements.<sup>154,155</sup> Testing for *BRAF* mutations is recommended (category 2A) in patients with metastatic nonsquamous NSCLC and may be considered in patients with squamous cell carcinoma NSCLC (category 2A) if small biopsy specimens were used to assess histology or mixed histology was reported.<sup>154,155</sup> Real-time PCR, Sanger sequencing, and NGS are the most commonly used methods to assess for *BRAF* mutations

(see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).

The NCCN NSCLC Panel recommends testing for *BRAF* mutations based on data showing the efficacy of dabrafenib/trametinib for patients with *BRAF* V600E mutations and on the FDA approval (see *Dabrafenib and Trametinib* in this Discussion).<sup>154</sup> Dabrafenib/trametinib or doublet chemotherapy regimens also used for initial cytotoxic therapy (eg, carboplatin/pemetrexed for nonsquamous NSCLC) are recommended for patients with *BRAF* V600E mutations. Single-agent therapy with dabrafenib or vemurafenib is recommended if combination therapy with dabrafenib/trametinib is not tolerated.<sup>154,155</sup>

### ALK Gene Rearrangements

About 5% of patients with NSCLC have *ALK* gene rearrangements.<sup>95</sup> Patients with *ALK* rearrangements are resistant to EGFR TKIs but have similar clinical characteristics to those with *EGFR* mutations (ie, adenocarcinoma histology, light or never-smokers).<sup>157</sup> *ALK* rearrangements are not routinely found in patients with squamous cell carcinoma. Patients with *ALK* gene rearrangements can have mixed squamous cell histology.<sup>150,232</sup> It can be challenging to accurately determine histology in small biopsy specimens; thus, patients may have mixed squamous cell histology (or squamous components) instead of pure squamous cell.

The NCCN NSCLC Panel recommends testing for *ALK* rearrangements in patients with metastatic nonsquamous NSCLC; testing can be considered if small biopsy specimens were used to assess histology, mixed histology was reported, or patients are light or never-smokers. The different testing methods for *ALK* rearrangements are described in the algorithm (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). A molecular diagnostic test (using FISH) has been approved

by the FDA for detecting *ALK* rearrangements. Rapid prescreening with IHC to assess for *ALK* rearrangements can be done.<sup>148,153,233-240</sup> An IHC assay for *ALK* rearrangements has also been approved by the FDA. NGS can also be used to assess whether *ALK* rearrangements are present, if the platform has been appropriately designed and validated to detect *ALK* rearrangements.<sup>241-243</sup>

### First-Line Therapy

Alectinib is an oral TKI that inhibits *ALK* and *RET* rearrangements but not *MET* or *ROS1* rearrangements.<sup>244</sup> A phase 3 randomized trial (ALEX) assessed first-line therapy with alectinib versus crizotinib in 303 patients with *ALK*-positive advanced NSCLC, including those with asymptomatic central nervous system (CNS) disease.<sup>244</sup> Disease progression or death occurred in fewer patients receiving alectinib (41% [62/152]; median follow-up of 18.6 months) when compared with crizotinib (68% [102/151]; median follow-up of 17.6 months). The HR was 0.47 (95% CI, 0.34–0.65;  $P < .001$ ) for disease progression or death. PFS was significantly increased with alectinib (68.4% [95% CI, 61.0%–75.9%] versus crizotinib (48.7% [95% CI, 40.4%–56.9%]). The median PFS was not reached for alectinib (95% CI, 17.7 months–not reached) when compared with crizotinib at 11.1 months (95% CI, 9.1–13.1). Fewer patients receiving alectinib had CNS progression (12% [18/152]) versus crizotinib (45% [68/151]). Response rates were 83% (126/152) in the alectinib group versus 75% (114/151) in the crizotinib group ( $P = .09$ ). Patients receiving alectinib had fewer grade 3 to 5 adverse events when compared with crizotinib (41% [63/152] vs. 50% [75/151], respectively) even though patients received alectinib for a longer duration than crizotinib (median, 17.9 vs. 10.7 months). Fewer deaths were reported in the alectinib arm (3.3% [5/152]) compared with the crizotinib arm (4.6% [7/151]); 2 treatment-related deaths were reported in the crizotinib arm and none were reported in the alectinib arm.

Another phase 3 randomized trial (J-ALEX) assessed first-line therapy with alectinib versus crizotinib in 207 Japanese patients with *ALK*-positive advanced NSCLC. The data showed that median PFS had not yet been reached with alectinib (95% CI, 20.3 months–not reached) versus 10.2 months (95% CI, 8.2–12.0) with crizotinib (HR, 0.34 [99.7% CI, 0.17–0.71], stratified log-rank  $P < .0001$ ). Grade 3 or 4 adverse events were less frequent with alectinib (26% [27/103]) when compared with crizotinib (52% [54/104]); adverse events did not lead to death in either group. Fewer patients stopped taking alectinib (9%) because of an adverse event when compared with crizotinib (20%). The NCCN NSCLC Panel recommends alectinib as a preferred first-line therapy option (category 1) for patients with *ALK*-positive metastatic NSCLC based on these clinical trials. Three other *ALK* inhibitors, crizotinib, brigatinib, and ceritinib, are also recommended (category 1 for all) by the NCCN NSCLC Panel as first-line therapy for patients with *ALK* rearrangements based on clinical trial data and FDA approvals for crizotinib and ceritinib (see *Brigatinib*, *Crizotinib*, and *Ceritinib* in this Discussion).

### Subsequent Therapy

Patients typically progress after first-line therapy with alectinib, brigatinib, crizotinib, or ceritinib; subsequent therapy recommendations are described in the algorithm [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion and the NCCN Guidelines for NSCLC). The phrase *subsequent* therapy was recently substituted for the terms *second-line or beyond* systemic therapy, because the line of therapy may vary depending on previous treatment with targeted agents.

Lorlatinib is a third-generation TKI that targets *ALK* and *ROS1* rearrangements; data show it is effective in select patients who have progressed after treatment with *ALK* inhibitors (see *Lorlatinib* in this Discussion).<sup>245,246</sup> For the 2019 update (Version 2), the NCCN NSCLC Panel now recommends lorlatinib (category 2A) as a subsequent therapy

option for select patients with *ALK*-positive NSCLC who have progressed after treatment with *ALK* inhibitors. For patients who progress on first-line crizotinib, subsequent treatment for *ALK*-positive NSCLC includes alectinib, brigatinib, or ceritinib (if not previously given) (see *Ceritinib*, *Alectinib*, and *Brigatinib* in this Discussion and the NCCN Guidelines for NSCLC).<sup>144,247-250</sup> For patients who progress on first-line alectinib, brigatinib, or ceritinib, subsequent treatment for *ALK*-positive NSCLC includes lorlatinib or the initial systemic therapy regimens that are used for first-line treatment of NSCLC (eg, carboplatin/paclitaxel) depending on the type of progression.<sup>251,252</sup> Continuing alectinib, brigatinib, crizotinib, or ceritinib with or without local therapy (eg, SABR, stereotactic radiosurgery [SRS], or surgery) may also be appropriate for select patients who progress on these agents depending on the type of progression [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion].<sup>253</sup> For patients who progress on second-line alectinib, brigatinib, or ceritinib, after initially receiving crizotinib, subsequent treatment for *ALK*-positive NSCLC includes lorlatinib or the initial systemic therapy regimens that are used for first-line treatment of NSCLC (eg, carboplatin/paclitaxel). For the 2019 update (Version 2), the NCCN NSCLC Panel also recommends lorlatinib (category 2A) as a subsequent therapy option for select patients with *ROS1*-positive NSCLC who have progressed after treatment with crizotinib or ceritinib.

*ALK* or *ROS1* rearrangements and sensitizing *EGFR* mutations are generally mutually exclusive.<sup>153,254,255</sup> Thus, *EGFR* TKI therapy is not recommended as subsequent therapy in patients with *ALK* or *ROS1* rearrangements who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib (see *ALK Positive: Subsequent Therapy* in the NCCN Guidelines for NSCLC).<sup>156,157</sup> Likewise, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended for patients with sensitizing *EGFR* mutations who relapse on *EGFR* TKI therapy.

### ROS1 Rearrangements

Although ROS proto-oncogene 1 (*ROS1*) is a distinct receptor tyrosine kinase, it is very similar to ALK and members of the insulin receptor family (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).<sup>139,256</sup> It is estimated that *ROS1* gene rearrangements occur in about 1% to 2% of patients with NSCLC; they occur more frequently in those who are negative for *EGFR* mutations, *KRAS* mutations, and *ALK* gene rearrangements.<sup>105,139,141,179</sup> Crizotinib is very effective for patients with *ROS1* rearrangements with response rates of about 70% to 80% including complete responses.<sup>138,139,257</sup> A phase 2 trial assessed crizotinib in 127 East Asian patients with *ROS1*-positive advanced NSCLC who had received 3 or fewer lines of therapy. The overall response rate was 72% (95% CI, 63%–79%) with 17 complete responses; the median duration of response was 19.7 months (95% CI, 14.1–not reached). The median PFS was 15.9 months (95% CI, 12.9–24.0).<sup>257</sup> In 50 patients, crizotinib yielded a response rate of 66% (95% CI, 51%–79%); the median duration of response was 18 months.<sup>139,258</sup> The FDA has approved crizotinib for patients with *ROS1* rearrangements.<sup>258</sup>

The NCCN NSCLC Panel recommends crizotinib, ceritinib, or entrectinib (all are category 2A) as first-line therapy options for patients with *ROS1*-positive metastatic NSCLC based on trial data. For the 2019 update (Version 7), the NCCN NSCLC Panel added a recommendation for entrectinib (category 2A, preferred) as a first-line therapy option for select patients with *ROS1*-positive metastatic NSCLC based on data and FDA approval (see *Entrectinib* in this Discussion).<sup>259-261</sup> The NCCN NSCLC Panel voted that crizotinib and entrectinib are the preferred agents for first-line therapy for patients with *ROS1*-positive metastatic NSCLC because they are better tolerated, have been assessed in more patients, and are approved by the FDA (see *Crizotinib* and *Entrectinib* in this Discussion). Although entrectinib has better CNS penetration than crizotinib, it is more toxic. For the 2019 update (Version 1), the NCCN

NSCLC Panel revised the *ROS1* algorithm to include recommendations for patients discovered to have *ROS1* rearrangements during first-line systemic therapy (eg, chemotherapy). Planned systemic therapy may be either completed or interrupted followed by crizotinib, ceritinib, or entrectinib.

The NCCN NSCLC Panel recommends *ROS1* testing in patients with metastatic nonsquamous NSCLC based on data showing the efficacy of crizotinib, ceritinib, and entrectinib for patients with *ROS1* rearrangements (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).<sup>138,139,258</sup> *ROS1* testing can be considered in patients with metastatic squamous cell carcinoma NSCLC if small biopsy specimens were used to assess histology or mixed histology was reported. Similar to testing for *ALK* rearrangements, testing for *ROS1* rearrangements is also done using FISH.<sup>141,233,262-264</sup> NGS can also be used to assess whether *ROS1* rearrangements are present, if the platform has been appropriately designed and validated to detect *ROS1* rearrangements.<sup>139</sup> Because a companion diagnostic test has not been approved for *ROS1* rearrangements, clinicians should use an appropriately validated test to detect *ROS1* rearrangements.<sup>258</sup> Alectinib, brigatinib, and ceritinib are not recommended in patients with *ROS1* rearrangements whose disease becomes resistant to crizotinib.<sup>139</sup> Studies are ongoing regarding new agents for patients with *ROS1* rearrangements whose disease becomes resistant to crizotinib, ceritinib, or entrectinib.<sup>265-268</sup> For the 2019 update (Version 2), the NCCN NSCLC Panel recommends lorlatinib (category 2A) as a subsequent therapy option for select patients with *ROS1*-positive metastatic NSCLC who have progressed after treatment with crizotinib or ceritinib (see *Lorlatinib* in this Discussion). Initial systemic therapy options that are used for adenocarcinoma or squamous cell carcinoma are also an option in this setting (eg, carboplatin/paclitaxel).

### NTRK Gene Fusions

*NTRK* gene fusions encode tropomyosin receptor kinase (*TRK*) fusion proteins (eg, *TRKA*, *TRKB*, *TRKC*) that act as oncogenic drivers for solid tumors including lung, salivary gland, thyroid, and sarcoma.<sup>269,270</sup> A diverse range of solid tumors in children and adults may be caused by *NTRK* gene fusions (eg, *NTRK1*, *NTRK2*, *NTRK3*). It is estimated that *NTRK* fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers such as *EGFR*, *ALK*, or *ROS1*.<sup>269</sup> Various methods can be used to detect *NTRK* gene fusions, including FISH, IHC, NGS, and PCR assays. In a recent clinical trial, *NTRK* gene fusions were detected with NGS (50 patients) and FISH (5 patients).<sup>270</sup> Larotrectinib and entrectinib are oral TKIs that inhibit TRK across a diverse range of solid tumors in younger and older patients with *NTRK* gene–fusion positive disease.<sup>261,270</sup> For the 2019 update (Version 3), the NCCN NSCLC Panel added a recommendation for *NTRK* gene fusion testing in patients with metastatic NSCLC based on clinical data and the approval of larotrectinib for patients with *NTRK* gene fusion–positive disease.<sup>270,271</sup> The NCCN NSCLC Panel recommends larotrectinib and entrectinib (both are category 2A) as either first-line or subsequent therapy options for patients with *NTRK* gene fusion–positive metastatic NSCLC based on data and the FDA approvals (see *Larotrectinib* and *Entrectinib* in this Discussion).<sup>259,261,272</sup>

### KRAS Mutations

*KRAS* is a G-protein with GTPase activity that is part of the MAP/ERK pathway; point mutations in *KRAS* most commonly occur at codon 12. Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have *KRAS* mutations; *KRAS* is the most common mutation in this population.<sup>93,135,172,173,178</sup> *KRAS* mutation prevalence is associated with cigarette smoking.<sup>273</sup> Patients with *KRAS* mutations appear to have a shorter survival than patients with wild-type *KRAS*; therefore, *KRAS* mutations are prognostic biomarkers.<sup>176,178,274</sup>

*KRAS* mutational status is also predictive of lack of therapeutic efficacy with *EGFR* TKIs; it does not appear to affect chemotherapeutic efficacy.<sup>93,135,177</sup> *KRAS* mutations do not generally overlap with *EGFR* mutations, *ALK* rearrangements, or *ROS1* rearrangements.<sup>152,153,275</sup> Therefore, *KRAS* testing may identify patients who may not benefit from further molecular testing.<sup>147,177</sup> Targeted therapy is not currently available for patients with *KRAS* mutations, although immune checkpoint inhibitors appear to be effective; MEK inhibitors are in clinical trials.<sup>173,276-278</sup>

### PD-L1 Expression Levels

Human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells (see *Immune Checkpoint Inhibitors* in this Discussion).<sup>279-281</sup> Nivolumab and pembrolizumab inhibit PD-1 receptors.<sup>282,104</sup> Atezolizumab and durvalumab inhibit PD-L1.<sup>283,284</sup> The NCCN NSCLC Panel recommends (category 1 ) IHC testing for PD-L1 expression ideally before first-line treatment in patients with metastatic NSCLC to assess whether PD-1 or PD-L1 inhibitors with or without chemotherapy are an option (see *Pembrolizumab* and *Atezolizumab* in this Discussion). The panel revised the recommendation for PD-L1 IHC testing to category 1 (from category 2A) for the 2019 update (Version 1) based on phase 3 randomized trial data.<sup>104,285</sup>

For the 2019 update (Version 1), the NCCN NSCLC Panel added new first-line treatment regimens based on PD-L1 expression levels for patients with metastatic NSCLC, negative or unknown test results for *EGFR* mutations and *ALK* rearrangements, and no contraindications to immunotherapy (eg, no active or previously documented autoimmune disease and/or no current use of immunosuppressive agents, or no oncogene that would predict lack of benefit). Single-agent pembrolizumab is recommended as first-line therapy for patients with metastatic NSCLC regardless of histology, PD-L1 levels of 50% or more (category 1



preferred), and negative or unknown test results for *EGFR* mutations and *ALK* rearrangements.<sup>104</sup> For the 2019 update (Version 4), the NCCN NSCLC Panel added another recommendation for single-agent pembrolizumab as first-line therapy in patients with metastatic NSCLC regardless of histology, PD-L1 levels of 1% to 49% (category 2B), and negative or unknown test results for *EGFR* mutations and *ALK* rearrangements (see *Pembrolizumab* in this Discussion).<sup>286</sup>

The NCCN NSCLC Panel clarified the recommendations for pembrolizumab/chemotherapy in patients with metastatic nonsquamous NSCLC and PD-L1 expression levels of 1% to 49% for the 2019 update (Version 5); all of the regimens are *preferred* category 1 recommendations in this setting. Thus, the pembrolizumab/carboplatin (or cisplatin)/pemetrexed regimens are category 1 recommended options for patients with metastatic nonsquamous NSCLC regardless of PD-L1 expression levels; however, these regimens are preferred for those whose PD-L1 levels are less than 50% or unknown.<sup>287</sup> First-line combination therapy with atezolizumab/bevacizumab/chemotherapy is category 1 recommended option for patients with nonsquamous NSCLC with negative or unknown test results for *EGFR* mutations and *ALK* rearrangements, regardless of PD-L1 expression levels.<sup>287,288</sup> For the 2019 update (Version 6), the NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the systemic therapy regimens containing bevacizumab (eg, carboplatin/paclitaxel/bevacizumab) that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.<sup>289-293</sup>

The NCCN NSCLC Panel also clarified the recommendations for pembrolizumab/carboplatin/paclitaxel (or albumin-bound paclitaxel) in patients with metastatic squamous cell carcinoma NSCLC and PD-L1 expression levels of 1% to 49% for the 2019 update (Version 5); these regimens are a *preferred* category 1 recommendation in this setting. The

pembrolizumab/carboplatin/paclitaxel (or albumin-bound paclitaxel) regimens are category 1 recommended options for patients with squamous cell carcinoma NSCLC regardless of PD-L1 expression levels; however, these regimens are preferred for those whose PD-L1 levels are less than 50% or unknown.<sup>294</sup> Pembrolizumab/cisplatin/paclitaxel (or albumin-bound paclitaxel) is a category 2A recommended option for patients with squamous cell carcinoma NSCLC whose PD-L1 levels are less than 50%. For patients with medical contraindications to immunotherapy, the initial cytotoxic regimens are recommended depending on histology (eg, carboplatin/paclitaxel). Regardless of PD-L1 expression levels, subsequent therapy with a single-agent PD-1 or PD-L1 inhibitor appears to be less effective in tumors with *EGFR* mutations or *ALK* rearrangements based on data in the second-line setting.<sup>279,282,295-297</sup> A small study suggests that single-agent pembrolizumab is not effective as first-line therapy in patients with metastatic NSCLC and *EGFR* mutations, even those with PD-L1 levels more than 50%.<sup>298</sup>

Although it is not an optimal biomarker, PD-L1 expression is currently the best available biomarker to assess whether patients are candidates for PD-1 or PD-L1 inhibitors.<sup>299,300</sup> Testing for PD-L1 is not required for prescribing single-agent nivolumab or atezolizumab for subsequent therapy. PD-L1 expression is continuously variable and dynamic; thus, a cutoff value for a positive result is artificial. Patients with PD-L1 expression levels just below and just above 50% will probably have similar responses.<sup>299</sup> Unique anti-PD-L1 IHC assays have been developed for each one of the different immune checkpoint inhibitors.<sup>299,301-303</sup> The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.<sup>303</sup> Extensive effort has been undertaken to examine the cross-comparability of different clones with regard to each other to facilitate adoption of testing.

### Treatment Approaches

Surgery, RT, and systemic therapy are the 3 modalities most commonly used to treat patients with NSCLC. They can be used either alone or in combination depending on the disease status. In the following sections, the clinical trials are described that have led to the recommended treatments. For tools to aid optimal assessment and management of older adults, see the NCCN Guidelines for Older Adult Oncology (available at [www.NCCN.org](http://www.NCCN.org)). Older adults may be at risk for treatment-related adverse events.<sup>304</sup>

#### Surgery

In general, for patients with stage I or II disease, surgery provides the best chance for cure.<sup>305</sup> Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. The overall plan of treatment and the necessary imaging studies should be determined before any nonemergency treatment is initiated. It is essential to determine whether patients can tolerate surgery or whether they are medically inoperable; some patients deemed inoperable may be able to tolerate minimally invasive surgery and/or sublobar resection.<sup>305-309</sup>

Although frailty is an increasingly recognized predictor of surgical and other treatment morbidity, a preferred frailty assessment system has not been established.<sup>310-312</sup>

The *Principles of Surgical Therapy* are described in the NSCLC algorithm and are summarized here (see the NCCN Guidelines for NSCLC). Determination of resectability, surgical staging, and pulmonary resection should be performed by board-certified thoracic surgeons who should participate in multidisciplinary clinics and/or tumor boards for patients with lung cancer. Surgery may be appropriate for select patients with uncommon types of lung cancer (eg, superior sulcus, chest wall involvement) (see the NCCN Guidelines for NSCLC).<sup>313</sup> Patients with pathologic stage II or greater disease can be referred to a medical

oncologist for evaluation. For resected stage IIIA, consider referral to a radiation oncologist. Treatment delays, because of poor coordination among specialists, should be avoided.

The surgical procedure used depends on the extent of disease and on the cardiopulmonary reserve of the patient. Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and if margin-negative resection can be achieved; lobectomy or pneumonectomy should be done if physiologically feasible.<sup>305,314,315</sup> Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients; the parenchymal resection margins are defined in the NSCLC algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).<sup>316-320</sup> Resection (including wedge resection) is preferred over ablation.<sup>305,315</sup> Wide wedge resection may improve outcomes.<sup>321</sup> Patients with medically inoperable disease may be candidates for SABR, also known as stereotactic body RT (SBRT).<sup>322,323</sup> If SABR is considered for patients at high risk, a multidisciplinary evaluation is recommended (see *Stereotactic Ablative Radiotherapy* in this Discussion).<sup>324-326</sup>

#### Lymph Node Dissection

A randomized trial (ACOSOG Z0030) compared systematic mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in patients with either N0 (no demonstrable metastasis to regional lymph nodes) or N1 (metastasis to lymph nodes in the ipsilateral peribronchial and/or hilar region, including direct extension) NSCLC disease. In patients with early-stage disease who had negative nodes by systematic lymph node dissection, complete mediastinal lymph node dissection did not improve survival.<sup>327,328</sup> Thus, systematic lymph node sampling is appropriate during pulmonary resection; one or more nodes should be sampled from all mediastinal stations. For right-sided cancers, an adequate mediastinal lymphadenectomy should include

stations 2R, 4R, 7, 8, and 9. For left-sided cancers, stations 4L, 5, 6, 7, 8, and 9 should be sampled.<sup>327</sup> Patients should have N1 and N2 node resection and mapping (American Thoracic Society map) with a minimum of 3 N2 stations sampled or a complete lymph node dissection.<sup>120</sup> The lymph node map from the IASLC may be useful.<sup>329</sup> Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease. For patients undergoing sublobular resection, the appropriate N1 and N2 lymph node stations should be sampled unless not technically feasible because sampling would substantially increase the surgical risk.

Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC): 1) those who are not eligible for lobectomy; and 2) those with a peripheral nodule 2 cm or less with very low-risk features. Segmentectomy (preferred) or wedge resection should achieve parenchymal resection margins that are: 1) 2 cm or more; or 2) the size of the nodule or larger.

### Stage IIIA N2 Disease

The role of surgery in patients with pathologically documented stage IIIA (N2) disease is described in the NSCLC algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC) and summarized here. Before treatment, it is essential to carefully evaluate for N2 disease using radiologic and invasive staging (ie, EBUS-guided procedures, mediastinoscopy, thorascopic procedures) and to discuss whether surgery is appropriate in a multidisciplinary team, which should include a board-certified thoracic surgeon.<sup>330,331</sup> Randomized controlled trials suggest that surgery does not increase survival in these patients.<sup>332,333</sup> However, one of these trials (EORTC) only enrolled patients with unresectable disease.<sup>333</sup> Most clinicians agree that resection is appropriate for patients with negative preoperative mediastinal nodes and with a single

positive node (<3 cm) found at thoracotomy.<sup>334</sup> Neoadjuvant (preoperative) therapy is recommended for select patients. The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and controversial.<sup>335,336</sup> In patients with N2 disease, 50% of the NCCN Member Institutions use preoperative chemoradiotherapy whereas 50% use preoperative chemotherapy.<sup>337,338</sup> There is no evidence that adding RT to induction regimens improves outcomes for patients with stage IIIA (N2) disease when compared with using chemotherapy alone.<sup>336</sup> Clinicians also agree that resection is not appropriate for patients with multiple pathologically proven malignant lymph nodes greater than 3 cm; definitive chemoradiotherapy is recommended for these patients.

The NCCN NSCLC Panel believes that surgery may be appropriate for select patients with N2 disease, especially those whose disease responds to induction chemotherapy (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).<sup>330,339</sup> It is controversial whether pneumonectomy after preoperative chemoradiotherapy is appropriate.<sup>332,339-345</sup> Patients with resectable N2 disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.<sup>339,346</sup>

### Thorascopic Lobectomy

Video-assisted thoracic surgery (VATS), which is also known as thorascopic lobectomy, is a minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).<sup>347,348</sup> Published studies suggest that thorascopic lobectomy has several advantages over thoracotomy.<sup>349-353</sup> Acute and chronic pain associated with thorascopic lobectomy is minimal; thus, this procedure requires a shorter length of hospitalization.<sup>354,355</sup> Thorascopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.<sup>356-360</sup> Thorascopic

lobectomy is associated with less morbidity, fewer complications, and more rapid return to function than lobectomy by thoracotomy.<sup>361-364</sup>

In patients with stage I NSCLC who had thoroscopic lobectomy with lymph node dissection, the 5-year survival rate, long-term survival, and local recurrence were comparable to those achieved by routine open lung resection.<sup>365-369</sup> Thoroscopic lobectomy has also been shown to improve discharge independence in older populations and patients at high risk.<sup>370,371</sup> Data show that thoroscopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.<sup>372,373</sup> Based on its favorable effects on postoperative recovery and morbidity, thoroscopic lobectomy (including robotic-assisted approaches) is recommended in the NSCLC algorithm as an acceptable approach for patients who are surgically resectable (and have no anatomic or surgical contraindications) as long as principles of thoracic surgery are not compromised (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).<sup>374-377</sup> Robotic VATS seems to be more expensive with longer operating times than conventional VATS.<sup>378,379</sup>

### Radiation Therapy

The *Principles of Radiation Therapy* in the NSCLC algorithm include the following: 1) general principles for early-stage, locally advanced, and advanced/metastatic NSCLC; 2) target volumes, prescription doses, and normal tissue dose constraints for early-stage, locally advanced, and advanced/metastatic NSCLC; and 3) RT simulation, planning, and delivery.<sup>380-385</sup> These RT principles are summarized in this section. Whole brain RT and SRS for brain metastases are also discussed in this section. The abbreviations for RT are defined in the NSCLC algorithm (see Table 1 in *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC). For the 2019 update (Version 1), the NCCN NSCLC Panel extensively revised the RT recommendations in the algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC). For example,

some of the normal tissue dose constraints for conventionally fractionated RT were revised (see Table 5).

### General Principles

Treatment recommendations should be made by a multidisciplinary team. Because RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy, input from board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice should be part of the multidisciplinary evaluation or discussion for all patients with NSCLC. Uses of RT for NSCLC include: 1) definitive therapy for locally advanced NSCLC, generally combined with chemotherapy; 2) definitive therapy for early-stage NSCLC in patients with contraindications for surgery; 3) preoperative or postoperative therapy for selected patients treated with surgery; 4) therapy for limited recurrences and metastases; and/or 5) palliative therapy for patients with incurable NSCLC.<sup>326,386-393</sup> The goals of RT are to maximize tumor control and to minimize treatment toxicity. Advanced technologies such as 4D-conformal RT simulation, intensity-modulated RT/volumetric modulated arc therapy (IMRT/VMAT), image-guided RT, motion management strategies, and proton therapy have been shown to reduce toxicity and increase survival in nonrandomized trials.<sup>394-400</sup> A secondary analysis of a randomized trial (RTOG 0617) reported that 2-year overall survival, PFS, local failure, and distant metastasis-free survival were not significantly different for IMRT when compared with 3D-conformal RT. IMRT yielded lower rates of severe pneumonitis when compared with 3D-conformal RT (3.5% vs. 7.9%;  $P = .039$ ).<sup>401</sup> CT-planned 3D-conformal RT is now considered to be the minimum level.

### Radiation Simulation, Planning, and Delivery

Simulation should be performed using CT scans obtained in the RT treatment position. Intravenous contrast CT scans, with or without oral contrast, are recommended for better target delineation whenever

possible, especially in patients with central tumors or nodal involvement. FDG PET/CT can significantly improve target delineation accuracy, especially when there is atelectasis or contraindications to intravenous CT contrast.<sup>402,403</sup> Ideally, PET/CT should be obtained 4 weeks before treatment because of the potential for rapid progression of NSCLC.<sup>404,405</sup> In the NSCLC algorithm, recommendations are provided for patients receiving chemoradiation (including those with compromised lung or cardiac function), photon beams, or IMRT (see *Radiation Therapy Simulation, Planning, and Delivery* in the *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).<sup>399,406-409</sup> Respiratory motion should be managed. The report from the AAPM Task Group 76 is a useful reference for implementing a broad range of motion management strategies as described in the NSCLC algorithm (see *Radiation Therapy Simulation, Planning, and Delivery* in the NCCN Guidelines for NSCLC).<sup>410</sup>

### **Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints**

Commonly used prescription RT (or SABR) doses and normal tissue dose constraints are summarized in the *Principles of Radiation Therapy* in the NSCLC algorithm (see Tables 2–5 in the NCCN Guidelines for NSCLC).<sup>381,383,390,411-416</sup> Reports 50, 62, and 83 from the International Commission on Radiation Units and Measurements provide a formalism for defining RT target volumes based on grossly visible disease, potential microscopic extension, and margins for target motion and daily positioning uncertainty.<sup>417,418</sup> The ACR Practice Parameters and Technical Standards are also a helpful reference.<sup>396,419,420</sup> It is essential to evaluate the dose-volume histogram (DVH) of critical structures and to limit the doses to the organs at risk (such as spinal cord, lungs, heart, esophagus, and brachial plexus) to minimize normal tissue toxicity (see Table 5 in *Principles of Radiation Therapy*).<sup>421</sup> For patients receiving postoperative RT (also known as PORT), stricter DVH parameters should be considered for the lungs. The QUANTEC review provides the most comprehensive

estimates from clinical data of dose-response relationships for normal tissue complications.<sup>422-426</sup>

For the 2019 update (Version 1), some of the normal tissue dose constraints for conventionally fractionated RT were revised based on a survey of radiation oncologists at NCCN Member Institutions (see Table 5 in *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC). These constraints are mainly empirical and have not, for the most part, been validated rigorously.<sup>411,427-433</sup> Therefore, the doses and constraints provided in the tables are not specific prescriptive recommendations; they are useful reference doses that have been commonly used or are from previous clinical trials. A caveat was added for the 2019 update (Version 1) that these constraints represent doses that generally should not be exceeded. Because the risk of toxicity increases progressively with dose to normal tissues, a key principle of radiation treatment planning is to keep normal tissue doses "as low as reasonably achievable" while adequately covering the target. The doses to any given organ at risk should typically be lower than these constraints, approaching them only when there is close proximity to the target volume. After surgery, lung tolerance to RT is much less than for patients with intact lungs; therefore, more conservative constraints should be used for postoperative RT.

For definitive RT, the commonly prescribed dose is 60 to 70 Gy in 2 Gy fractions over 6 to 7 weeks.<sup>434,435</sup> The use of higher RT doses is discussed in the NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).<sup>436-441</sup> Doses more than 74 Gy are not currently recommended for routine use.<sup>440,442-446</sup> Results from a phase 3 randomized trial (RTOG 0617) suggest that high-dose radiation using 74 Gy with concurrent chemotherapy does not improve survival, and might be harmful, when compared with a dose of 60 Gy.<sup>441,443,445,447-449</sup> Although optimal RT dose intensification remains a valid question, at higher RT doses, normal tissue constraints become even more important.<sup>449</sup> Although

the RT dose to the heart was decreased in the RTOG 0617 trial, survival was decreased; thus, more stringent constraints may be appropriate.

### General Treatment Information

The RT recommendations for patients with stages I to IV are described in the NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).

Definitive RT, particularly SABR, is recommended for patients with early-stage NSCLC (ie, stage I-II, N0) who are medically inoperable or those who refuse surgery (see *Stereotactic Ablative Radiotherapy* in this Discussion).<sup>322,323,326,393,450,451</sup> Interventional radiology ablation is an option for selected patients who are medically inoperable.<sup>305,452,453</sup> By extrapolation from surgical data, chemotherapy (category 2B) may be considered after definitive RT/SABR in patients with high-risk factors for recurrence (eg, large tumors >4 cm in size).<sup>324,454</sup> SABR is also an option for patients at high surgical risk who cannot tolerate a lobectomy (eg, major medical comorbidity or severely limited lung function). Resection is recommended for patients with early-stage NSCLC who are medically fit (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).<sup>455</sup> The indications for using preoperative or postoperative chemoradiation or RT alone are described in the NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC). In patients with clinical stage I or II NSCLC who are upstaged to N2+ after surgery, postoperative chemotherapy can be administered followed by postoperative RT depending on the margin status (see the NCCN Guidelines for NSCLC). Postoperative RT has been associated with increased mortality in patients with pathologic stage N0 to 1 disease, although the study used older RT techniques.<sup>456</sup>

Definitive chemoradiation is recommended for patients with stage II to III disease who are not appropriate surgical candidates.<sup>457</sup> For patients with locally advanced NSCLC (stage III), the most commonly prescribed

conventionally fractionated doses for definitive RT are 60 to 70 Gy in 2 Gy fractions. Doses of at least 60 Gy should be given.<sup>458</sup> Dose escalation is associated with better survival in non-randomized comparisons in RT alone, sequential chemo/RT, or concurrent chemo/RT.<sup>436,446,459</sup> A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens.<sup>460</sup> Involved-field RT (also known as involved-field irradiation or IFI) is an option for treating nodal disease in patients with locally advanced NSCLC; IFI may offer advantages over elective nodal irradiation (ENI).<sup>461-468</sup>

The optimal management of patients with potentially operable stage IIIA NSCLC is controversial and is discussed in detail in the algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).<sup>330,332,344,469</sup> For patients undergoing preoperative therapy before surgical resection of stage IIIA NSCLC, some oncologists prefer chemotherapy alone rather than chemoradiotherapy for the preoperative treatment;<sup>336</sup> RT should generally be given postoperatively if not given preoperatively.<sup>470</sup> The NCCN NSCLC Panel recommends a preoperative RT dose of 45 to 54 Gy in 1.8 to 2 Gy fractions.<sup>335,471</sup> Definitive RT doses delivered as preoperative chemo/RT can safely be administered and achieve promising nodal clearance and survival rates;<sup>414-416,472</sup> the risk of surgical complications after high-dose RT can be minimized with expert thoracic surgical techniques. NCCN Member Institutions are evenly split in their use of preoperative chemotherapy versus preoperative chemoradiation in patients with stage IIIA N2 NSCLC.<sup>330</sup> Similarly, some consider the need for pneumonectomy to be a contraindication to a combined modality surgical approach given the excess mortality observed in clinical trials,<sup>332</sup> but NCCN Member Institutions are split on this practice as well.

In postoperative RT, the clinical target volume (CTV) includes the bronchial stump and high-risk draining lymph node stations.<sup>473</sup> Standard

doses after complete resection are 50 to 54 Gy in 1.8 to 2 Gy fractions, but a boost may be administered to high-risk regions including areas of nodal extracapsular extension or microscopic positive margins.<sup>382,474,475</sup> Lung dose constraints should be more conservative, because tolerance appears to be reduced after surgery. The ongoing European LungART trial provides useful guidelines for postoperative RT technique.<sup>476</sup> Surgery is associated with potentially greater risk of complications, particularly stump breakdown and bronchopleural fistula, in a field that has had high-dose RT (eg, 60 Gy). Thus, surgeons are often wary of resection in areas that have previously received RT doses of more than 45 to 50 Gy, especially in patients who have received definitive doses of concurrent chemoradiation (ie, ≥60 Gy) preoperatively. Soft tissue flap coverage and reduced intraoperative fluid administration and ventilator pressures can reduce the risk of these complications.<sup>414-416</sup> When giving preoperative RT to less than definitive doses (eg, 45 Gy), one should be prepared up front to continue to a full definitive dose of RT without interruption if the patient does not proceed to surgery for some reason. For these reasons, when considering trimodality therapy, the treatment plan—including assessment for resectability and the type of resection—should be decided before initiation of any therapy.

For patients with advanced lung cancer (ie, stage IV) with extensive metastases, systemic therapy is recommended; palliative RT can be used for symptom relief and potentially for prophylaxis at primary or distant sites (such as pain, bleeding, or obstruction).<sup>393,477-479</sup> Shorter courses of palliative RT are preferred for patients with symptomatic chest disease who have poor PS and/or shorter life expectancy (eg, 17 Gy in 8.5 Gy fractions), because they provide similar pain relief as longer courses, although there is a higher potential need for retreatment (see Table 4 in the *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).<sup>480-483</sup> Higher dose and longer course thoracic RT (eg, ≥30 Gy in 10 fractions) are associated with modestly improved survival and

symptoms, especially in patients with good PS.<sup>477,484</sup> When higher doses (>30 Gy) are warranted, technologies to reduce normal tissue irradiation may be used (at least 3D-CRT and including IMRT or proton therapy as appropriate).

Local therapy (RT, SABR, or surgery) to primary and oligometastatic lesions should be considered for patients without progression on systemic therapy.<sup>485,486</sup> Definitive local therapy to isolated or limited metastatic sites (oligometastases) (including but limited to 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.<sup>487</sup> Definitive RT to oligometastases, particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.<sup>488,489</sup> In 2 randomized phase II trials, significantly improved PFS was found for local consolidative therapy (RT or surgery) to primary and oligometastatic lesions versus maintenance systemic therapy or observation for patients not progressing on systemic therapy.<sup>485,486</sup>

### **Stereotactic Ablative Radiotherapy**

SABR (also known as SBRT) uses short courses of very high (ablative), highly conformal, and dose-intensive RT precisely delivered to limited-size targets.<sup>322,490-493</sup> Studies, including prospective multi-institutional trials, have demonstrated the efficacy of SABR for patients with inoperable stage I NSCLC or for those who refuse surgery.<sup>326,494-498</sup> With conventionally fractionated RT, 3-year survival is only about 20% to 35% in these patients, with local failure rates of about 40% to 60%.<sup>323</sup> In prospective clinical trials, local control and overall survival appear to be considerably increased with SABR, generally more than 85%, and about 60% at 3 years (median survival, 4 years), respectively, in patients who are medically inoperable.<sup>305,323,409,453,455,497,499-504</sup> A 7-year follow-up of 65 patients with medically inoperable stage I NSCLC reported that overall survival rates were 55.7% at 5 years and 47.5% at 7 years.<sup>450</sup> In 12 patients (18.5%), a

second primary lung carcinoma developed after SABR at a median of 35 months (range, 5–67 months); 27% (18/65) had disease recurrence a median of 14.5 months (range, 4.3–71.5 months) after SABR.

Substantially higher survival has been observed in patients with potentially operable disease who are treated with SABR; survival is comparable in population-based comparisons to surgical outcomes, but locoregional recurrences are more frequent.<sup>455,496,505-510</sup> It has not been shown that use of SABR for medically operable patients provides long-term outcomes equivalent to surgery. Late recurrences have been reported more than 5 years after SABR, highlighting the need for careful surveillance.<sup>511</sup> If possible, biopsy should confirm NSCLC before use of SABR.<sup>512</sup> SABR is recommended in the NSCLC algorithm for patients with stage I and II (T1–3,N0,M0) NSCLC who are medically inoperable; SABR is a reasonable alternative to surgery for patients with potentially operable disease who are high risk, elderly, or refuse surgery after appropriate consultation (see the NCCN Guidelines for NSCLC).<sup>305,498,500,513,514</sup> A combined analysis of 2 randomized trials (that individually did not complete accrual) compared SABR to lobectomy.<sup>513</sup> This analysis does not provide sufficient data to change the standard of care for good surgical candidates but helps to confirm the indication for SABR in patients with relative contraindications for surgery or those who refuse surgery. SABR can also be used for patients with limited lung metastases or limited metastases to other body sites.<sup>491,498,515-521</sup> After SABR, assessment of recurrences by imaging can be challenging because of benign inflammatory/fibrotic changes that can remain FDG-PET avid for 2 or more years after treatment, emphasizing the importance of follow-up by a team with experience interpreting such post-treatment effects.<sup>522,523</sup> This careful follow-up is particularly relevant, because selected patients with localized recurrences after SABR may benefit from surgery or re-treatment with SABR.<sup>524-528</sup>

SABR fractionation regimens and a limited subset of historically used maximum dose constraints are provided in the NSCLC algorithm; 1 to 5 fractions are generally used (see Tables 2 and 3 in the *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).<sup>322,495,497,504,529-539</sup> In the United States, only regimens of 5 fractions or less meet the arbitrary billing code definition for SABR; however, slightly more protracted regimens are also appropriate.<sup>539,540</sup> Prescription doses do not completely describe the actual delivered doses.<sup>541,542</sup> These dose constraints are point-of-reference doses and are not intended to be prescriptive; they are used commonly or have been used in clinical trials. Although none of these dose constraints has been validated as a maximally tolerated dose, outcomes of clinical trials to date suggest that they are safe constraints. The bronchial tree, esophagus, and brachial plexus are critical structures for SABR. For centrally located tumors—those within 2 cm in all directions of any mediastinal critical structure, including the bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve—regimens of 54 to 60 Gy in 3 fractions are not safe and should be avoided; 4 to 10 fraction SABR regimens appear to be effective and safe (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).<sup>324,532,543-545</sup> Preliminary results (RTOG 0813) suggest that 5-fraction regimens are safe.<sup>546</sup>

SRS or SABR for limited oligometastases to the brain or other body sites, respectively, is recommended for patients with good PS if their thoracic disease can be treated with definitive therapy (see *Stage IV, M1b* in the NCCN Guidelines for NSCLC).<sup>313,488,489,498,547-550</sup> SRS or SABR can be considered for select patients with stage M1c disease who have a limited number and volume of metastatic lesions that are amenable to treatment with definitive local therapy; limited number is not defined but clinical trials have included up to 3 to 5 small metastases.<sup>547,548</sup> Targeted therapy and consideration of local therapy (eg, surgery or SABR [or SRS] for isolated lesions) is recommended for patients with *ALK* rearrangements or



sensitizing *EGFR* mutations who have progressed on targeted therapy, depending on the type of progression.<sup>551-554</sup> Decisions about whether to recommend SABR should be based on multidisciplinary discussion. Hypofractionated or dose-intensified conventional 3D-conformal RT is an option if an established SABR program is not available.<sup>555-557</sup> Nonrandomized clinical data indicate that local tumor control with SABR is higher than with interventional radiology ablation techniques. Interventional radiology ablation may be appropriate for selected patients for whom local control is not necessarily the highest priority.<sup>305,326,453</sup>

### **Whole Brain RT and Stereotactic Radiosurgery**

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.<sup>12,558</sup> Options for treatment of limited brain metastases include: 1) SRS alone; and 2) surgical resection for selected patients followed by SRS or whole brain RT. Selected patients include those with symptomatic metastases or whose tumor tissue is needed for diagnosis (see the NCCN Guidelines for NSCLC).<sup>518,558-566</sup> Treatment of limited brain metastases in patients with NSCLC differs from that recommended in the NCCN Guidelines for Central Nervous System Cancers, because patients with NSCLC and brain metastases often have long-term survival; therefore, the potential neurocognitive issues that may occur with whole brain RT are a concern.<sup>567</sup> Clinicians are not using whole brain RT as often in patients with limited brain metastases.<sup>559</sup>

A randomized trial assessed cognitive function in 213 patients with 1 to 3 brain metastases who received SRS alone versus SRS with whole brain RT; most patients had lung cancer.<sup>559</sup> At 3 months after SRS alone, patients had less cognitive deterioration (40/63 patients [63.5%]) than those receiving SRS plus whole brain RT (44/48 patients [91.7%]; difference, -28.2%; 90% CI, -41.9% to -14.4%;  $P < .001$ ). Decisions about whether to recommend SRS alone or brain surgery followed by whole brain RT or SRS for limited brain metastases should be based on

multidisciplinary discussion, weighing the potential benefit over the risk for each individual patient.<sup>560,568-570</sup> Treatment should be individualized for patients with recurrent or progressive brain lesions.<sup>571</sup>

For multiple metastases (eg, >3), whole brain RT is recommended; SRS may be preferred for patients who have good PS and low systemic tumor burden (see the NCCN Guidelines for Central Nervous System Cancers, available at [www.NCCN.org](http://www.NCCN.org)).<sup>572-575</sup> Whole brain RT is associated with measurable declines in neurocognitive function in clinical trials, particularly with increasing dose and advanced age of the patient.<sup>576-578</sup> However, control of brain metastases confers improved neurocognitive function.<sup>579,580</sup> For limited metastases, randomized trials have found that the addition of whole brain RT to SRS decreases intracranial recurrence but does not improve survival and may increase the risk of cognitive decline.<sup>580,581</sup> Thus, SRS or whole brain RT alone is recommended for patients with limited volume metastases.<sup>572</sup> Some have suggested that resection followed by SRS to the cavity (instead of resection followed by whole brain RT) will decrease the risk of neurocognitive problems.<sup>582,583</sup> A study suggests that using IMRT to avoid the hippocampus may help decrease memory impairment after whole brain RT.<sup>584</sup> A phase 3 randomized trial assessed optimal supportive care (including dexamethasone) with whole brain RT versus optimal supportive care alone in patients with NSCLC and brain metastases who were not eligible for brain surgery or SRS.<sup>585</sup> Overall survival was similar between the groups (HR, 1.06; 95% CI, 0.90–1.26). Overall quality of life, use of dexamethasone, and reported adverse events were also similar between the arms.

### **Combined Modality Therapy**

As previously mentioned, surgery provides the best chance for cure for patients with stage I or II disease who are medically fit and can tolerate surgery. SABR can be considered for patients with unresectable stage I or II (T1–3, N0) disease or those who refuse surgery if their disease is node

negative (see *Stereotactic Ablative Radiotherapy* in this Discussion and see the NCCN Guidelines for NSCLC). In patients with completely resected NSCLC, adjuvant (postoperative) chemotherapy has been shown to improve survival in patients with early-stage disease.<sup>586-589</sup> Some studies suggest that preoperative chemotherapy (also referred to as neoadjuvant chemotherapy or induction chemotherapy) is as effective as and better tolerated than postoperative chemotherapy (see *Preoperative Chemotherapy Followed by Surgery: Trial Data* in this Discussion).<sup>330,590-596</sup> A randomized trial found no difference in survival with preoperative versus postoperative chemotherapy.<sup>597</sup> The NCCN Guidelines state that patients with stage II or IIIA (T3, N1) disease may be treated with induction chemotherapy before surgery if they are candidates for therapy after surgery.<sup>305,598</sup> Concurrent chemoradiation is more efficacious than sequential chemoradiation for patients with unresectable stage III disease.<sup>599-602</sup>

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.<sup>603-608</sup> Data show that early palliative care combined with systemic therapy improved quality of life, mood, and survival in patients with metastatic NSCLC, even if these patients had less aggressive end-of-life care, when compared with those not receiving palliative care alone.<sup>609,610</sup> Patients should receive treatment for debilitating symptoms.<sup>12,611,612</sup> A study also suggests that social support, such as being married, is as effective as systemic therapy.<sup>613</sup> Preliminary results from a recent study indicate that systematic symptom monitoring during outpatient chemotherapy treatment increases overall survival when compared with usual care.<sup>614</sup> Surgery is rarely recommended for patients with stage IV disease. However, surgical resection of limited brain metastases may improve survival in selected patients with stage IV disease and is recommended for selected patients in the NCCN Guidelines (see the NCCN Guidelines for NSCLC, available at [www.NCCN.org](http://www.NCCN.org)).<sup>615</sup> Definitive local therapy with surgical resection or RT is

recommended for limited single-organ metastases located in sites other than the brain if definitive thoracic therapy is feasible (see *Stage IVA, M1b* in the NCCN Guidelines for NSCLC).<sup>313,485,487,498,547,548</sup> The trials supporting the recommendations for combined modality therapy are discussed in the following sections.

### ***Surgery Followed by Chemotherapy: Trial Data***

In the NSCLC algorithm for resected stage IA disease, postoperative chemotherapy is not recommended based on the trials described in the following paragraphs.<sup>616</sup> Postoperative chemotherapy may be considered for high-risk, margin-negative, stage IB disease (see the NCCN Guidelines for NSCLC). Recommended chemotherapy regimens for preoperative and postoperative therapy are provided in the NCCN Guidelines.<sup>586,616</sup> The NCCN NSCLC Panel recently added 2 preoperative and postoperative therapy regimens for patients with comorbidities or those not able to tolerate cisplatin, including 1) carboplatin/gemcitabine; and 2) carboplatin/pemetrexed (nonsquamous only).<sup>617-620</sup>

The International Adjuvant Lung Cancer Trial (IALT) reported a statistically significant survival benefit with cisplatin-based postoperative therapy in patients with completely resected stage I, II, or III NSCLC.<sup>587</sup> The study included 1867 patients with surgically resected lung cancer who were randomly assigned either to cisplatin-based postoperative chemotherapy or to observation, with a median follow-up duration of 56 months. A higher survival rate (45% vs. 40% at 5 years; HR for death, 0.86; 95% CI, 0.76–0.98;  $P < .03$ ) and disease-free survival rate (39% vs. 34% at 5 years; HR, 0.83; 95% CI, 0.74–0.94;  $P < .003$ ) were reported for patients assigned to chemotherapy when compared with observation. IALT data suggest that cisplatin-based postoperative chemotherapy improves survival 5 years after treatment in patients with completely resected NSCLC. However, after 7.5 years of follow-up, there were more deaths in the chemotherapy

group and the benefit of chemotherapy decreased over time.<sup>621</sup> Data show that postoperative chemotherapy prevents recurrences.

The NCIC CTG JBR.10 trial and the ANITA trial compared the effectiveness of postoperative vinorelbine/cisplatin versus observation in early-stage NSCLC. In the JBR.10 trial, 482 patients (ECOG PS of 0–1) with completely resected stage IB (T2a,N0) or stage II (T1,N1, or T2,N1) NSCLC were randomly assigned either to vinorelbine/cisplatin or to observation.<sup>588</sup> Postoperative chemotherapy significantly prolonged overall survival (94 vs. 73 months; HR for death, 0.69;  $P = .04$ ) and relapse-free survival (not reached vs. 47 months, HR for recurrence, 0.60;  $P < .001$ ) when compared with observation alone. The 5-year survival rates were 69% and 54%, respectively ( $P = .03$ ). When compared with observation alone, postoperative chemotherapy is beneficial for patients with stage II disease but not for stage IB disease as shown by updated data from JBR.10 after 9 years of follow-up.<sup>622</sup> In patients with stage II disease receiving postoperative chemotherapy, median survival is 6.8 versus 3.6 years in those who were only observed. Of note, patients receiving chemotherapy did not have an increased death rate.

In the ANITA trial, 840 patients with stage IB (T2a,N0), II, or IIIA NSCLC were randomly assigned either to postoperative vinorelbine/cisplatin or to observation.<sup>589</sup> Grade 3/4 toxicities were manageable in the chemotherapy group; 7 toxic deaths were reported. After a median follow-up of 76 months, median survival was 66 months in the chemotherapy group and 44 months in the observation group.<sup>589</sup> Postoperative chemotherapy significantly improved (8.6%) the 5-year overall survival in patients with completely resected stage II and IIIA disease, although no benefit was observed in stage I. Some clinicians consider vinorelbine/cisplatin to be the preferred regimen for completely resected early-stage NSCLC based on the number of trials and the amount of use;<sup>623</sup> however, most clinicians in the United States prefer to use regimens with less toxicity.<sup>624,625</sup>

A meta-analysis of 4,584 patients (LACE) found that postoperative cisplatin-based chemotherapy increased survival over 5 years (absolute benefit of 5.4%); there was no difference among the chemotherapy regimens (vinorelbine, etoposide, and others).<sup>626</sup> A subgroup analysis found that cisplatin/vinorelbine also increased survival.<sup>623</sup> The benefit was greater in patients with stage II and III disease and with good PS. Postoperative chemotherapy benefited elderly patients up to 80 years of age.<sup>308,627</sup>

The CALGB 9633 trial assessed paclitaxel/carboplatin in patients with stage IB (T2a,N0,M0) lung cancer.<sup>628-630</sup> In this trial, 344 patients were randomly assigned either to paclitaxel/carboplatin or to observation (within 4–8 weeks of resection) with a median follow-up duration of 74 months. Postoperative chemotherapy was well tolerated with no chemotherapy-related toxic deaths. Overall survival at 6 years was not significantly different (although a subset analysis showed a benefit for tumors 4 cm or more), although 3-year survival was significant (80% vs. 73%,  $P = .02$ ).<sup>629,630</sup> Thus, the carboplatin/paclitaxel regimen is only recommended for early-stage disease if patients cannot tolerate cisplatin (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy* in the NCCN Guidelines for NSCLC).<sup>631</sup> It is important to note that the CALGB trial was underpowered for patients with stage 1B disease.<sup>632</sup>

### **Preoperative Chemotherapy Followed by Surgery: Trial Data**

Data from clinical trials in patients with resected NSCLCs indicate that delivery of chemotherapy is an important problem. In the postoperative setting, significant comorbidities and incomplete recovery after surgery often make it difficult for patients to tolerate systemic therapy. This problem was demonstrated in the NATCH phase 3 trial (which compared surgery alone to preoperative or postoperative chemotherapy with paclitaxel/carboplatin), because 90% of the preoperative cohort completed 3 cycles of chemotherapy but only 61% of the postoperative cohort

completed chemotherapy; however, survival was equivalent among all 3 arms.<sup>595</sup> A randomized trial found no difference in 3-year overall survival (67.4% vs. 67.7%) with preoperative versus postoperative chemotherapy in patients with early-stage NSCLC; response rate and quality of life were similar in both arms.<sup>597</sup> Postoperative chemotherapy (with or without RT or resection) is recommended and typically used for early-stage disease in the NCCN Guidelines.<sup>305</sup>

Several trials suggest that preoperative therapy is beneficial in patients with N2 disease.<sup>330,336,594</sup> Other trials suggest that preoperative therapy is beneficial in patients with earlier stage disease.<sup>591,592,596</sup> A follow-up, randomized intergroup trial (SWOG 9900) evaluated preoperative paclitaxel/carboplatin in 354 patients with stage IB to IIIA (but not N2) disease versus surgery alone. The trial closed prematurely because of practice changes and was therefore not appropriately powered. This SWOG trial did show a trend toward improved PFS (33 vs. 20 months) and overall survival (62 vs. 41 months) with preoperative chemotherapy, and no difference in resection rates between the 2 arms.<sup>596</sup>

Scagliotti et al published a phase 3 trial of preoperative cisplatin/gemcitabine versus surgery alone in 270 patients with stage IB to IIIA disease. Although the trial closed early, a significant survival benefit was seen in patients with stages IIB and IIIA disease who received chemotherapy (HR, 0.63).<sup>591</sup> Song et al published a meta-analysis of all available randomized clinical trials evaluating preoperative chemotherapy in resectable NSCLCs. This meta-analysis evaluated 13 randomized trials; the HR suggests that overall survival in the preoperative chemotherapy arm is similar to the surgery alone arm (HR, 0.84; 95% CI, 0.77–0.92;  $P = .0001$ ).<sup>590</sup> These results are similar to those reported in another meta-analysis (HR, 0.89; 95% CI, 0.81–0.98;  $P = .02$ ).<sup>591</sup> The benefit from preoperative chemotherapy is similar to that attained with postoperative chemotherapy.<sup>591,597,626</sup>

### **Chemoradiation: Trial Data**

The major controversies in NSCLC relate to the management of patients with stage IIIA disease (see the *Role of Surgery in Patients with Stage IIIA (N2) NSCLC* in *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC). All 3 treatment modalities—surgical resection, chemotherapy, and radiation—may be used when treating stage III disease. The ongoing debate centers on which modalities to use and in what sequence.<sup>633-637</sup> For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is more efficacious than radiation alone.<sup>633,634,636-638</sup> Concurrent chemoradiation is more efficacious than sequential chemoradiation.<sup>599-602,639</sup> However, concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential chemoradiation. Selection of patients should be based not only on the anticipated response to therapy but also on how well the patient is anticipated to tolerate therapy. Accelerated RT regimens may be useful if concurrent chemoradiation would not be tolerated.<sup>460,640</sup> Sequential chemoradiation or RT alone is recommended for frail patients who cannot tolerate concurrent chemoradiation.<sup>306,641</sup>

A recent study reported that patients with N2 disease and an R0 resection had improved survival with postoperative chemotherapy followed by postoperative RT (ie, sequential chemoradiation) compared with postoperative concurrent chemoradiation (median overall survival, 58.8 vs. 40.4 months, respectively;  $P < .001$ ).<sup>470</sup> However, there was no difference in overall survival when patients with N2 disease and positive margins had postoperative sequential chemoradiation compared with postoperative concurrent chemoradiation (median overall survival, 42.6 vs. 38.5 months, respectively;  $P = .42$ ). Although the optimal sequence is not established, postoperative RT is generally administered after adjuvant chemotherapy or concurrently for positive resection margins.<sup>381,383,384,642</sup>

Concurrent chemoradiation regimens that may be used for all histologies for initial treatment include cisplatin/etoposide, cisplatin/vinblastine, and carboplatin/paclitaxel (see *Chemotherapy Regimens Used with Radiation Therapy* in the NCCN Guidelines for NSCLC).<sup>443,599,601,643-647</sup> For nonsquamous NSCLC, additional concurrent chemoradiation regimens may be used including carboplatin/pemetrexed and cisplatin/pemetrexed.<sup>648-650</sup> A weekly paclitaxel/carboplatin regimen is another chemoradiation option.<sup>443</sup> The different options for preoperative, definitive, and postoperative chemotherapy/RT are described in detail in the algorithm. Recently, the NCCN NSCLC Panel removed the *preferred* designation for the cisplatin/etoposide and cisplatin/vinblastine concurrent regimens based on data from a phase 3 randomized trial and a retrospective assessment of the Veterans Administration data.<sup>643,647,651</sup> Recently, the NCCN NSCLC Panel expanded the list of regimens for sequential chemoradiation to include regimens that are also used for preoperative and postoperative chemotherapy (ie, cisplatin combined with pemetrexed [nonsquamous only], docetaxel, etoposide, gemcitabine, or vinorelbine; carboplatin combined with paclitaxel) and also added 2 new carboplatin regimens for patients with comorbidities or those not able to tolerate cisplatin, including 1) carboplatin/gemcitabine; and 2) carboplatin/pemetrexed (nonsquamous only).

### *Durvalumab*

Durvalumab is a human immune checkpoint inhibitor antibody that inhibits PD-L1 (see *PD-L1 Expression Levels and Immunotherapies* in this Discussion).<sup>279-281,283</sup> A recent phase 3 randomized trial (PACIFIC) compared consolidation therapy (ie, after chemoradiation) with durvalumab versus placebo in patients with unresectable stage III NSCLC (PS 0–1) who had not progressed after 2 or more cycles of definitive concurrent platinum-based chemoradiation.<sup>283,652</sup> Patients received durvalumab after receiving concurrent chemoradiation (1–42 days). Most patients were current or former smokers and did not have

*EGFR* mutations; their PD-L1 status was typically less than 25% or unknown. An updated analysis of this trial reported that overall survival was increased after durvalumab consolidation when compared with placebo. The overall survival rate at 24 months was 66.3% for durvalumab (95% CI, 61.7%–70.4%) versus 55.6% for placebo (95% CI, 48.9%–61.8%).<sup>652</sup> The PFS was 17.2 months for durvalumab (95% CI, 13.1–23.9) versus 5.6 months for placebo (95% CI, 4.6–7.7) (stratified HR for disease progression or death, 0.51; 95% CI, 0.41–0.63;  $P < .001$ ). The median time to death or distant metastasis was significantly longer with durvalumab when compared with placebo (28.3 months vs. 16.2 months;  $P < .001$ ). Patients receiving durvalumab had a higher ongoing response at 18 months when compared with placebo (73.5% vs. 52.2%). Durvalumab was effective in patients with both squamous and nonsquamous NSCLC. Grade 3 or 4 adverse events occurred at a similar rate in both groups of patients (durvalumab, 30.5% vs. placebo, 26.1%). Pneumonia was the most common grade 3 or 4 adverse event (durvalumab, 4.4% vs. placebo, 3.8%).

The NCCN NSCLC Panel recommends durvalumab (category 1) as consolidation immunotherapy (regardless of PD-L1 status) for patients (PS 0–1) with unresectable stage III NSCLC who have not progressed after 2 or more cycles of definitive concurrent platinum-based chemoradiation based on this trial and FDA approval.<sup>283</sup> Durvalumab may be used as consolidation immunotherapy after any of the concurrent chemoradiation regimens described in the algorithm (eg, cisplatin/etoposide, carboplatin/paclitaxel) (see *Chemotherapy Regimens Used With Radiation Therapy* in the NCCN Guidelines for NSCLC). The panel noted that a few patients with stage II NSCLC were included in the PACIFIC trial, which used the older AJCC staging (7th edition). For the 2019 update (Version 1), the NCCN NSCLC Panel revised the durvalumab consolidation immunotherapy recommendation to category 1 (from category 2A) based on updated data from the PACIFIC trial.<sup>652</sup> In addition, the panel deleted

the recommendation to add an additional 2 cycles of full-dose chemotherapy if patients have not received full-dose chemotherapy concurrently with RT based on concerns that consolidation chemotherapy will increase the risk of pneumonitis if patients are also receiving durvalumab. Durvalumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information). Consolidation chemotherapy is an option after concurrent chemoradiation for patients who are not receiving durvalumab because of medical contraindications or other reasons.

### **Chemotherapy: Trial Data**

Patients with stage IV disease who have a good PS benefit from chemotherapy, usually with a platinum-based regimen.<sup>605-607</sup>

Chemotherapy is recommended for patients with stage IV NSCLC and negative or unknown test results for *ALK* rearrangements or sensitizing *EGFR* mutations, PD-L1 expression less than 1% or unknown, and contraindications to immunotherapy. Recommended chemotherapy regimens are based on PS and include platinum agents (eg, cisplatin, carboplatin), taxanes (eg, paclitaxel, albumin-bound paclitaxel [also known as nab-paclitaxel], docetaxel), vinorelbine, etoposide, pemetrexed, and gemcitabine (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). To clarify use of systemic therapy, the NCCN Guidelines list all of the combination systemic therapy regimens and single agents that are recommended for patients with metastatic NSCLC depending on histology and PS (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). Combinations using many of these drugs produce 1-year survival rates of 30% to 40% and are more efficacious than single agents.<sup>252,631,653-655</sup> In the United States, frequently used initial cytotoxic regimens for nonsquamous NSCLC include: 1) cisplatin (or carboplatin)/pemetrexed; or 2) carboplatin/paclitaxel with (or without) bevacizumab.<sup>656,657</sup>

Gemcitabine/cisplatin is recommended for patients with either squamous cell carcinoma or nonsquamous NSCLC.<sup>252,656-658</sup> These regimens are recommended based on phase 3 randomized trials (eg, cisplatin/pemetrexed, carboplatin/paclitaxel [with or without bevacizumab], gemcitabine/cisplatin).<sup>251,252</sup>

The initial cytotoxic systemic therapy regimens were recently revised by deleting options that are less effective, more toxic, and/or infrequently used in the United States based on each panel member's experience and data generated by surveying the NCCN NSCLC Panel (see the NCCN Guidelines With Evidence Blocks™ for NSCLC, available at [www.NCCN.org](http://www.NCCN.org)). For patients with nonsquamous NSCLC and NSCLC NOS, panel members deleted carboplatin/vinorelbine, cisplatin/vinorelbine, etoposide, irinotecan, and vinorelbine. For patients with squamous cell NSCLC, panel members deleted carboplatin/etoposide, carboplatin/vinorelbine, cisplatin/gemcitabine/necitumumab, cisplatin/vinorelbine, etoposide, irinotecan, and vinorelbine.

The NCCN NSCLC Panel recently voted unanimously to delete the necitumumab/cisplatin/gemcitabine regimen from the NCCN Guidelines for patients with metastatic squamous cell NSCLC. This decision reflects the fact that the NCCN NSCLC Panel feels the addition of necitumumab to the regimen is not beneficial based on toxicity, cost, and limited improvement in efficacy when compared with cisplatin/gemcitabine. A phase 3 randomized trial only showed a slight improvement in overall survival (11.5 months [95% CI, 10.4–12.6] vs. 9.9 months [95% CI, 8.9–11.1]).<sup>659</sup> The stratified HR was only 0.84 (95% CI, 0.74–0.96; *P* = .01). In addition, there were more grade 3 or higher adverse events in patients receiving the necitumumab regimen (388 [72%] of 538 patients) than in patients receiving only the gemcitabine/cisplatin (333 [62%] of 541). Although it has been suggested that adding necitumumab to cisplatin/gemcitabine adds value and is cost-effective, the NCCN NSCLC Panel does not agree.<sup>660</sup>

Many oncologists use pemetrexed-based regimens for adenocarcinomas (if patients are not candidates for targeted therapy or immunotherapy), because taxane-based regimens are associated with more toxicity (eg, neurotoxicity).<sup>252,661</sup> There are no agents for the prevention of peripheral neuropathy, and few agents are useful for treatment.<sup>662</sup> The POINTBREAK trial showed that carboplatin/pemetrexed/bevacizumab is a reasonable option and confirmed that taxane-based regimens are more toxic than pemetrexed-based regimens.<sup>663</sup> The POINTBREAK trial also showed that both regimens are similar in regard to overall survival rates; therefore, oncologists may return to using taxane-based regimens, which are well established. A retrospective cohort study suggests that the addition of bevacizumab (to carboplatin/paclitaxel) does not increase survival in older patients ( $\geq 65$  years) with advanced nonsquamous NSCLC.<sup>664</sup> However, another retrospective cohort study reported increased survival in older patients.<sup>665</sup> A combined analysis of the ECOG 4599 and POINTBREAK trials found a survival benefit with the addition of bevacizumab (to carboplatin/paclitaxel) in patients younger than 75 years but no benefit in those older than 75 years.<sup>666</sup>

For patients with advanced NSCLC who have a PS of 2, platinum-based combinations and a few single-agent chemotherapy agents are recommended in the NCCN Guidelines; cisplatin-based regimens are not recommended in this setting.<sup>667</sup> For nonsquamous NSCLC or NSCLC NOS, single-agent chemotherapy includes gemcitabine, pemetrexed, or taxanes; combination chemotherapy regimens include carboplatin/paclitaxel or carboplatin/pemetrexed.<sup>668-670</sup> Patients with a PS of 2 are often just treated with single-agent chemotherapy because of concerns about toxicity.<sup>671</sup> Results from a trial reported that treatment with carboplatin/pemetrexed increased median overall survival when compared with pemetrexed alone (9.3 vs. 5.3 months,  $P = .001$ ) in patients with a PS of 2; however, 4 treatment-related deaths occurred in the carboplatin/pemetrexed arm.<sup>668,672</sup> The NCCN NSCLC Panel recently

deleted etoposide, irinotecan, and vinorelbine from the list of recommended single-agent chemotherapy for patients with all histologies because these agents are rarely used in the United States.

Phase 3 randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.<sup>673,674</sup> The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients.<sup>658,675-677</sup> Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;<sup>653,678-680</sup> non-platinum-based regimens such as gemcitabine/vinorelbine and gemcitabine/docetaxel are also options.<sup>681-684</sup> In spite of the development of new chemotherapy regimens, the prognosis for advanced inoperable lung cancer remains poor.

Note that albumin-bound paclitaxel (also known as nab-paclitaxel) can be substituted for paclitaxel or docetaxel for patients: 1) who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication; or 2) in whom premedications (ie, dexamethasone, H2 blockers, H1 blockers) to prevent hypersensitivity are contraindicated.<sup>685,686</sup> A phase 3 randomized trial reported that an albumin-bound paclitaxel/carboplatin regimen is associated with less neurotoxicity and improved response rate, when compared with the control arm of paclitaxel/carboplatin, in patients with advanced NSCLC.<sup>687</sup> The FDA has approved albumin-bound paclitaxel/carboplatin for patients with locally advanced or metastatic NSCLC who are not candidates for curative surgery or RT. Based on the trial and the FDA approval, the NCCN NSCLC Panel recommends an albumin-bound paclitaxel/carboplatin regimen as initial cytotoxic therapy for patients with advanced NSCLC and good PS.

### Targeted Therapies

Specific targeted therapies are available for the treatment of advanced NSCLC.<sup>146,688,689</sup> Afatinib, alectinib, brigatinib, ceritinib, crizotinib, erlotinib, gefitinib, osimertinib, dacomitinib, dabrafenib, and trametinib are oral TKIs. Bevacizumab and ramucirumab are recombinant monoclonal antibodies that target vascular endothelial growth factor (VEGF) or VEGF receptor, respectively. Cetuximab is a monoclonal antibody that targets EGFR. Erlotinib, gefitinib, afatinib, and dacomitinib inhibit *EGFR* sensitizing mutations; osimertinib inhibits both *EGFR* sensitizing mutations and T790M. Crizotinib inhibits *ALK* rearrangements, *ROS1* rearrangements, and *MET* (ie, high-level *MET* amplification, *MET*<sub>ex14</sub> mutation). Ceritinib inhibits *ALK* rearrangements and IGF-1 receptor. Alectinib inhibits *ALK* and *RET* rearrangements. Brigatinib inhibits various *ALK* rearrangements and other targets.<sup>690</sup> Dabrafenib/trametinib inhibits *BRAF* V600E mutations; trametinib also inhibits MEK; both agents inhibit different kinases in the RAS/RAF/MEK/ERK pathway.<sup>154,155</sup> Other targeted therapies are being developed (see *Emerging Biomarkers to Identify Novel Therapies for Patients With Metastatic NSCLC* in the NCCN Guidelines for NSCLC).

#### VEGF or VEGF Receptor Inhibitors

##### Bevacizumab

Bevacizumab is a recombinant monoclonal antibody that targets VEGF. In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC.<sup>691</sup> The ECOG recommends bevacizumab in combination with paclitaxel/carboplatin for select patients with advanced nonsquamous NSCLC based on the results of phase 2 to 3 clinical trials (ECOG 4599).<sup>251</sup> To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: 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. Bevacizumab in combination with chemotherapy (ie, carboplatin/paclitaxel, carboplatin/pemetrexed, cisplatin/pemetrexed) is a recommended option for patients with a PS 0 to 1, nonsquamous NSCLC or NSCLC NOS, negative or unknown test results for *ALK* rearrangements or sensitizing *EGFR* mutations, PD-L1 expression less than 1% or unknown, and contraindications to immunotherapy (see *Sensitizing EGFR Mutation Positive/First-Line Therapy* or *ALK Positive/First-Line Therapy* in the NCCN Guidelines for NSCLC).

Bevacizumab in combination with a PD-L1 inhibitor plus chemotherapy (eg, atezolizumab/carboplatin/paclitaxel/bevacizumab) is a recommended option (category 1) regardless of PD-L1 expression for patients with PS 0 to 1, nonsquamous NSCLC or NSCLC NOS, negative or unknown test results for *ALK* rearrangements or sensitizing *EGFR* mutations, and no contraindications to immunotherapy or bevacizumab. However, bevacizumab is not recommended for patients with squamous cell NSCLC. For the 2019 update (Version 6), the NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the systemic therapy regimens containing bevacizumab (eg, carboplatin/paclitaxel/bevacizumab) that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.<sup>289-293</sup>

##### Ramucirumab

Ramucirumab is a recombinant monoclonal antibody that targets VEGF receptor. A phase 3 randomized trial (REVEL) assessed ramucirumab/docetaxel versus docetaxel alone in patients with metastatic NSCLC that had progressed.<sup>692</sup> The median overall survival was reported to be slightly increased with ramucirumab/docetaxel versus docetaxel alone (10.5 vs. 9.1 months; HR, 0.86, 95% CI, 0.75–0.98; *P* < .023). Ramucirumab in combination with docetaxel is approved by the FDA for patients with metastatic NSCLC with disease progression on or after



platinum-based chemotherapy.<sup>693</sup> The NCCN NSCLC Panel added ramucirumab/docetaxel (category 2A) as an option for subsequent therapy for metastatic NSCLC that has progressed after first-line chemotherapy based on the phase 3 randomized trial and the FDA approval.<sup>692,693</sup> Some panel members feel that the data are statistically significant but not clinically relevant. More than 70% of patients had grade 3 or higher adverse events in both groups (79% for ramucirumab/docetaxel vs. 71% for docetaxel alone). Adverse events of special concern with ramucirumab/docetaxel therapy include risk for severe hemorrhage, grade 3 to 4 gastrointestinal bleeding, gastrointestinal perforation or fistula, impaired wound healing, and poorly controlled hypertension. There were 16 deaths from grade 3 or worse pulmonary hemorrhage and other adverse events in the REVEL trial: 8 deaths in the ramucirumab/docetaxel arm and 8 deaths in the docetaxel alone arm.

### Oral TKIs

#### Erlotinib and Gefitinib

Erlotinib and gefitinib are oral TKIs that inhibit sensitizing *EGFR* mutations. In a phase 3 randomized trial (IPASS), patients with sensitizing *EGFR* mutations who received gefitinib had increased PFS (24.9% vs. 6.7%), response rate (71.2% vs. 47.3%), and quality of life with fewer side effects (eg, neutropenia) when compared with those receiving chemotherapy (carboplatin/paclitaxel).<sup>207</sup> Updated results from the IPASS study showed that overall survival was similar in patients receiving gefitinib or chemotherapy regardless of sensitizing *EGFR* mutation status.<sup>694</sup> These results probably occurred because patients who had been assigned to first-line chemotherapy were able to receive TKIs as subsequent therapy if they were found to have sensitizing *EGFR* mutations. A phase 3 randomized trial (EURTAC) in European patients with metastatic NSCLC and sensitizing *EGFR* mutations showed increased PFS and response rate for those receiving erlotinib when compared with chemotherapy.<sup>206</sup>

For erlotinib, the median PFS was 9.7 months (95% CI, 8.4–12.3) compared with 5.2 months (95% CI, 4.5–5.8) for chemotherapy (HR, 0.37; 95% CI, 0.25–0.54;  $P < .0001$ ). Fewer patients receiving erlotinib had severe adverse events or died when compared with those receiving chemotherapy. The FDA has approved the use of erlotinib as first-line therapy in patients with sensitizing *EGFR* mutations.<sup>695</sup> Previously, erlotinib was commonly used in the United States in patients with sensitizing *EGFR* mutations because of restrictions on the use of gefitinib. However, gefitinib was re-approved by the FDA based on a phase 4 study and is available in the United States.<sup>145,696</sup> The NCCN NSCLC Panel recommends erlotinib and gefitinib (category 1) as first-line therapy in patients with advanced, recurrent, or metastatic nonsquamous NSCLC who have known active sensitizing *EGFR* mutations (regardless of their PS) based on these trials and FDA approvals (see *Sensitizing EGFR Mutation Positive* in the NCCN Guidelines for NSCLC).<sup>93,207,697,698</sup>

*EGFR* TKIs are recommended in patients with metastatic NSCLC and sensitizing *EGFR* mutations, because quality of life is improved when compared with chemotherapy. Erlotinib and gefitinib are orally active TKIs that are very well tolerated by most patients.<sup>699,700</sup> An analysis of 5 clinical trials in patients, mainly from the Western hemisphere, (n = 223) with advanced NSCLC (stage IIIB or IV) found that those with sensitizing *EGFR* mutations who received TKIs had a 67% response rate and an overall survival of about 24 months.<sup>701</sup> The TORCH trial suggested that *EGFR* mutation testing should be done in patients with advanced nonsquamous NSCLC.<sup>702</sup> Survival was increased in patients with wild-type *EGFR* who received first-line chemotherapy compared with those who received erlotinib first followed by subsequent chemotherapy (11.6 vs. 8.7 months). The OPTIMAL trial reported that PFS was increased in patients with sensitizing *EGFR* mutations who received erlotinib.<sup>227,228</sup> ASCO recommends that patients be tested for *EGFR* mutations.<sup>703</sup> The ESMO Guidelines specify that only patients with nonsquamous NSCLC (eg,

adenocarcinoma) be assessed for *EGFR* mutations.<sup>147,667</sup> Patients with pure squamous cell carcinoma are unlikely to have sensitizing *EGFR* mutations; those with adenosquamous carcinoma may have mutations.<sup>149</sup>

An updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel as first-line therapy in patients (mainly Caucasian) with advanced NSCLC.<sup>704</sup> The data showed that erlotinib alone was associated with fewer side effects in patients with sensitizing *EGFR* mutations when compared with erlotinib/chemotherapy. Thus, it is appropriate to interrupt or complete planned chemotherapy and switch to *EGFR* TKI therapy in patients found to have sensitizing *EGFR* mutations during chemotherapy (see *EGFR Mutation Positive/First-Line Therapy* in the NCCN Guidelines for NSCLC).<sup>705</sup> The NCCN Guidelines do not recommend adding *EGFR* TKIs to current chemotherapy based on this CALGB study.<sup>704</sup> *EGFR* TKIs may be continued in patients who have progressed if patients do not have multiple systemic symptomatic lesions (see *Continuation of Targeted Therapy After Progression on Initial Therapy* in this Discussion).

A phase 3 trial (WJOG 5108L) assessed gefitinib versus erlotinib for patients with advanced lung cancer who had been previously treated with chemotherapy; most patients (72%) were positive for *EGFR* mutations.<sup>706</sup> The median PFS for gefitinib versus erlotinib was 8.3 and 10.0 months, respectively, in patients positive for *EGFR* mutations (HR, 1.093; 95% CI, 0.879–1.358;  $P = .424$ ). The main grade 3 or 4 toxicities included rash (gefitinib: 2.2% vs. erlotinib: 18.1%) and increases in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels (gefitinib: 6.1%/13.0% vs. erlotinib: 2.2%/3.3%).

### Afatinib

Afatinib is a second-generation oral TKI that irreversibly inhibits the ErbB/HER family of receptors including *EGFR* and ERBB2.<sup>707,708</sup> A randomized phase 3 trial reported that first-line therapy with afatinib

improved PFS when compared with cisplatin/pemetrexed in patients with metastatic adenocarcinoma who have sensitizing *EGFR* mutations (11.1 vs. 6.9 months,  $P = .001$ ).<sup>224</sup> The FDA has approved afatinib for first-line treatment of patients with metastatic NSCLC who have sensitizing *EGFR* mutations.<sup>709,710</sup> Based on this phase 3 randomized trial and the FDA approval, the NCCN NSCLC Panel recommends afatinib for first-line therapy (category 1) in patients with metastatic nonsquamous NSCLC who have sensitizing *EGFR* mutations (see the NCCN Guidelines for NSCLC).<sup>224,249,707</sup> Afatinib may also be continued in patients who have progressed if patients do not have multiple systemic symptomatic lesions (see *Continuation of Targeted Therapy After Progression on Initial Therapy* in this Discussion).<sup>189</sup> However, afatinib is not recommended as subsequent therapy based on a phase 3 randomized trial [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion].<sup>711</sup>

A phase 2B trial assessed afatinib compared with gefitinib for first-line therapy in patients with metastatic adenocarcinoma and sensitizing *EGFR* mutations.<sup>712</sup> The PFS was essentially the same in patients receiving afatinib when compared with those receiving gefitinib (median PFS, 11.0 months [95% CI, 10.6–12.9] with afatinib vs. 10.9 months [9.1–11.5] with gefitinib; HR, 0.73 [95% CI, 0.57–0.95];  $P = .017$ ). These slight PFS differences are not clinically relevant and the NCCN Guidelines do not state that one *EGFR* TKI is more efficacious than another (see the NCCN Guidelines With Evidence Blocks™ for NSCLC, available at [www.NCCN.org](http://www.NCCN.org)).<sup>706</sup> Overall survival data are not yet available. Patients receiving afatinib had more serious treatment-related side effects when compared with those receiving gefitinib (11% [17/160] for afatinib vs. 4% [7/159] for gefitinib). One patient receiving gefitinib died from treatment-related hepatic and renal failure; other deaths were not considered to be related to treatment (9% vs. 6% [15/160 vs. 10/159]). More patients receiving afatinib had diarrhea (13% vs. 1%), whereas more

patients receiving gefitinib had elevations in liver enzyme levels (0% vs. 9%). Afatinib is rated as slightly less safe than erlotinib or gefitinib (ie, a rating of 3 for afatinib vs. 4 for erlotinib and gefitinib) (see the NCCN Guidelines With Evidence Blocks™ for NSCLC, available at [www.NCCN.org](http://www.NCCN.org)).

### Osimertinib

Osimertinib (AZD9291) is an oral TKI that inhibits both *EGFR* sensitizing mutations and T790M. *EGFR* T790M is a mutation associated with acquired resistance to first-line therapy with EGFR TKI therapy and has been reported in about 60% of patients with disease progression after initial response to sensitizing EGFR TKI therapy.<sup>185,198-204</sup> Most patients with sensitizing *EGFR* mutations and metastatic NSCLC typically progress after about 9.7 to 13 months of therapy with erlotinib, gefitinib, or afatinib.<sup>199,206-208</sup> Data show that patients receiving osimertinib as first-line therapy have PFS of about 19 months.<sup>713,714</sup>

#### First-Line Therapy

A recent phase 3 trial (FLAURA) assessed first-line therapy with osimertinib compared with either erlotinib or gefitinib in patients with advanced or metastatic NSCLC and *EGFR* mutations regardless of T790M status.<sup>713-715</sup> Data show that osimertinib improved PFS (18.9 months [95% CI, 15.2–21.4]) when compared with either erlotinib or gefitinib (10.2 months [95% CI, 9.6–11.1]; HR, 0.46; 95% CI, 0.37–0.57;  $P < .001$ ). The median duration of response was longer with osimertinib when compared with erlotinib or gefitinib (median, 17.2 vs. 8.5 months). Only 6% (17/279) of patients receiving osimertinib had CNS progression events when compared with 15% (42/277) of those receiving erlotinib or gefitinib. Grade 3 or higher adverse events were reported in 34% (94/279) of patients receiving osimertinib and 45% (124/277) of patients receiving erlotinib or gefitinib.

The NCCN NSCLC Panel recommends (category 1) osimertinib as a preferred first-line therapy option for patients with advanced or metastatic NSCLC who have sensitizing *EGFR* mutations based on the phase 3 trial.<sup>713</sup> For the 2019 update (Version 1), the panel voted that osimertinib is the preferred EGFR TKI in this setting based on clinical trial data.<sup>713</sup> For patients with sensitizing *EGFR* mutations who progress during or after first-line therapy with osimertinib, recommended subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes: 1) considering local therapy; 2) continuing osimertinib; or 3) a first-line systemic therapy regimen for either nonsquamous or squamous cell NSCLC (such as cisplatin/pemetrexed or cisplatin/gemcitabine, respectively). There are no data to support using erlotinib, gefitinib, afatinib, or dacomitinib after progression on first-line therapy with osimertinib.

#### Subsequent Therapy

A recent phase 3 randomized trial assessed osimertinib versus platinum-pemetrexed chemotherapy in patients with *EGFR* T790M-positive metastatic NSCLC who had progressed on first-line erlotinib, gefitinib, or afatinib. Data show that PFS was increased with osimertinib when compared with chemotherapy (10.1 vs. 4.4 months; HR, 0.30; 95% CI, 0.23–0.41;  $P < .001$ ).<sup>208</sup> PFS was also increased in patients with CNS metastases who received osimertinib (8.5 vs. 4.2 months; HR, 0.32; 95% CI, 0.21–0.49). In addition, the objective response rate was improved with osimertinib (71%; 95% CI, 65%–76%) when compared with chemotherapy (31%; 95% CI, 24%–40%) (odds ratio for objective response, 5.39; 95% CI, 3.47–8.48;  $P < .001$ ). The disease control rate is about 93% with osimertinib (95% CI, 90%–96%) and about 74% with chemotherapy (95% CI, 66%–81%). Patients receiving osimertinib had fewer grade 3 or higher adverse events when compared with those receiving chemotherapy (23% vs. 47% [63/279 vs. 64/136]). There were 4

fatal events with osimertinib (respiratory failure [2], pneumonitis, ischemic stroke) and one with chemotherapy (hypovolemic shock).

The FDA has approved osimertinib for patients with metastatic *EGFR* T790M-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after first-line therapy with erlotinib, gefitinib, or afatinib. Based on a phase 3 randomized trial and FDA approval, the NCCN NSCLC Panel recommends osimertinib (category 1) as subsequent therapy for patients with metastatic *EGFR* T790M-positive NSCLC who have progressed on erlotinib, gefitinib, or afatinib [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion].<sup>208</sup> T790M can be assessed using an FDA-approved test or other validated laboratory test done in a CLIA-approved laboratory. Data suggest that plasma genotyping (also known as plasma testing or liquid biopsy) may be considered at progression instead of tissue biopsy to detect whether patients have T790M; however, if plasma testing is negative, then tissue biopsy is recommended.<sup>716-718</sup> The NCCN NSCLC Panel also recommends osimertinib (category 1) for patients with T790M who have progression with symptomatic brain metastases based on data showing an improvement.<sup>208,719-722</sup>

Several studies suggest that pulse erlotinib is beneficial for patients with *EGFR* mutations who have progressive leptomeningeal disease.<sup>723-725</sup> In one study of high-dose erlotinib, neurologic symptoms and PS improved in 50% (6/12) and 33% (4/12) of patients, respectively; median survival was 6.2 months (95% CI, 2.5–8.5).<sup>725</sup> Preliminary data from a recent study (BLOOM) suggest that osimertinib is beneficial for patients with *EGFR* mutations (regardless of T790M status) who have progressive leptomeningeal disease.<sup>726</sup> In this study (n = 32), 23 patients receiving osimertinib (160 mg once daily) had brain imaging assessment; 10 had radiologic improvement and 13 had stable disease. At a 12-week neurologic assessment, 88% (7/8) of symptomatic patients improved and

one had stable disease. Of 15 asymptomatic patients, 87% (13/15) remained asymptomatic.<sup>726</sup> Based on these studies, the NCCN NSCLC Panel feels that osimertinib (regardless of T790M status) or pulse erlotinib can be considered for patients with *EGFR* mutations who have progressive leptomeningeal disease. Data also suggest that afatinib may be beneficial in patients with *EGFR* mutations who have progressive leptomeningeal disease.<sup>727,728</sup>

### Dacomitinib

Like afatinib, dacomitinib is a second-generation oral TKI that irreversibly inhibits ErbB/HER receptors including *EGFR*, *HER1*, *HER2*, and *HER4*. A recent phase 3 randomized trial (ARCHER 1050) compared dacomitinib versus gefitinib as first-line therapy for patients with sensitizing *EGFR*-positive metastatic NSCLC.<sup>729</sup> Patients with brain metastases were not eligible for enrollment. PFS was increased in patients receiving dacomitinib (14.7 months [95% CI, 11.1–16.6]) compared with those receiving gefitinib (9.2 months [95% CI, 9.1–11.0]). Serious adverse events related to treatment were reported in 21 (9%) patients given dacomitinib and in 10 (4%) patients given gefitinib. Treatment-related deaths included 2 patients in the dacomitinib group (one related to untreated diarrhea and one to untreated cholelithiasis/liver disease) and one patient in the gefitinib group (related to sigmoid colon diverticulitis/rupture complicated by pneumonia). For the 2019 update (Version 1), the NCCN NSCLC Panel voted to recommend dacomitinib (category 1) as a first-line treatment option for patients with sensitizing *EGFR*-positive metastatic NSCLC based on these clinical trial data and the FDA approval.

### Crizotinib

Crizotinib inhibits *ALK* rearrangements, *ROS1* rearrangements, and some *MET* tyrosine kinases (high-level *MET* amplification or *MET*<sub>ex14</sub> mutation); it is approved by the FDA for patients with metastatic NSCLC who have *ALK* gene rearrangements (ie, *ALK*-positive disease) or *ROS1*

rearrangements.<sup>138,730-736</sup> The NCCN NSCLC Panel recommends 4 agents for patients with ALK-positive disease—alectinib, crizotinib, brigatinib, and ceritinib—and all are category 1 based on phase 3 randomized trials and FDA approvals (see the *Alectinib* and *Ceritinib* and *ALK Rearrangements* in this Discussion and the NCCN Guidelines for NSCLC). The NCCN NSCLC Panel voted that alectinib (category 1) is the preferred agent for first-line therapy for patients with metastatic NSCLC who are positive for *ALK* gene rearrangements (see *Alectinib* in this Discussion). The NCCN NSCLC Panel recommends 2 agents for patients with *ROS1* rearrangements—crizotinib (preferred) and ceritinib—based on trial data and FDA approvals (see *Ceritinib* in this Discussion).

### *ALK Rearrangements*

Crizotinib yields very high response rates (>60%) when used in patients with advanced NSCLC who have *ALK* rearrangements, including those with brain metastases.<sup>95,248,732,737,738</sup> Patients whose disease responds to crizotinib may have rapid improvement in symptoms; median time to progression on crizotinib is about 7 months to 1 year.<sup>739,740</sup> Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in renal function).<sup>248,741,742</sup> However, some patients have had pneumonitis; crizotinib should be discontinued in these patients.<sup>734</sup> Patients who do not tolerate crizotinib may be switched to alectinib, ceritinib, or brigatinib (if not previously given) unless an adverse side effect requiring discontinuation has occurred (eg, pneumonitis). Randomized phase 3 trials have compared crizotinib with first-line therapy (PROFILE 1014) and with subsequent chemotherapy (PROFILE 1007).<sup>7,732,743</sup> First-line therapy with crizotinib improved PFS, response rate (74% vs. 45%;  $P < .001$ ), lung cancer symptoms, and quality of life when compared with chemotherapy (pemetrexed with either cisplatin or carboplatin).<sup>732</sup>

The NCCN NSCLC Panel recommends first-line therapy with crizotinib (category 1) based on this phase 3 trial and the FDA approval. Crizotinib

may also be continued for patients with *ALK* rearrangements who have progressed, depending on the type of progression.<sup>733</sup> For the 2019 update (Version 1), the NCCN NSCLC Panel deleted the option to continue crizotinib for patients with brain metastases who had progressed after first-line therapy with crizotinib; the other ALK inhibitors are recommended options in this setting because they have better CNS response rates (ie, ceritinib, alectinib, brigatinib).<sup>744-747</sup> The NCCN NSCLC Panel also deleted the recommendation to consider switching ALK inhibitors before considering whole brain RT for patients with *ALK* rearrangements and brain metastases in the 2019 update (Version 1). Subsequent therapy with crizotinib improved PFS (7.7 vs. 3.0 months;  $P < .001$ ) and response rate (65% vs. 20%;  $P < .001$ ) when compared with single-agent therapy (either docetaxel or pemetrexed) in patients with *ALK*-positive NSCLC who had progressed after first-line chemotherapy.<sup>733</sup> Based on this trial, crizotinib is recommended as subsequent therapy in patients with *ALK*-positive disease.

### *ROS1 Rearrangements*

Crizotinib is also very effective for patients with *ROS1* rearrangements with response rates of about 70% to 80% including complete responses (see other section on *ROS1 Rearrangements* in this Discussion).<sup>138,139,257,258</sup> A phase 2 trial assessed crizotinib in 127 East Asian patients with *ROS1*-positive advanced NSCLC who had received 3 or fewer lines of therapy. The overall response rate was 72% (95% CI, 63%–79%) with 17 complete responses; the median duration of response was 19.7 months (95% CI, 14.1–not reached). The median PFS was 15.9 months (95% CI, 12.9–24.0).<sup>257</sup> In 50 patients with advanced NSCLC who were positive for *ROS1* rearrangements, crizotinib yielded an objective response rate of 72% (95% CI, 58%–84%); there were 3 complete responses and 33 partial responses.<sup>139</sup> The median duration of response was 17.6 months (95% CI, 14.5–not reached), and the median PFS was 19.2 months (95% CI, 14.4–not reached). The safety profile of crizotinib

was similar to the safety seen in patients with ALK-rearranged NSCLC. A retrospective European study in patients (n = 30 evaluable) with stage IV NSCLC and *ROS1* rearrangements also assessed crizotinib.<sup>138</sup> There were 5 complete responses (overall response rate, 80%; disease control rate, 86.7%). The median PFS was 9.1 months. Many patients (n = 26) received pemetrexed (either alone or in combination with platinum and either before or after crizotinib) and had a response rate of 57.7% and a median PFS of 7.2 months.

The NCCN NSCLC Panel recommends *ROS1* testing based on data showing the efficacy of crizotinib for patients with *ROS1* rearrangements and on the FDA approval (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).<sup>138,139,258</sup> The NCCN NSCLC Panel voted that crizotinib and entrectinib are the preferred agents for first-line therapy in patients with *ROS1* rearrangements, when compared with ceritinib, because they are better tolerated, have been assessed in more patients, and are approved by the FDA (see *Ceritinib* and *Entrectinib* in this Discussion). Lorlatinib is recommended in patients with *ROS1* positive metastatic NSCLC whose disease becomes resistant to crizotinib, ceritinib, or entrectinib.

### Ceritinib

Ceritinib is an oral TKI that inhibits *ALK* and *ROS1* rearrangements.<sup>748</sup>

#### *ALK* Rearrangements

A recent phase 3 trial assessed ceritinib versus platinum-based chemotherapy as first-line therapy for patients with *ALK*-positive metastatic NSCLC.<sup>749</sup> PFS was improved when using ceritinib when compared with platinum-based chemotherapy; the median PFS was 16.6 months (95% CI, 12.6–27.2) for ceritinib and 8.1 months (95% CI, 5.8–11.1) for chemotherapy (HR, 0.55 [95% CI, 0.42–0.73]; *P* < .00001). For ceritinib, common adverse events included diarrhea (85% [160/189] of

patients), nausea (69% [130/189]), vomiting (66% [125/189]), and an increase in ALT (60% [114/189]). For chemotherapy, common adverse events included nausea (55% [97/175 patients]), vomiting (36% [63/175]), and anemia (35% [62/175]). The NCCN NSCLC Panel recommends (category 1) ceritinib as first-line therapy for patients with *ALK*-positive metastatic NSCLC based on this phase 3 trial and FDA approval. However, the NCCN NSCLC Panel voted that alectinib (category 1) is the preferred agent for first-line therapy for patients with metastatic NSCLC who are positive for *ALK* gene rearrangements (see *Alectinib* in this Discussion).

Ceritinib is approved by the FDA for patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.<sup>750</sup> The approval is based on an expanded phase 1 study (ASCEND-1) showing overall response rates of 56% to ceritinib in patients (92/163) who had previously received crizotinib; the median duration of response was 8.3 months (6.8–9.7).<sup>751,752</sup> Common grade 3 to 4 adverse events included increased ALT (73 [30%] patients) and increased AST (25 [10%]).<sup>751</sup> Some patients with CNS lesions responded to ceritinib. Based on the study and the FDA approval, the NCCN NSCLC Panel recommends ceritinib as subsequent therapy for patients with *ALK*-positive NSCLC who have progressed after crizotinib. Patients who do not tolerate crizotinib may be switched to alectinib, ceritinib, or brigatinib, if not previously given.

A recent phase 3 trial (ASCEND-5) assessed subsequent therapy with ceritinib versus chemotherapy (with pemetrexed or docetaxel) in patients with advanced *ALK*-positive NSCLC who had previously received at least 2 or more treatments (including chemotherapy and crizotinib) and had progressed.<sup>746</sup> Patients receiving ceritinib had a significant improvement in median PFS when compared with chemotherapy (5.4 months [95% CI, 4.1–6.9] for ceritinib vs. 1.6 months [1.4–2.8] for chemotherapy; HR, 0.49 [0.36–0.67]; *P* < .0001). Serious adverse events were reported in 43%

(49/115) of patients receiving ceritinib versus 32% (36/113) of those receiving chemotherapy. A phase 2 trial (ASCEND-2) assessed ceritinib in patients who had previously received at least 2 or more treatments, had progressed on crizotinib, and had brain metastases.<sup>745</sup> The overall response rate was 38%; the duration of response was 9.7 months (95% CI, 7.1–11.1).<sup>745</sup> The intracranial overall response rate was 45.0% (95% CI, 23.1%–68.5%).

### *ROS1* Rearrangements

A phase 2 trial assessed ceritinib as first-line therapy in patients (n = 28 evaluable) with NSCLC and *ROS1* rearrangements.<sup>748</sup> One complete response and 19 partial responses (overall response rate, 62% [95% CI, 45%–77%]) were reported in patients receiving ceritinib. PFS was 19.3 months (95% CI, 1–37) for crizotinib-naïve patients and 9.3 months (95% CI, 0–22) for all patients. The median overall survival was 24 months (95% CI, 5–43). The NCCN NSCLC Panel recommends ceritinib (category 2A) for patients with *ROS1*-positive advanced NSCLC based on this trial. However, the NCCN NSCLC Panel voted that crizotinib and entrectinib are the preferred agents for first-line therapy for patients with advanced NSCLC and *ROS1* rearrangements because they are better tolerated, have been assessed in more patients, and are approved by the FDA (see *Crizotinib* and *Entrectinib* in this Discussion). Lorlatinib is recommended in patients with *ROS1* positive metastatic NSCLC whose disease becomes resistant to crizotinib, ceritinib, or entrectinib.

### **Alectinib**

Alectinib is an oral TKI that inhibits *ALK* and *RET* rearrangements but not *MET* or *ROS1* rearrangements.

### *First-Line Therapy*

The ALEX phase 3 trial assessed first-line therapy with alectinib versus crizotinib in 303 patients with *ALK*-positive advanced NSCLC including

those with asymptomatic CNS disease.<sup>244</sup> Disease progression or death occurred in fewer patients receiving alectinib (41% [62/152]; median follow-up of 18.6 months) when compared with crizotinib (68% [102/151]; median follow-up of 17.6 months). The HR was 0.47 (95% CI, 0.34–0.65;  $P < .001$ ) for disease progression or death. PFS was significantly increased with alectinib (68.4% [95% CI, 61.0%–75.9%]) versus crizotinib (48.7% [95% CI, 40.4%–56.9%]). The median PFS was not reached for alectinib (95% CI, 17.7–not reached) when compared with crizotinib at 11.1 months (95% CI, 9.1–13.1). Fewer patients receiving alectinib had CNS progression (12% [18/152]) versus crizotinib (45% [68/151]). Response rates were 83% (126/152) in the alectinib group versus 75% (114/151) in the crizotinib group ( $P = .09$ ). Patients receiving alectinib had fewer grade 3 to 5 adverse events when compared with crizotinib (41% [63/152] vs. 50% [75/151], respectively) even though patients received alectinib for a longer duration than crizotinib (median, 17.9 vs. 10.7 months). There were also fewer deaths in the alectinib arm (3.3% [5/152]) versus the crizotinib arm (4.6% [7/151]); 2 treatment-related deaths were reported in the crizotinib arm and none in the alectinib arm.

The J-ALEX phase 3 randomized trial assessed first-line therapy with alectinib versus crizotinib in 207 Japanese patients with *ALK*-positive advanced NSCLC. The data showed that median PFS had not yet been reached with alectinib (95% CI, 20.3 months–not reached) versus 10.2 months (95% CI, 8.2–12.0) with crizotinib (HR, 0.34 [99.7% CI, 0.17–0.71], stratified log-rank  $P < .0001$ ). Grade 3 or 4 adverse events were less frequent with alectinib (26% [27/103]) when compared with crizotinib (52% [54/104]); adverse events did not lead to death in either group. Fewer patients stopped taking alectinib (9%) because of an adverse event when compared with crizotinib (20%).

The NCCN NSCLC Panel recommends alectinib as first-line therapy (category 1) for patients with *ALK*-positive metastatic NSCLC based on

these two randomized phase 3 trials and recent FDA approval.<sup>244,753</sup> Panel members voted that alectinib is the preferred agent for first-line therapy for patients with metastatic NSCLC who are positive for *ALK* gene rearrangements based on these trials. For the 2019 update (Version 1), the NCCN NSCLC Panel recommends that alectinib is also the preferred *ALK* inhibitor when an *ALK* rearrangement is discovered during first-line chemotherapy. Crizotinib, brigatinib, or ceritinib are also recommended (category 1) as first-line therapy options in patients with *ALK*-positive NSCLC (see *Crizotinib* and *Ceritinib* in this Discussion).

### Subsequent Therapy

Alectinib is approved by the FDA for patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.<sup>754</sup> The FDA approval is based on phase 2 trials showing overall response rates of 48% to 50% to alectinib in patients who had previously received crizotinib.<sup>144,755</sup> In the larger trial (138 patients) by Ou et al, patients on alectinib had a

response rate of 50% (95% CI, 41%–59%), and median duration of response of 11.2 months (95% CI, 9.6–not reached).<sup>144</sup> For CNS disease, the control rate was 83% (95% CI, 74%–91%) and the median duration of response was 10.3 months (95% CI, 7.6–11.2). Of 84 patients with baseline CNS metastases, 23 (27%) had a complete CNS response to alectinib. Of 23 patients with baseline CNS metastases and no previous brain RT, 10 (43%) had a complete CNS response to alectinib. Most adverse events were only grade 1 to 2 (constipation, fatigue, and peripheral edema); 4 patients (3%) had grade 3 dyspnea. One death due to intestinal perforation may have been related to alectinib. Based on these trials and the FDA approval, the NCCN NSCLC Panel recommends alectinib as subsequent therapy for patients with *ALK*-positive NSCLC who have progressed after crizotinib; patients who do not tolerate crizotinib may be switched to alectinib, ceritinib, or brigatinib (if not previously given).

### Brigatinib

Brigatinib is an oral TKI that inhibits *ALK* rearrangements.

#### First-Line Therapy

A recent phase 3 trial assessed brigatinib versus crizotinib as first-line therapy for patients with *ALK*-positive metastatic NSCLC.<sup>756</sup> PFS was increased in patients receiving brigatinib (67% [95% CI, 56%–75%]) versus those receiving crizotinib (43% [95% CI, 32%–53%]) (HR for disease progression or death, 0.49 [95% CI, 0.33–0.74];  $P < .001$ ). Intracranial response was also increased with brigatinib (78% [95% CI, 52%–94%]) versus crizotinib (29% [95% CI, 11%–52%]). For the 2019 update (Version 1), the NCCN NSCLC Panel voted to recommend brigatinib (category 1) as a first-line therapy option for patients with *ALK*-positive NSCLC based on this phase 3 trial.

#### Subsequent Therapy

Brigatinib is approved by the FDA for patients with *ALK*-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. The FDA approval is based on data from a phase 2 trial (ALTA) assessing 2 different doses of brigatinib: 90 mg (arm A) or 180 mg (arm B) every day.<sup>250,757</sup> The overall response rates were 45% (97% CI, 34%–56%) and 54% (97% CI, 43%–65%) in arms A and B, respectively. Many patients had brain metastases (71% and 67%, respectively). The intracranial overall response rates were 42% (11/26) and 67% (12/18), respectively, in patients with measureable brain metastases. The median PFS was 9.2 months (95% CI, 7.4–15.6) and 12.9 months (95% CI, 11.1–not reached), respectively. Grade 3 or higher adverse events included hypertension (6% and 6%, respectively) and pneumonia (3% and 5%, respectively). Patients receiving brigatinib should be carefully monitored for respiratory symptoms, especially during the first week of treatment. The NCCN NSCLC Panel recommends brigatinib (category 2A) as subsequent therapy for patients with *ALK*-positive NSCLC who have progressed after



crizotinib based on this trial and the FDA approval.<sup>250,757</sup> Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, or ceritinib (if not previously given). A recent retrospective study (22 patients) assessed brigatinib in patients with alectinib-refractory advanced ALK-positive NSCLC.<sup>758</sup> Objective responses occurred in 17% (3/18) of patients; 50% (9/18) of patients had stable disease.

### Lorlatinib

Lorlatinib is an oral third-generation TKI that targets *ALK* and *ROS1* tyrosine kinases and has good CNS penetration; it inhibits a broad range of *ALK* resistance mutations that develop after treatment with first- and second-generation ALK inhibitors.<sup>245,246</sup>

#### Subsequent Therapy

Data show that lorlatinib is effective in select patients who have progressed after treatment with ALK inhibitors, including those with CNS metastases.<sup>245,246</sup> A phase 2 trial assessed lorlatinib in patients with *ALK*-positive or *ROS1*-positive metastatic NSCLC who had progressed after ALK inhibitor therapy; many patients had asymptomatic CNS metastases.<sup>245</sup> In patients who had received at least one previous ALK inhibitor, objective responses were achieved in 47% of patients (93/198; 95% CI, 39.9%–54.2%); there were 4 complete responses and 89 partial responses. In those with measurable baseline CNS lesions, an objective intracranial response was observed in 63% of patients (51/81; 95% CI, 51.5%–73.4%). Lorlatinib was effective in patients who had received up to 3 previous ALK inhibitors. Grade 3 to 4 adverse events included hypercholesterolemia and hypertriglyceridemia (43/275 [16%] for both). Serious treatment-related adverse events occurred in 7% of patients (19/275) including cognitive effects in 1% (2/275); the cognitive effects resulted in permanent discontinuation of lorlatinib. No treatment-related deaths were reported.

For the 2019 update (Version 2), the NCCN NSCLC Panel recommends lorlatinib (category 2A) as a subsequent therapy option for select patients with *ALK*-positive NSCLC who have progressed after treatment with ALK inhibitors based on clinical trial data and FDA approval. The NCCN NSCLC Panel also recommends subsequent therapy with lorlatinib (category 2A) for select patients with *ROS1*-positive NSCLC who have progressed after treatment with crizotinib, ceritinib, or entrectinib.

### Dabrafenib and Trametinib

Dabrafenib and trametinib inhibit kinases in the RAS/RAF/MEK/ERK pathway.<sup>154,155</sup> Dabrafenib inhibits *BRAF* harboring V600E mutations; trametinib inhibits MEK 1/2, which is downstream of *BRAF* signaling. The combination regimen of dabrafenib/trametinib is approved by the FDA for patients with *BRAF* V600E mutations and metastatic NSCLC.<sup>759</sup>

A phase 2 trial assessed first-line combination therapy with dabrafenib/trametinib for 36 patients with metastatic NSCLC and *BRAF* V600E mutations.<sup>760</sup> The overall response rate was 64% (23/36; 95% CI, 46%–79%); there were 2 complete responses. The median PFS was 10.9 months (95% CI, 7.0–16.6). Many patients (69% [25/36]) had one or more grade 3 or 4 adverse events. Serious adverse events included increased ALT (14% [5/36]), increased AST (8% [3/36]), pyrexia (11% [4/36]), and decreased ejection fraction (8% [3/36]).

A phase 2 study assessed the dabrafenib/trametinib regimen as subsequent therapy in 57 patients with advanced NSCLC and *BRAF* V600E mutations who had progressed on chemotherapy.<sup>154,761</sup> Patients had a response rate of 63% (36/57) with dabrafenib/trametinib; however, considerable toxicity was reported. PFS was 9.7 months (6.9–19.6). Serious adverse events occurred in 56% (32/57) of patients, including pyrexia, anemia, confusional state, hemoptysis, hypercalcemia, and cutaneous squamous cell carcinoma. Grade 3 to 4 adverse events included neutropenia in 9% of patients (5/57), hyponatremia in 7% (4/57),

and anemia in 5% (3/57). Four patients died during the study, but these deaths were not felt to be related to treatment (deaths were due to retroperitoneal hemorrhage, subarachnoid hemorrhage, respiratory distress, or severe disease progression). Preliminary data from an updated analysis of this phase 2 trial reported that patients receiving dabrafenib/trametinib had a median overall survival of 18.2 months (95% CI, 14.3–not reached).<sup>762</sup>

The NCCN NSCLC Panel recommends combination therapy with dabrafenib/trametinib as first-line therapy for patients with metastatic NSCLC and *BRAF* V600E mutations based on these trials and the FDA approval.<sup>759,760,762</sup> Chemotherapy regimens (with or without immunotherapy) are also recommended for patients with *BRAF* V600E mutations; the same initial systemic regimens used for patients with metastatic NSCLC may be used (eg, carboplatin/paclitaxel). Single-agent therapy with dabrafenib or vemurafenib is also an option for patients with *BRAF* V600E mutations who do not tolerate combination therapy with dabrafenib/trametinib.<sup>155,160,762</sup> If patients with *BRAF* V600E mutations have not received dabrafenib/trametinib as first-line therapy and have progressed after first-line therapy chemotherapy regimens (with or without immunotherapy), then the NCCN NSCLC Panel recommends dabrafenib/trametinib as subsequent therapy.

### Larotrectinib

*NTRK* gene fusions encode *TRK* fusion proteins that act as oncogenic drivers for various solid tumors, including lung, salivary gland, thyroid, and sarcoma (see *NTRK Gene Fusions* in this Discussion).<sup>270</sup> Larotrectinib is an oral TKI that inhibits *TRK* fusion proteins across a diverse range of solid tumors in younger and older patients with unresectable or metastatic disease; thus, larotrectinib is referred to as an age- and tumor-agnostic therapy.<sup>270</sup> A study in 55 patients with *NTRK* gene–fusion positive disease across a range of solid tumors showed that larotrectinib yielded an overall

response rate of 75% (95% CI, 61%–85%).<sup>270</sup> A recent update of this study showed that 90% of patients were still alive after 1 year, 18% of patients had a complete response, 69% of patients were still responding, and 58% of patients had not progressed.<sup>271</sup> An additional 35 patients with *NTRK* gene fusion–positive disease had an overall response rate of 74%.<sup>271</sup> Fewer than 3% of patients had adverse events of grade 3 to 4. For the 2019 update (Version 3), the NCCN NSCLC Panel recommends larotrectinib (category 2A) as either a first-line or subsequent therapy option for patients with *NTRK* gene fusion–positive metastatic NSCLC based on these data and the FDA approval.<sup>270</sup>

### Entrectinib

Entrectinib is an oral TKI that inhibits several tyrosine kinases including *ROS1* and *TRK* (see *ROS1* rearrangements and *NTRK Gene Fusions* in this Discussion).<sup>261,763</sup> Entrectinib has been assessed in several phase 1 and 2 trials in patients with *ROS1* positive metastatic NSCLC (phase 2 STARTRK-2 trial, phase 1 STARTRK-1 trial, phase 1 ALKA-372-001 trial).<sup>260,764</sup> Pooled data from these 3 trials in 53 patients with *ROS1* positive metastatic NSCLC receiving first-line entrectinib showed an overall response rate of 77% (95% CI, 64%–88%; 3 complete responses).<sup>260</sup> The intracranial overall response rate was 55% (95% CI, 32%–77%; 4 complete responses, 7 partial responses).<sup>260,764</sup> In the larger *ROS1* population (n = 134), grade 3 adverse events were seen in 31% of patients; grade 4 events occurred in 4% of patients. One adverse event occurred in 93% of all patients. Although entrectinib has better CNS penetration than crizotinib, it is more toxic.

Similar to larotrectinib, entrectinib inhibits *TRK* fusion proteins across a range of solid tumors in young and older patients with unresectable or metastatic disease; thus, entrectinib is also an age- and tumor-agnostic therapy. Entrectinib has been assessed in several phase 1 and 2 trials in patients with *NTRK* gene positive metastatic NSCLC (phase 2

STARTRK-2 trial, phase 1 STARTRK-1 trial, phase 1 ALKA-372-001 trial).<sup>260,764</sup> Grade 3 adverse events with entrectinib were observed in 32.4% of all assessed patients (n = 68) across a range of solid tumors and included anemia, fatigue, diarrhea, peripheral edema, increased blood creatinine, increased weight. Grade 4 adverse events occurred in 3 patients (increased aspartate aminotransferase, increased alanine aminotransferase, blood uric acid, hyperuricemia). Pooled data from these 3 trials in 10 patients with *NTRK* gene–fusion positive NSCLC showed that entrectinib yielded an overall response rate of 70.0% (95% CI, 35%–93%; 7/10: 7/7 adenocarcinoma NSCLC, 0/3 squamous cell carcinoma, unclassified, or undifferentiated NSCLC); there was one complete response.<sup>259</sup> Most patients (70%) with *NTRK* gene–fusion positive NSCLC had received one or more lines of previous therapy. In 6 patients with CNS disease, entrectinib yielded an intracranial response rate of 67% (4/6; 2 complete responses and 2 partial responses).

For the 2019 update (Version 7), the NCCN NSCLC Panel recommends entrectinib as a first-line option for patients with *ROS1* positive metastatic NSCLC (category 2A, preferred) and also recommends entrectinib as either a first-line or subsequent therapy option for *NTRK* gene fusion–positive metastatic NSCLC (category 2A) based on these data and the recent FDA approval.<sup>259-261,764</sup> Subsequent therapy with lorlatinib is also recommended (category 2A) for select patients with *ROS1*-positive metastatic NSCLC who have progressed after treatment with crizotinib, ceritinib, or entrectinib.

### **EGFR Inhibitor**

#### **Cetuximab**

Cetuximab is a monoclonal antibody that targets EGFR. A large phase 3 randomized trial (FLEX) assessed cisplatin/vinorelbine with (or without) cetuximab for patients with advanced NSCLC; most patients had stage IV disease.<sup>765</sup> Adding cetuximab was reported to slightly increase overall

survival (11.3 vs. 10.1 months; HR for death, 0.87 [95% CI, 0.762–0.996];  $P = .044$ ). Patients receiving cetuximab had increased grade 4 events versus control (62% vs. 52%,  $P < .01$ ); cetuximab was also associated with grade 2 acne-like rash.

The cetuximab/cisplatin/vinorelbine regimen is not recommended in the NCCN Guidelines. The benefits of this cetuximab-based regimen are very slight, it is a difficult regimen to administer, and patients have poorer tolerance for this regimen when compared with other regimens; for example, almost 40% of patients have grade 4 neutropenia.<sup>603</sup> Patients may also have comorbid conditions that prevent them from receiving cisplatin such as poor kidney function. Cisplatin/vinorelbine with (or without) cetuximab is generally not used in the United States because of concerns about toxicity.<sup>603,624,765</sup> Some oncologists feel that although the FLEX trial results were reported to be statistically significant, they were not clinically significant.<sup>603</sup> The NCCN NSCLC Panel recently deleted the cisplatin/vinorelbine and carboplatin/vinorelbine regimens from the list of recommended cytotoxic therapy regimens for metastatic NSCLC with all histologies.

#### **Immune Checkpoint Inhibitors**

Human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.<sup>279-281</sup> Immune checkpoint inhibitors are associated with a delay in benefit when compared with targeted therapy or cytotoxic chemotherapy. The single-agent immunotherapy or combination immunotherapy/chemotherapy regimens are not recommended if patients have contraindications to immunotherapy (eg, active or previously documented autoimmune disease, current use of immunosuppressive agents, or presence of an oncogene that would predict lack of benefit). The following briefly summarizes the use of immune checkpoint inhibitors as first-line or subsequent therapy in select

patients with NSCLC; detailed information, including clinical trial data, are provided in the following sections. The immune checkpoint inhibitors nivolumab and pembrolizumab inhibit PD-1 receptors;<sup>282,104</sup> atezolizumab and durvalumab inhibit PD-L1.<sup>283,284</sup> Single-agent pembrolizumab is recommended (category 1 preferred) as first-line therapy for patients with PD-L1 expression levels greater than 50% and with negative or unknown test results for *EGFR* mutations and *ALK* rearrangements. For the 2019 update (Version 4), the NCCN NSCLC Panel added another recommendation for single-agent pembrolizumab as first-line therapy in patients with metastatic NSCLC regardless of histology, PD-L1 levels of 1% to 49% (category 2B), and negative or unknown test results for *EGFR* mutations and *ALK* rearrangements (see *Pembrolizumab* in this Discussion).<sup>286</sup> Combination therapy with pembrolizumab (or atezolizumab/bevacizumab)/chemotherapy is recommended (category 1) as a first-line therapy option for patients with negative or unknown test results for *EGFR* mutations and *ALK* rearrangements, regardless of PD-L1 expression levels. Durvalumab is recommended (category 1) as consolidation immunotherapy by the NCCN NSCLC Panel for patients with unresectable stage III NSCLC who have not progressed after definitive concurrent chemoradiation; appropriate use and clinical trial data for durvalumab are described in greater detail elsewhere (see *Durvalumab* in this Discussion).<sup>283</sup>

Single-agent pembrolizumab is recommended (category 1 preferred) as subsequent therapy for select patients with metastatic NSCLC and PD-L1 levels greater than 1%; nivolumab or atezolizumab is recommended (category 1 preferred) as subsequent monotherapy for select patients with metastatic NSCLC regardless of PD-L1 levels (see *Pembrolizumab*, *Nivolumab*, and *Atezolizumab* in this Discussion). Based on data in the second-line setting, PD-1 or PD-L1 inhibitor monotherapy appears to be less effective in patients with *EGFR* mutations or *ALK* rearrangements regardless of PD-L1 expression levels.<sup>279,282,295-297</sup> Therefore, if patients

have progressed on PD-1/PD-L1 inhibitor therapy (with or without chemotherapy), then switching to another PD-1/PD-L1 inhibitor is not routinely recommended. A small study suggests that single-agent pembrolizumab is not effective as first-line therapy in patients with metastatic NSCLC and *EGFR* mutations, even those with PD-L1 levels more than 50%.<sup>298</sup>

Checkpoint inhibitors are associated with unique immune-mediated adverse events that are not seen with traditional cytotoxic chemotherapy (eg, endocrine disorders); therefore, health care providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage the adverse events, and educate their patients about possible side effects (see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at [www.NCCN.org](http://www.NCCN.org)).<sup>766,767</sup> Nivolumab, pembrolizumab, durvalumab, and atezolizumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information). Pseudoprogression has been reported; therefore, traditional RECIST criteria may not be applicable.<sup>768</sup>

### *Nivolumab*

If patients have not previously received a PD-1/PD-L1 inhibitor, the NCCN NSCLC Panel recommends single-agent nivolumab (category 1 preferred) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC who have progressed on or after first-line chemotherapy based on data from two phase 3 randomized trials (CheckMate-057, CheckMate-017) and FDA approvals.<sup>279,282,769,770</sup> The NCCN NSCLC Panel recommends nivolumab, atezolizumab, or pembrolizumab as preferred agents for subsequent therapy based on improved overall survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy.<sup>279,282,296,771</sup>

For patients with metastatic nonsquamous NSCLC, the category 1 recommendation for subsequent therapy with nivolumab is based on data from a phase 3 randomized trial (CheckMate-057) and FDA approval. For patients receiving nivolumab in the CheckMate-057 trial, median overall survival was 12.2 months compared with 9.4 months for docetaxel (HR, 0.73; 95% CI, 0.59–0.89;  $P = .002$ ).<sup>279</sup> The median duration of response was 17.2 months with nivolumab compared with 5.6 months for docetaxel. At 18 months, the overall survival rate was 39% (95% CI, 34%–45%) with nivolumab compared with 23% (95% CI, 19%–28%) with docetaxel. Fewer grade 3 to 5 adverse events were reported for nivolumab (10%) when compared with docetaxel (54%). Although many patients with metastatic nonsquamous NSCLC benefit from nivolumab, those whose tumors have PD-L1 staining of 1% to 10% or more have an overall survival of 17 to 19 months compared with 8 to 9 months for docetaxel. For patients who did not have PD-L1 expression, there was no difference in overall survival for nivolumab versus docetaxel; however, nivolumab was associated with a longer duration of response and fewer side effects.

To help clinicians determine which patients with nonsquamous NSCLC may benefit most from treatment with nivolumab, the FDA has approved a complementary diagnostic biomarker test to assess for PD-L1 protein expression.<sup>772</sup> Testing for PD-L1 is not required for prescribing nivolumab but may provide useful information.<sup>303</sup> Current or former smoking status correlated with the response rate to immune checkpoint inhibitors.<sup>279</sup> Data suggest that mismatch repair deficiency is associated with response to immune checkpoint inhibitors.<sup>773,774</sup>

The NCCN NSCLC Panel also recommends (category 1) nivolumab as subsequent therapy for patients with metastatic squamous cell NSCLC who have progressed on or after first-line chemotherapy based on data from a phase 3 randomized trial (CheckMate-017), and FDA approval.<sup>282,775</sup> In the CheckMate-017 trial, the median overall survival was 9.2 months

with nivolumab compared with 6.0 months for docetaxel.<sup>282</sup> Patients had a response rate of 20% with nivolumab compared with 9% for docetaxel ( $P = .008$ ). PD-L1 expression was not associated with response to nivolumab in patients with squamous cell NSCLC. There were fewer grade 3 to 4 adverse events with nivolumab (7%) when compared with docetaxel (55%). No patients died in the nivolumab arm versus 3 deaths in the docetaxel arm.

In a recent long-term analysis of both trials (CheckMate-057 and CheckMate-017), 2-year survival and durable responses were improved in patients with advanced NSCLC receiving nivolumab when compared with docetaxel.<sup>769</sup> For patients with nonsquamous NSCLC, 2-year survival was 29% (95% CI, 24%–34%) with nivolumab versus 16% (95% CI, 12%–20%) with docetaxel. For those with squamous NSCLC, 2-year survival was 23% (95% CI, 16%–30%) with nivolumab versus 8% (95% CI, 4%–13%) with docetaxel. Fewer severe treatment-related adverse events were reported with nivolumab compared with docetaxel (grade 3–4, 10% vs. 55%).

Immune-related adverse events, such as pneumonitis, may occur with nivolumab.<sup>281,775-781</sup> Intravenous high-dose corticosteroids should be administered based on the severity of the reaction for patients with immune-mediated adverse events. Nivolumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

A recent phase 3 randomized trial compared first-line nivolumab/ipilimumab, nivolumab monotherapy, and chemotherapy in patients with metastatic nonsquamous or squamous NSCLC who had high TMB levels ( $\geq 10$  mutations/megabase), PS 0 to 1, and no *EGFR* mutations or *ALK* rearrangements.<sup>170</sup> The PFS rate at 1 year was 42.6%

for nivolumab/ipilimumab versus 13.2% for chemotherapy alone. The median PFS for nivolumab/ipilimumab was 7.2 months (95% CI, 5.5–13.2) compared with 5.5 months for chemotherapy alone (95% CI, 4.4–5.8) (HR for disease progression or death, 0.58; 97.5% CI, 0.41–0.81;  $P < .001$ ). The objective response rate for nivolumab/ipilimumab was 45.3% versus 26.9% with chemotherapy alone; nivolumab/ipilimumab was beneficial regardless of PD-L1 expression levels or histology. The rate of grade 3 or 4 adverse events was similar for nivolumab/ipilimumab versus chemotherapy alone (31% vs. 36%). The median PFS was not significantly different when comparing nivolumab monotherapy (N = 71) (4.2 months [95% CI, 2.7–8.3]) versus chemotherapy (N = 79) (5.6 months [95% CI, 4.5–7.0]). An earlier exploratory study assessed nivolumab monotherapy (N = 47) versus chemotherapy (N = 60) in patients with metastatic nonsquamous or squamous NSCLC who had high TMB levels.<sup>171</sup> The median PFS for nivolumab monotherapy was 9.7 months (95% CI, 5.1–not reached) versus 5.8 months (95% CI, 4.2–8.5) for chemotherapy. For the 2019 update (Version 1), the NCCN NSCLC Panel recommends (category 2A) nivolumab with or without ipilimumab for patients with high TMB levels based on these trials.<sup>170,171</sup> TMB is considered to be an emerging biomarker; there is no consensus on how to measure TMB.

### *Pembrolizumab*

#### **First-Line Therapy**

As previously mentioned, human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.<sup>280,281</sup> Pembrolizumab inhibits the PD-1 receptor.<sup>104</sup> Testing for PD-L1 expression levels is required before prescribing pembrolizumab. A phase 3 randomized trial (KEYNOTE-024) compared single-agent pembrolizumab versus platinum-based chemotherapy as first-line therapy

for patients with advanced nonsquamous or squamous NSCLC and PD-L1 expression levels of 50% or more, but without *EGFR* mutations or *ALK* rearrangements.<sup>9,104</sup> The FDA approved single-agent pembrolizumab for first-line therapy based on this trial.<sup>782</sup> At 6 months, the rate of overall survival was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (HR for death, 0.60; 95% CI, 0.41–0.89;  $P = .005$ ). Responses were higher for pembrolizumab than for chemotherapy (44.8% vs. 27.8%).<sup>104</sup> There were fewer severe treatment-related adverse events (grades 3–5) in patients receiving pembrolizumab compared with those receiving chemotherapy (26.6% vs. 53.3%). Another phase 3 randomized trial (KEYNOTE-042) compared single-agent pembrolizumab versus platinum-based chemotherapy as first-line therapy for patients with advanced nonsquamous or squamous NSCLC and PD-L1 expression levels of 1% or more, but without *EGFR* mutations or *ALK* rearrangements.<sup>286</sup> Overall survival appeared to be similar in patients with PD-L1 levels of 1% to 49% who received single-agent pembrolizumab (13.4 months; 95% CI, 10.7–18.2) compared with chemotherapy (12.1 months; 95% CI, 11.0–14.0) in a subgroup analysis. However, overall survival was improved in patients with PD-L1 levels of 50% or more who received single-agent pembrolizumab (20.0 months; 95% CI, 15.4–24.9) compared with chemotherapy (12.2 months (10.4–14.2) (HR, 0.69; 95% CI, 0.56–0.85;  $P = .0003$ ).

The NCCN NSCLC Panel recommends single-agent pembrolizumab (category 1, preferred) as a first-line therapy option for patients with advanced nonsquamous or squamous NSCLC, PD-L1 expression levels of 50% or more, no contraindications to immunotherapy, and negative or unknown tests results for *EGFR* mutations and *ALK* rearrangements based on the phase 3 randomized trial (KEYNOTE-024) and FDA approval. For the 2019 update (Version 1), the panel voted that single-agent pembrolizumab is the preferred first-line therapy when compared with the pembrolizumab (or atezolizumab/bevacizumab) plus

chemotherapy regimens in this setting.<sup>104</sup> For patients who progress on first-line therapy with single-agent pembrolizumab, subsequent therapy with initial cytotoxic systemic therapy regimens (eg, carboplatin/paclitaxel) is recommended by the NCCN NSCLC Panel for the 2019 update (Version 1). For the 2019 update (Version 4), the NCCN NSCLC Panel added a new recommendation (category 2B) for single-agent pembrolizumab as first-line therapy for patients with metastatic NSCLC, PD-L1 expression levels of 1% to 49%, no contraindications to immunotherapy, and negative or unknown tests results for *EGFR* mutations and *ALK* rearrangements based on the phase 3 randomized trial (KEYNOTE-042) and FDA approval.<sup>286</sup> The NCCN NSCLC Panel feels that single-agent pembrolizumab is useful in patients with PD-L1 levels of 1% to 49% who cannot tolerate or refuse platinum-based chemotherapy. Based on clinical trial data, the NCCN NSCLC Panel retained the category 1 preferred recommendation for single-agent pembrolizumab as first-line therapy in patients with metastatic NSCLC, PD-L1 levels of 50% or more, and negative or unknown tests results for *EGFR* mutations and *ALK* rearrangements.<sup>104,286</sup>

The NCCN NSCLC Panel recommends (category 1) IHC testing for PD-L1 expression before first-line treatment in patients with metastatic NSCLC based on the efficacy of pembrolizumab with or without chemotherapy.<sup>285</sup> The FDA has approved a companion diagnostic biomarker test for assessing PD-L1 expression and determining which patients are eligible for pembrolizumab therapy. Although it is not an optimal biomarker, PD-L1 expression is currently the best available biomarker to assess whether patients are candidates for pembrolizumab.<sup>299,300</sup> PD-L1 expression is continuously variable and dynamic; thus, a cutoff value for a positive result is artificial. Patients with PD-L1 expression levels just below and just above 50% will probably have similar responses.<sup>299</sup> Unique anti-PD-L1 IHC assays are being developed for each one of the different immune checkpoint inhibitors currently in clinical trials.<sup>299,303</sup> The definition

of a positive PD-L1 test result varies depending on which biomarker assay is used.<sup>303</sup>

Ideally, PD-L1 expression levels are assessed before first-line therapy in patients with metastatic NSCLC. Every effort needs to be made to establish the genetic alteration status. If the risk of biopsy is high and genetic alteration testing is not feasible and therefore technically unknown, then it is appropriate to test for PD-L1 expression levels. Of note, plasma-based testing can be used to evaluate for *EGFR* mutations and *ALK* rearrangements, although these assays are less sensitive than tissue assays.

The NCCN NSCLC Panel recommends pembrolizumab/carboplatin (or cisplatin)/pemetrexed (category 1, preferred) as a first-line therapy option for patients with metastatic nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or NSCLC NOS based on phase 3 and phase 2 trials (KEYNOTE-189, KEYNOTE-021) and on FDA approval, depending on their PD-L1 expression levels.<sup>287,783</sup> The NCCN NSCLC Panel clarified the recommendations for pembrolizumab/chemotherapy in patients with metastatic nonsquamous NSCLC and PD-L1 expression levels of 1% to 49% for the 2019 update (Version 5); all of the regimens are a *preferred* category 1 recommendation in this setting. Thus, these pembrolizumab/chemotherapy regimens are recommended (category 1) as first-line therapy options for patients with no contraindications to immunotherapy, with negative or unknown test results for *EGFR* mutations and *ALK* rearrangements, regardless of their PD-L1 expression levels; however, they are preferred for those with PD-L1 levels of 50% or less. Maintenance therapy with pembrolizumab/pemetrexed is also a recommended option (category 1). For patients who progress on combination therapy with PD-1/PD-L1 inhibitors/chemotherapy, subsequent therapy with docetaxel (with or without ramucirumab), pemetrexed (nonsquamous only), or gemcitabine

is recommended if not previously given by the NCCN NSCLC Panel for the 2019 update (Version 1).

The NCCN NSCLC Panel recommends pembrolizumab/cisplatin/pemetrexed (category 1) based on a recent phase 3 randomized trial and FDA approval.<sup>287</sup> Most patients received pembrolizumab/carboplatin/pemetrexed (72% [445/616]) in the phase 3 trial, but some received pembrolizumab/cisplatin/pemetrexed (28% [171/616]); patients did not have *EGFR* mutations or *ALK* rearrangements. The estimated rate of overall survival at 1 year was 69.2% (95% CI, 64.1%–73.8%) in patients receiving pembrolizumab-chemotherapy versus 49.4% (95% CI, 42.1%–56.2%) for chemotherapy alone (HR for death, 0.49; 95% CI, 0.38–0.64;  $P < .001$ ) after a median follow-up of 10.5 months. Overall survival was improved regardless of PD-L1 expression levels. For the pembrolizumab-chemotherapy group, median PFS was 8.8 months (95% CI, 7.6–9.2) compared with 4.9 months (95% CI, 4.7–5.5) for chemotherapy alone (HR for disease progression or death, 0.52; 95% CI, 0.43–0.64;  $P < .001$ ). Grade 3 or higher adverse events occurred at a similar rate in both arms (pembrolizumab/chemotherapy, 67.2% vs. chemotherapy, 65.8%). In a phase 2 trial (123 patients), the objective response rate was improved in patients receiving pembrolizumab/carboplatin/pemetrexed (55% [95% CI, 42%–68%]) when compared with those receiving chemotherapy alone (29% [95% CI, 18%–41%];  $P = .0016$ ).<sup>783</sup> Positive PD-L1 expression levels were not required for treatment; however, patients with PD-L1 expression of 50% or more who received pembrolizumab/carboplatin/pemetrexed had higher response rates (80% [16/20]) when compared with chemotherapy alone (35% [6/17]). There were no complete responses. The median PFS was 13 months (95% CI, 8.3–not reached) for those receiving pembrolizumab/carboplatin/pemetrexed versus 8.9 months (95% CI, 4.4–10.3) for those receiving chemotherapy alone. Overall survival rates

were similar in both groups after 10.6 months of follow-up. Treatment-related adverse events of grade 3 or worse were 39% (23/59) in the pembrolizumab/carboplatin/pemetrexed group versus 26% (16/62) in the chemotherapy alone group. Often patients received pembrolizumab maintenance therapy for 24 months. Patients also received pemetrexed maintenance therapy (85% [50/59] vs. 69% [43/62], respectively).

The NCCN NSCLC Panel recommends carboplatin/paclitaxel (or albumin-bound paclitaxel)/pembrolizumab (category 1, preferred) as a first-line therapy option for patients with metastatic squamous cell carcinoma NSCLC based on data from a phase 3 trial (KEYNOTE-407) and FDA approval; 32% of patients received albumin-bound paclitaxel (also known as nab-paclitaxel).<sup>294,784</sup> The NCCN NSCLC Panel clarified the recommendations for carboplatin/paclitaxel (or albumin-bound paclitaxel)/pembrolizumab in patients with metastatic squamous cell carcinoma NSCLC and PD-L1 expression levels of 1% to 49% for the 2019 update (Version 5); all of the regimens are a *preferred* category 1 recommendation in this setting. Thus, carboplatin/paclitaxel (or albumin-bound paclitaxel)/pembrolizumab is recommended (category 1) for patients with negative or unknown tests results for *EGFR* mutations and *ALK* rearrangements, regardless of PD-L1 expression levels; however, they are preferred for those with PD-L1 levels of 50% or less. Pembrolizumab/cisplatin/paclitaxel (or albumin-bound paclitaxel) is a category 2A recommended option for patients with squamous cell carcinoma NSCLC whose PD-L1 levels are less than 50%. Maintenance therapy with pembrolizumab is also a recommended option (category 2A). Patients receiving pembrolizumab/chemotherapy had an overall response rate of 58.4% compared to 35.0% for those receiving chemotherapy alone ( $P = .0004$ ). Only 35% of patients had a PD-L1 tumor proportion score (TPS) less than 1%.



### Subsequent Therapy

If patients have not previously received a PD-1/PD-L1 inhibitor, the NCCN NSCLC Panel recommends single-agent pembrolizumab (category 1, preferred) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC and PD-L1 expression levels of 1% or more based on a randomized phase 2/3 trial (KEYNOTE-010), and FDA approval.<sup>296,785,786</sup> Testing for PD-L1 expression levels is required before prescribing pembrolizumab. The FDA has approved pembrolizumab as subsequent therapy for patients with metastatic NSCLC whose disease has progressed after platinum-based chemotherapy if their tumors express PD-L1.<sup>786</sup> Other immunotherapeutic agents are being investigated.<sup>284,771,787,788</sup>

A randomized phase 2/3 trial (KEYNOTE-010) assessed pembrolizumab in patients with previously treated advanced nonsquamous and squamous NSCLC who were PD-L1 positive ( $\geq 1\%$ ); most patients were current or former smokers.<sup>296</sup> There were 3 arms in this trial: pembrolizumab at 2 mg/kg, pembrolizumab at 10 mg/kg, and docetaxel at 75 mg/m<sup>2</sup> every 3 weeks. The median overall survival was 10.4 months for the lower dose of pembrolizumab, 12.7 months for the higher dose, and 8.5 months for docetaxel. Overall survival was significantly longer for both doses of pembrolizumab versus docetaxel (pembrolizumab 2 mg/kg: HR, 0.71; 95% CI, 0.58–0.88;  $P = .0008$ ) (pembrolizumab 10 mg/kg: HR, 0.61; CI, 0.49–0.75;  $P < .0001$ ). For those patients with at least 50% PD-L1 expression in tumor cells, overall survival was also significantly longer at either dose of pembrolizumab when compared with docetaxel (pembrolizumab 2 mg/kg: 14.9 vs. 8.2 months; HR, 0.54; 95% CI, 0.38–0.77;  $P = .0002$ ) (pembrolizumab 10 mg/kg: 17.3 vs. 8.2 months; HR, 0.50; CI, 0.36–0.70;  $P < .0001$ ). When compared with docetaxel, there were fewer grade 3 to 5 treatment-related adverse events at either dose of pembrolizumab (pembrolizumab 2 mg/kg: 13% [43/339] of patients, pembrolizumab 10 mg/kg: 16% [55/343] of patients; and docetaxel: 35% [109/309] of

patients). A total of 6 treatment-related deaths occurred in patients receiving pembrolizumab (3 at each dose) and 5 treatment-related deaths occurred in the docetaxel arm.

Similar to nivolumab and atezolizumab, immune-mediated adverse events may also occur with pembrolizumab.<sup>776,778,789</sup> For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered based on the severity of the reaction. Pembrolizumab should also be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

### Atezolizumab

#### First-Line Therapy

The NCCN NSCLC Panel recommends atezolizumab/bevacizumab plus chemotherapy (carboplatin/paclitaxel) (category 1) as a first-line therapy option for patients with metastatic nonsquamous NSCLC (including adenocarcinoma) based on a recent phase 3 randomized trial (IMpower150) and FDA approval.<sup>288</sup> This atezolizumab/bevacizumab/chemotherapy regimen is recommended as a first-line therapy option for patients with negative or unknown test results for *EGFR* mutations and *ALK* rearrangements, regardless of PD-L1 expression levels. Maintenance therapy with atezolizumab, bevacizumab, or both is also a recommended option (category 1) (see *Maintenance Therapy* in this Discussion). Median overall survival was 19.2 months (95% CI, 17.0–23.8) in the atezolizumab arm compared with 14.7 months (95% CI, 13.3–16.9) in the control arm of carboplatin/paclitaxel/bevacizumab; the HR for death was 0.78 (95% CI, 0.64–0.96;  $P = .02$ ). PFS was increased in the atezolizumab arm versus chemotherapy/bevacizumab (8.3 vs. 6.8 months; HR, 0.62 [95% CI, 0.52–0.74];  $P < .001$ ). Some patients with *EGFR* mutations or *ALK*

rearrangements (n =108) who had progressed on (or were intolerant of) prior TKI were enrolled in this trial, although most patients (87%) did not have these genetic alterations. In these patients with *EGFR* mutations or *ALK* rearrangements, PFS was also increased compared with chemotherapy alone (9.7 vs. 6.1 months; HR, 0.59 [95% CI, 0.37–0.94]). Therefore, this atezolizumab/bevacizumab plus chemotherapy regimen is an option for patients with *EGFR* mutations or *ALK* rearrangements who have progressed after initial therapy with TKIs. For the 2019 update (Version 6), the NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the systemic therapy regimens containing bevacizumab (eg, atezolizumab/bevacizumab/chemotherapy) that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.<sup>289-293</sup>

### Subsequent Therapy

If patients have not previously received a PD-1/PD-L1 inhibitor, the NCCN NSCLC Panel recommends atezolizumab (category 1 preferred) as subsequent therapy for patients with metastatic nonsquamous or squamous cell NSCLC based on a recent phase 3 trial and FDA approval.<sup>284,295,790</sup> Testing for PD-L1 expression levels is not required for prescribing atezolizumab but may provide useful information. Human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.<sup>280,281</sup> Atezolizumab inhibits PD-L1.<sup>284</sup>

A phase 3 randomized trial (OAK) assessed atezolizumab versus docetaxel alone in patients with metastatic NSCLC who had progressed during or after systemic therapy.<sup>295,790</sup> Most patients were current or former smokers and had received platinum-based chemotherapy; few patients (10%) had *EGFR* mutations and *ALK* rearrangements were not reported.<sup>295,790</sup> Data show that patients with nonsquamous NSCLC who received atezolizumab had improved overall survival when compared

with those receiving docetaxel (15.6 vs. 11.2 months; HR, 0.73 [0.6–0.89]; *P* = .0015). Overall survival was only slightly improved in patients with squamous cell NSCLC receiving atezolizumab versus docetaxel (8.9 vs. 7.7 months; HR, 0.73 [0.54–0.98]; *P* = .038); there were fewer patients in the squamous group when compared with the nonsquamous group (222 vs. 628). There were fewer treatment-related severe adverse events (grades 3–4) for atezolizumab versus docetaxel (15% vs. 43% [90/609 vs. 247/578]).

Similar to nivolumab and pembrolizumab, immune-mediated adverse events may also occur with atezolizumab.<sup>295</sup> For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered based on the severity of the reaction. Atezolizumab should also be permanently discontinued for patients with severe or life-threatening pneumonitis and should be discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

### Maintenance Therapy

Maintenance therapy refers to systemic therapy that may be given for patients with advanced NSCLC after 4 to 6 cycles of first-line chemotherapy.<sup>791</sup> Patients are only candidates for maintenance therapy if their tumors have responded to their previous treatment (ie, tumor response) or have stable disease and their tumors have not progressed. *Continuation maintenance* therapy refers to the use of at least one of the agents that was given in the first-line regimen. *Switch maintenance* therapy refers to the initiation of a different agent that was not included as part of the first-line regimen. Selection of appropriate maintenance therapy depends on several factors (eg, histologic type, presence of mutations or gene rearrangements, PS). Maintenance therapy is an option in the NCCN Guidelines for select patients with tumor response or stable disease and is not recommended for all patients (eg, not recommended for PS 3–4, those

with progression); close observation (category 2A) is also a valid treatment option (see the NCCN Guidelines for NSCLC).<sup>792</sup>

### *Continuation Maintenance Therapy*

For continuation maintenance therapy, select agents (which were initially given in combination with conventional chemotherapy) may be continued until evidence of disease progression or unacceptable toxicity based on the design of the clinical trials that led to their approval. Single-agent bevacizumab (category 1) may be continued beyond 4 to 6 cycles of initial therapy (ie, platinum-doublet chemotherapy given with bevacizumab or atezolizumab/carboplatin/paclitaxel/bevacizumab) in patients with nonsquamous NSCLC.<sup>251,793,794</sup> For the 2019 update (Version 6), the NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the systemic therapy regimens containing bevacizumab (eg, carboplatin/paclitaxel/bevacizumab) that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.<sup>289-293</sup> Single-agent pemetrexed (category 1) may also be given as continuation maintenance therapy in patients with nonsquamous NSCLC if given in the initial regimen.<sup>793,795</sup> A phase 3 randomized trial (PARAMOUNT) found that continuation maintenance therapy with pemetrexed slightly increased PFS when compared with placebo (4.1 vs. 2.8 months).<sup>795</sup> Results show that continuation maintenance therapy with pemetrexed also improves overall survival (13.9 vs. 11.0 months).<sup>796</sup> Based on the trial and the FDA approval, the NCCN NSCLC Panel recommends single-agent pemetrexed as continuation maintenance therapy (category 1) in patients with nonsquamous NSCLC.

Continuation maintenance therapy using bevacizumab/pemetrexed (category 2A) is also an option in patients with nonsquamous NSCLC if initially given as part of a bevacizumab/pemetrexed/platinum regimen. Data from the POINTBREAK study reported a very slight improvement in PFS (6 vs. 5.6 months) when comparing bevacizumab/pemetrexed versus

bevacizumab alone as maintenance therapy; the initial regimens were either bevacizumab/carboplatin/pemetrexed or bevacizumab/carboplatin/paclitaxel.<sup>663</sup> It is important to note that the pemetrexed-based arm was associated with less toxicity (eg, less neurotoxicity, less neutropenia, less hair loss) than the paclitaxel-based arm. When using bevacizumab/pemetrexed versus bevacizumab alone as maintenance therapy, data from the AVAPERL study showed a 3.7-month increase in PFS (7.4 vs. 3.7 months); the initial regimen was bevacizumab/cisplatin/pemetrexed.<sup>797,798</sup>

Continuation maintenance therapy with atezolizumab, bevacizumab, or both is also a recommended option (category 1) in patients with metastatic nonsquamous NSCLC who have received atezolizumab/carboplatin/paclitaxel/bevacizumab.<sup>288</sup> In the clinical trial, patients received maintenance therapy until disease progression or development of toxic side effects that were not manageable. In patients who received maintenance therapy with atezolizumab, bevacizumab, or both, there was a low rate of serious adverse reactions. Likewise, if patients with metastatic nonsquamous NSCLC have received pembrolizumab/carboplatin (or cisplatin)/pemetrexed, then continuation maintenance therapy with pembrolizumab/pemetrexed is also a recommended option (category 1).<sup>287</sup> Patients received maintenance therapy until disease progression or development of toxic side effects that were not manageable.

A phase 3 randomized trial compared using maintenance therapy with either gemcitabine or erlotinib after first-line therapy with cisplatin-gemcitabine. Continuation maintenance therapy with single-agent gemcitabine was reported to increase PFS to a greater extent (3.8 months) than switch maintenance therapy with erlotinib (2.9 months) when compared with observation (1.9 months).<sup>799,800</sup> Another phase 3 randomized trial assessed continuation maintenance therapy with

gemcitabine versus best supportive care after an initial regimen of cisplatin/gemcitabine.<sup>801</sup> The data showed a slight difference in PFS but no difference in overall survival. The NCCN Guidelines recommend using gemcitabine (category 2B) as continuation maintenance therapy regardless of histology in patients without *ALK* rearrangements, sensitizing *EGFR* mutations, or PD-L1 expression. 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.<sup>661</sup> Some clinicians feel that continuation maintenance therapy is only appropriate for select patients, because it has only been shown to improve overall survival or quality of life for a few agents and not all agents, although it has been shown to improve PFS.<sup>661,802</sup> In addition, maintenance therapy has not been shown to be superior to subsequent therapy, which is initiated at disease progression. A phase 3 randomized trial suggests that conventional cytotoxic agents should not be continued beyond 4 to 6 cycles of therapy; however, many patients assigned to a longer duration of therapy did not receive the planned number of cycles (see *Maintenance Therapy* in this Discussion).<sup>802,803</sup>

### *Switch Maintenance Therapy*

Issues have been raised about switch maintenance therapy, including the design of the trials, modest survival benefits, quality of life, and toxicity.<sup>661,804</sup> Two phase 3 randomized trials reported a benefit in PFS and overall survival with the initiation of pemetrexed after first-line chemotherapy (4–6 cycles) in patients with nonsquamous NSCLC and no apparent disease progression.<sup>805,806</sup> Switch maintenance therapy with pemetrexed is recommended in patients with nonsquamous cell carcinoma; negative or unknown test results for *ALK* rearrangements or sensitizing *EGFR* mutations; and PD-L1 expression less than 1% or unknown.<sup>806</sup> The FDA has approved maintenance therapy with pemetrexed.<sup>807</sup>

Recently, the NCCN NSCLC Panel revised the recommendation for switch maintenance therapy with pemetrexed to category 2A (from 2B) based on clinical experience and reassessment of trial data (see *Maintenance Therapy* in this Discussion).<sup>806</sup> The NCCN NSCLC Panel does not recommend erlotinib as switch maintenance therapy (or as subsequent therapy) for patients with nonsquamous NSCLC and good PS but without *EGFR* mutations based on results from a randomized trial (IUNO) and revised indication from the FDA.<sup>808</sup> The NCCN NSCLC Panel also deleted the recommendations for switch maintenance therapy with erlotinib in patients with squamous cell NSCLC, because overall survival and quality of life were not improved.<sup>799,809</sup> A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.<sup>810</sup> Switch maintenance therapy with docetaxel is a category 2B recommendation in the NCCN Guidelines for patients with squamous cell carcinoma, because many patients in the delayed chemotherapy arm did not receive docetaxel.

### Clinical Evaluation

The workup and evaluation of incidental lung nodules that are detected on imaging for other conditions is described in the NSCLC algorithm (see *Incidental Lung Nodules* in this Discussion and the NCCN Guidelines for NSCLC). Recently, the NCCN NSCLC Panel revised the diagnostic algorithms for incidental solid and subsolid lung nodules detected on chest CT based on the updated Fleischner criteria (see the NCCN Guidelines for NSCLC).<sup>70-74</sup> The cutoff thresholds have been increased to 6 mm for a positive scan result. As previously described, low-dose CT screening is recommended for asymptomatic select patients who are at high risk for lung cancer and management of these nodules is described elsewhere (see the NCCN Guidelines for Lung Cancer Screening, available at [www.NCCN.org](http://www.NCCN.org)).

After patients are confirmed to have NSCLC based on a pathologic diagnosis, a clinical evaluation needs to be done (see the NCCN Guidelines for NSCLC). In patients with symptoms, 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 *Evaluation and Clinical Stage* in the NCCN Guidelines for NSCLC). The NCCN NSCLC Panel also recommends that smoking cessation advice, counseling, and pharmacotherapy be provided to patients.<sup>33,811-813</sup> After the clinical stage is determined, the patient is assigned to one of the pathways that are defined by the stage, specific subdivision of the particular stage, and location of the tumor. Note that for some patients, diagnosis, staging, and surgical resection are done during the same operative procedure. A multidisciplinary evaluation should be done before treatment.

### Additional Pretreatment Evaluation

As previously noted, evaluation of the mediastinal nodes is a key step in the further staging of the patient. FDG PET/CT scans can be used as an initial assessment of the hilar and mediastinal nodes (ie, to determine whether the N1, N2, or N3 nodes are positive for cancer, which is a key determinant of stage II and stage III disease); however, CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer.<sup>87,814-816</sup> When compared with noninvasive staging methods (EBUS, EUS), surgical staging with mediastinoscopy is more appropriate for certain settings when evaluating mediastinal nodes; however, clinicians use both methods when staging patients.<sup>87</sup> Thus, mediastinoscopy is encouraged as part of the initial evaluation, particularly if the results of imaging are not conclusive and the probability of mediastinal involvement is high (based on tumor size and location). Therefore, mediastinoscopy is appropriate for patients with T2 to T3 lesions even if the FDG PET/CT scan does not suggest mediastinal node involvement.

Mediastinoscopy may also be appropriate to confirm mediastinal node involvement in patients with a positive FDG PET/CT scan. In patients with solid tumors less than 1 cm or those with purely nonsolid tumors (ie, GGOs) less than 3 cm, pathologic mediastinal lymph node evaluation is optional if the nodes are FDG PET/CT negative because there is a low likelihood of positive mediastinal nodes.<sup>817</sup> Mediastinal evaluation can be considered in patients with clinical stage 1A disease (T1ab,N0). In patients with peripheral T2a, central T1ab, or T2a lesions with negative FDG PET/CT scans, the risk for mediastinal lymph node involvement is higher and mediastinoscopy and/or EUS-FNA and EBUS-TBNA are recommended. Dillemans et al have reported a selective mediastinoscopy strategy, proceeding straight to thoracotomy without mediastinoscopy for T1 peripheral tumors without enlarged mediastinal lymph nodes on preoperative CT.<sup>818</sup> This strategy resulted in a 16% incidence of positive N2 nodes discovered only at the time of thoracotomy.

For identifying N2 disease, chest CT scans had sensitivity and specificity rates of 69% and 71%, respectively. Using the chest CT scan plus mediastinoscopy was significantly more accurate (89% vs. 71%) than using the chest CT scan alone for identifying N2 disease. When using CT scans, node positivity is based on the size of the lymph nodes. Therefore, the CT scan will miss small metastases that do not result in node enlargement. To address this issue, Arita et al specifically examined lung cancer metastases to normal size mediastinal lymph nodes in 90 patients and found an incidence of 16% (14/90) false-negative chest CT scans with histologic identification of occult N2 or N3 disease.<sup>819</sup> Bronchoscopy is used in diagnosis and local staging of both central and peripheral lung lesions and is recommended for pretreatment evaluation of stage I to IIIA tumors. In patients who present with a solitary pulmonary nodule where the suspicion of malignancy is high, surgical resection without prior invasive testing may be reasonable.

As previously mentioned, CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer.<sup>814</sup> 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. The NCCN NSCLC Panel believes that PET scans can play a role in the evaluation and more accurate staging of NSCLC, for example, in identifying stage I (peripheral and central T1–2,N0), stage II, stage III, and stage IV diseases.<sup>87,820,821</sup> However, FDG PET/CT is even more sensitive and is recommended by NCCN.<sup>822-824</sup> PET/CT is typically done from the skull base to the knees; whole body PET/CT may also be done.

The NCCN NSCLC Panel assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.<sup>825</sup> Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported.<sup>826</sup> Because they detect tumor physiology, as opposed to anatomy, PET scans may be more sensitive than CT scans. Moreover, if postobstructive pneumonitis is present, there is little correlation between the size of the mediastinal lymph nodes and tumor involvement.<sup>827</sup> Chin et al found that PET, when used to stage the mediastinal nodes, was 78% sensitive and 81% specific with a negative predictive value of 89%.<sup>828</sup> Kernstine et al compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.<sup>829</sup> The PET scan was found to be more sensitive than the CT scan in identifying mediastinal node disease (70% vs. 65%). FDG PET/CT has been shown to be useful in restaging patients after adjuvant therapy.<sup>830,831</sup>

When patients with early-stage disease are accurately staged using FDG PET/CT, inappropriate surgery is avoided.<sup>822</sup> Positive FDG PET/CT scan findings for distant disease need pathologic or other radiologic confirmation (eg, MRI of bone). If the FDG PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation.<sup>87,832</sup>

Transesophageal EUS-FNA and EBUS-TBNA have proven useful to stage patients or to diagnose mediastinal lesions; these techniques can be used instead of invasive staging procedures in select patients.<sup>833-836</sup> When 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.<sup>837</sup> In patients with positive nodes on CT or PET, EBUS-TBNA can be used to clarify the results.<sup>838,839</sup> In patients with negative findings on EBUS-TBNA, conventional mediastinoscopy can be done to confirm the results.<sup>834,839-841</sup> Note that EBUS is also known as endosonography.

The routine use of bone scans (to exclude bone metastases) is not recommended. Brain MRI (with contrast) is recommended to rule out asymptomatic brain metastases in patients with stage II, III, and IV disease if aggressive combined-modality therapy is being considered.<sup>842</sup> Patients with stage IB NSCLC are less likely to have brain metastases; therefore, brain MRI is optional in this setting and can be considered for select patients at high risk (eg, tumors greater than 5 cm, central location). If brain MRI cannot be done, then CT of the head with contrast is an option. Note that PET scans are not recommended for assessing whether brain metastases are present (see the NCCN Guidelines for Central Nervous System Cancers, available at [www.NCCN.org](http://www.NCCN.org)).

### Initial Therapy

As previously mentioned, accurate pathologic assessment and staging are essential before treatment for NSCLC, because management varies depending on the stage, histology, presence of genetic alterations, and PS. Before treatment, it is strongly recommended that determination of tumor resectability be made by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC). *Principles of Radiation Therapy* recommends doses for RT (see the NCCN Guidelines for NSCLC). In addition, the NCCN Guidelines also

recommend regimens for chemotherapy and chemoradiation (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy*, *Chemotherapy Regimens Used with Radiation Therapy*, and *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). Targeted therapy is recommended for patients with metastatic NSCLC and positive test results for *ALK* or *ROS1* rearrangements, *BRAF* V600E mutations, or sensitizing *EGFR* mutations.

### Stage I, Stage II, and Stage IIIA Disease

Depending on the extent and type of comorbidity present, patients with stage I or a subset of stage II (T1–2,N1) tumors are generally candidates for surgical resection and mediastinal lymph node dissection. Definitive RT, including SABR, is recommended for patients with early-stage NSCLC who are medically inoperable or refuse surgery; RT can be considered as an alternative to surgery in patients at high risk of complications (see *Stereotactic Ablative Radiotherapy* in this Discussion and see *Initial Treatment for Stage I and II* in the NCCN Guidelines for NSCLC).<sup>305,323,326,393,451,843</sup> In some instances, positive mediastinal nodes (N2) are discovered at surgery; in this setting, an additional assessment of staging and tumor resectability must be made, and the treatment (ie, inclusion of systematic mediastinal lymph node dissection) must be modified accordingly. Therefore, the NCCN Guidelines include 2 different tracks for T1–2,N2 disease (ie, stage IIIA disease): 1) T1–2,N2 disease discovered unexpectedly at surgical exploration; and 2) T1–2,N2 disease confirmed before thoracotomy. In the second case, an initial brain MRI (with contrast) and FDG PET/CT scan (if not previously done) are recommended to rule out metastatic disease.

For patients with clinical stage IIB (T3,N0) and stage IIIA tumors who have different treatment options (surgery, RT, or chemotherapy), a multidisciplinary evaluation is recommended. For the subsets of stage IIB (T3,N0) and stage IIIA (T4,N0–1) tumors, treatment options are organized

according to the location of the tumor such as the superior sulcus, chest wall, proximal airway, or mediastinum.<sup>313</sup> For each location, a thoracic surgeon needs to determine whether the tumor is resectable (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).

For patients with resectable tumors (T3 invasion,N0–1) in the superior sulcus, the NCCN NSCLC Panel recommends preoperative concurrent chemoradiation therapy followed by surgical resection and chemotherapy (see *Initial Treatment for Superior Sulcus Tumors* in the NCCN Guidelines for NSCLC). Preoperative concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has shown 2-year survival in the 50% to 70% range.<sup>313,413,415,844–847</sup> The overall 5-year survival rate is approximately 40%.<sup>413,848</sup> Patients with possibly resectable superior sulcus tumors should undergo preoperative concurrent chemoradiation before surgical re-evaluation (including CT ± PET/CT). For patients with unresectable tumors (T4 extension,N0–1) in the superior sulcus, definitive concurrent chemoradiation is recommended. Two additional cycles of full-dose chemotherapy can be given if full-dose chemotherapy was not given concurrently with RT.<sup>646,849</sup> The NCCN NSCLC Panel recommends durvalumab (category 1) as consolidation immunotherapy after treatment with definitive concurrent chemoradiation for patients with unresectable stage III NSCLC based on data from a phase 3 randomized trial and FDA approval (see *Chemoradiation: Trial Data* in this Discussion and the NCCN Guidelines for NSCLC).<sup>283</sup> The recommendation for consolidation immunotherapy with durvalumab occurs in multiple places in the NCCN Guidelines.

Surgical resection is the preferred treatment option for patients with tumors of the chest wall, proximal airway, or mediastinum (T3–4,N0–1). Other treatment options include preoperative chemotherapy or concurrent chemoradiation before surgical resection. For unresectable tumors (T4,N0–1) without pleural effusion, definitive concurrent chemoradiation

(category 1) is recommended followed by consolidation immunotherapy with durvalumab (category 1).<sup>332,599</sup> For the 2019 update (Version 1), the panel deleted the recommendation to add an additional 2 cycles of full-dose chemotherapy if patients have not received full-dose chemotherapy concurrently with RT, based on concerns that consolidation chemotherapy will increase the risk of pneumonitis if patients are also receiving durvalumab. However, consolidation chemotherapy is an option if patients are not receiving durvalumab.

Multimodality therapy is recommended for most patients with stage III NSCLC.<sup>641</sup> For patients with stage IIIA disease and positive mediastinal nodes (T1–2,N2), treatment is based on the findings of pathologic mediastinal lymph node evaluation (see the NCCN Guidelines for NSCLC). Patients with negative mediastinal biopsy findings are candidates for surgery. For those patients with resectable lesions, mediastinal lymph node dissection or lymph node sampling should be performed during the operation. Those individuals who are medically inoperable should be treated according to the clinical stage (see the NCCN Guidelines for NSCLC). For patients with (T1–2) N2 node-positive disease, a brain MRI (with contrast) and FDG PET/CT scan (if not done previously) are recommended to search for distant metastases. When distant metastases are not present, the NCCN NSCLC Panel recommends that the patient be treated with definitive concurrent chemoradiation therapy (see the NCCN Guidelines for NSCLC).<sup>392,600</sup> Recommended therapy for metastatic disease depends on whether disease is in a solitary site or is widespread (see the NCCN Guidelines for NSCLC).

When a lung metastasis is present, it usually occurs in a patient with other systemic metastases; 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 (see *Multiple Lung Cancers* in this Discussion).<sup>850</sup> Patients with separate pulmonary nodule(s) in the same lobe (T3,N0–1) or ipsilateral non-primary lobe (T4,N0–1) without other systemic metastases are potentially curable by surgery; 5-year survival rates are about 30%.<sup>851</sup> For those with N2 nodes after surgery, concurrent chemoradiation is recommended for those with positive margins and an R2 resection; either sequential or concurrent chemoradiation is recommended after an R1 resection. Most NCCN Member Institutions favor concurrent chemoradiation for positive margins, but sequential chemoradiation is reasonable in frailer patients.<sup>642</sup> For those with N2 nodes and negative margins, sequential chemotherapy (category 1) with RT is recommended. Chemotherapy alone is recommended for those with N0–1 nodes (see the NCCN Guidelines for NSCLC). In patients with synchronous solitary nodules (contralateral lung), the NCCN NSCLC Panel recommends treating them as 2 primary lung tumors if both are curable, even if the histology of the 2 tumors is similar (see the NCCN Guidelines for NSCLC).<sup>852</sup>

### Multiple Lung Cancers

Patients with a history of lung cancer or those with biopsy-proven synchronous lesions may be suspected of having multiple lung cancers (see *Clinical Presentation* in the NCCN Guidelines for NSCLC).<sup>853,854</sup> It is important to determine whether the multiple lung cancers are metastases or separate lung primaries (synchronous or metachronous), because most multiple lung tumors are metastases.<sup>65,313,855,856</sup> Therefore, it is essential to determine the histology of the lung tumor (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC). Infection and other benign diseases also need to be ruled out (eg, inflammatory granulomas).<sup>857,858</sup> Although criteria have been established for diagnosing multiple lung cancers, no definitive method has been established before treatment.<sup>858-861</sup> The Martini and Melamed criteria are often used to diagnose multiple lung cancers as follows: 1) the histologies are different; or 2) the histologies are



the same, but there is no lymph node involvement and no extrathoracic metastases.<sup>861</sup>

Treatment of multiple lung cancers depends on the status of the lymph nodes (eg, N0–1) and on whether the lung cancers are asymptomatic, symptomatic, or at high or low risk of becoming symptomatic (see *Initial Treatment* in the NCCN Guidelines for NSCLC).<sup>855,862-864</sup> Patients should be evaluated in a multidisciplinary setting (eg, surgeons, radiation oncologists, medical oncologists). In patients eligible for definitive local therapy, parenchymal-sparing resection is preferred (see the *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).<sup>854,855</sup> VATS or SABR are reasonable options depending on the number and distribution of the tumors requiring local treatment.<sup>865</sup> Multiple lung nodules (eg, solid, subsolid nodules) may also be detected on CT scans; some of these nodules can be followed with imaging, whereas others need to be biopsied or excised (see *Incidental Lung Nodules* in this Discussion and the NCCN Guidelines for Lung Cancer Screening, available at [www.NCCN.org](http://www.NCCN.org)).<sup>866</sup>

### Stage IIIB Disease

Stage IIIB tumors comprise 2 unresectable groups, including: 1) T1–2,N3 tumors; and 2) T3–4,N2 tumors, which include contralateral mediastinal nodes (T4,N3). Surgical resection is not recommended in patients with T1–2,N3 disease. However, in patients with suspected N3 disease, the NCCN Guidelines recommend pathologic confirmation of nodal status (see *Pretreatment Evaluation* in the NCCN Guidelines for NSCLC).<sup>867,868</sup> In addition, FDG PET/CT scans (if not previously done) and brain MRI (with contrast) should also be included in the pretreatment evaluation. If these imaging tests are negative, then treatment options for the appropriate nodal status should be followed (see the NCCN Guidelines for NSCLC). If N3 disease is confirmed, definitive concurrent chemoradiation (category 1) is recommended; 2 additional cycles of full-dose chemotherapy can be given if full-dose chemotherapy was not given concurrently with

RT.<sup>332,599,646,869,870</sup> As previously mentioned, durvalumab is recommended (category 1) as consolidation immunotherapy after treatment with definitive concurrent chemoradiation for patients with unresectable stage III NSCLC (see *Chemoradiation: Trial Data* in this Discussion and the NCCN Guidelines for NSCLC).<sup>283</sup> For metastatic disease that is confirmed by FDG PET/CT scan and brain MRI (with contrast), treatment is described in the NCCN Guidelines for limited or metastatic disease.

For patients with T4,N2–3 disease (stage IIIB), surgical resection is not recommended. The initial workup includes biopsies of the N3 and N2 nodes. If these biopsies are negative, the same treatment options may be used as for stage IIIA (T4,N0–1) disease (see the NCCN Guidelines for NSCLC). If either the contralateral or ipsilateral mediastinal node is positive, definitive concurrent chemoradiation therapy is recommended (category 1) followed by 2 cycles of full-dose chemotherapy if full-dose chemotherapy was not given concurrently with RT as initial treatment (see the NCCN Guidelines for NSCLC).<sup>332,599,646,869-871</sup> Again, durvalumab is recommended (category 1) after definitive concurrent chemoradiation for patients with unresectable stage III NSCLC.<sup>283</sup>

### Stage IV Disease

In general, systemic therapy is recommended for patients with metastatic disease (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).<sup>705</sup> In addition, palliative treatment, including RT, may be needed during the disease course to treat localized symptoms, diffuse brain metastases, or bone metastases (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for NSCLC). This section focuses on patients with limited metastatic disease; management of widespread distant metastases is described in another section (see *Treatment of Recurrences and Distant Metastases* in this Discussion and *Systemic Therapy for Metastatic Disease* in the NCCN Guidelines for NSCLC).

Pleural or pericardial effusion is a criterion for stage IV, M1a disease. T4 with pleural effusion is classified as stage IV, M1a (see Table 3 in *Staging* in the NCCN Guidelines for NSCLC).<sup>127</sup> Pleural or pericardial effusions are malignant in 90% to 95% of patients; however, they may be related to obstructive pneumonitis, atelectasis, lymphatic or venous obstruction, or a pulmonary embolus. Therefore, pathologic confirmation of a malignant effusion by using thoracentesis or pericardiocentesis is recommended. In certain cases where 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 or pericardial effusion is considered negative for malignancy (M0), recommended treatment is based on the confirmed T and N stage (see the NCCN Guidelines for NSCLC). All pleural or pericardial effusions, whether malignant or not, are associated with unresectable disease in 95% of cases.<sup>872</sup> In patients with effusions that are positive for malignancy, the tumor is defined as M1a and is treated with local therapy (ie, ambulatory small catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease (see the NCCN Guidelines for NSCLC).<sup>873</sup>

Management of patients with distant metastases in limited sites (ie, stage IVA, M1b) and good PS depends on the location and number of the metastases; the diagnosis is aided by mediastinoscopy, bronchoscopy, FDG PET/CT scan, and brain MRI (with contrast). The increased sensitivity of FDG PET/CT scans, compared with other imaging methods, may identify additional metastases and, thus, spare some patients from unnecessary futile surgery. Positive FDG PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If the FDG PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation. Patients with limited oligometastatic disease (eg, brain metastases) and otherwise limited disease in the chest may benefit

from aggressive local therapy to both the primary chest and metastatic sites.<sup>487,874</sup> The NCCN NSCLC Panel recently revised the recommendations for treatment of limited brain metastases by decreasing recommendations for whole brain RT (see *Whole Brain RT and Stereotactic Radiosurgery* in this Discussion text). Clinicians are not using whole brain RT as often in patients with limited brain metastases because of concerns about neurocognitive problems.<sup>559</sup> Aggressive local therapy may comprise surgery and/or definitive RT including SRS and SABR, and may be preceded or followed by chemotherapy. After progression on TKIs, patients with *EGFR* mutations may be able to continue with their current TKIs; local therapy can be considered to treat their limited metastases (eg, SRS to brain metastases or other sites, SABR for thoracic disease).<sup>875,876</sup>

## Postoperative Treatment

### Chemotherapy or Chemoradiation

Post-surgical treatment options for patients with stage IA tumors (T1abc, N0) and with positive surgical margins (R1, R2) include re-resection (preferred) or RT (category 2B). Observation is recommended for patients with T1abc–T2ab, N0 tumors and with negative surgical margins (R0). Postoperative chemotherapy is a category 2A recommendation for patients with T2ab, N0 tumors and negative surgical margins who have high-risk features (including poorly differentiated tumors, vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status [Nx]) (see the NCCN Guidelines for NSCLC).<sup>630,877</sup> If the surgical margins are positive in patients with T2ab, N0 tumors, options include: 1) re-resection (preferred) with (or without) chemotherapy; or 2) RT with (or without) chemotherapy (chemotherapy is recommended for T2b, N0).<sup>382,630</sup>

The NCCN NSCLC Panel recommends chemotherapy (category 1) for patients with negative surgical margins and stage IIB disease, including 1) T1abc–T2a, N1; 2) T2b, N1; or 3) T3, N0 disease.<sup>626,878</sup> If surgical margins

are positive in these patients, options after an R1 resection include: 1) re-resection and chemotherapy; or 2) chemoradiation (either sequential or concurrent). Options after an R2 resection include: 1) re-resection and chemotherapy; or 2) concurrent chemoradiation. Most NCCN Member Institutions favor concurrent chemoradiation for positive margins, but sequential chemoradiation is reasonable in frailer patients.<sup>642</sup>

Postoperative chemotherapy can also be used in patients with stage III NSCLC who have had surgery (see the NCCN Guidelines for NSCLC). Patients with T1–3,N2 or T3,N1 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be treated with chemoradiation; either sequential or concurrent chemoradiation is recommended for an R1 resection, whereas concurrent chemoradiation is recommended for an R2 resection (see the NCCN Guidelines for NSCLC). Patients with negative margins may be treated with either 1) chemotherapy (category 1); or 2) sequential chemotherapy plus RT (for N2 only).<sup>626</sup>

For stage IIIA superior sulcus tumors (T4 extension,N0–1) that become resectable after preoperative concurrent chemoradiation, resection followed by chemotherapy is recommended (see the NCCN Guidelines for NSCLC). Surgical reevaluation (including chest CT with or without contrast and with or without PET/CT) is done to determine whether the tumor is resectable after treatment. If the lesion remains unresectable after preoperative concurrent chemoradiation, the full course of definitive chemo/RT should be completed followed by durvalumab (category 1 for durvalumab). Among patients with chest wall lesions with T3 invasion–T4 extension,N0–1 disease, those who are initially treated with surgery (preferred) may receive chemotherapy alone if the surgical margins are negative. When surgical margins are positive, they may receive either 1) sequential or concurrent chemoradiation; or 2) re-resection and chemotherapy. As previously mentioned, most NCCN Member Institutions favor concurrent chemoradiation for positive margins, but sequential is

reasonable in frailer patients.<sup>642</sup> A similar treatment plan is recommended for resectable tumors of the proximal airway or mediastinum (T3–4,N0–1).

For patients with stage III disease and positive mediastinal nodes (T1–3,N2) with no apparent disease progression after initial treatment, recommended treatment includes surgery with (or without) RT (if not given preoperatively) and/or with (or without) chemotherapy (category 2B for chemotherapy) (see the NCCN Guidelines for NSCLC). Alternatively, if the disease progresses, patients may be treated with either 1) local therapy using RT (if not given previously) with (or without) chemotherapy; or 2) systemic therapy. In patients with separate pulmonary nodules in the same lobe (T3,N0–1) or ipsilateral non-primary lobe (T4,N0–1), surgery is recommended. In patients with N2 disease and negative margins, options include 1) chemotherapy (category 1); or 2) sequential chemotherapy with radiation. If the resection margins are positive in patients with N2 disease, concurrent chemoradiation is recommended for an R2 resection, whereas either concurrent or sequential chemoradiation is recommended for an R1 resection. Concurrent chemoradiation is often used for positive margins, but sequential is reasonable in frailer patients.

Because patients with stage III disease have both local and distant failures, theoretically, the use of chemotherapy may eradicate micrometastatic disease obviously present but undetectable at diagnosis. The timing of this chemotherapy varies (see the NCCN Guidelines for NSCLC). Such chemotherapy may be given alone, sequentially, or concurrently with RT. In addition, chemotherapy could be given preoperatively or postoperatively in appropriate patients.

On the basis of clinical studies,<sup>587-589</sup> the NCCN NSCLC Panel recommends cisplatin combined with docetaxel, etoposide, gemcitabine, or vinorelbine for postoperative chemotherapy for all histologies in the NCCN Guidelines; other options include cisplatin combined with pemetrexed for nonsquamous NSCLC (see *Chemotherapy Regimens for*

*Neoadjuvant and Adjuvant Therapy* in the NCCN Guidelines for NSCLC).<sup>252,631,653</sup> For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin may be combined with pemetrexed (nonsquamous only), paclitaxel, or gemcitabine.<sup>631,879</sup> Recently, the NCCN NSCLC Panel expanded the list of regimens for sequential chemoradiation to include regimens that are also used for preoperative and postoperative chemotherapy (ie, cisplatin combined with pemetrexed [nonsquamous only], docetaxel, etoposide, gemcitabine, or vinorelbine; carboplatin combined with paclitaxel) and also added 2 new carboplatin regimens for patients with comorbidities or those not able to tolerate cisplatin, including 1) carboplatin/gemcitabine; and 2) carboplatin/pemetrexed (nonsquamous only).<sup>617-620</sup>

Three phase 3 trials have assessed preoperative chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.<sup>594,880-882</sup> The S9900 trial (a SWOG study)—one of the largest randomized trials examining preoperative chemotherapy in early-stage NSCLC—assessed surgery alone compared with surgery plus preoperative paclitaxel/carboplatin in patients with stage IB/IIA and stage IIB/IIIA NSCLC (excluding superior sulcus tumors). PFS and overall survival were improved with preoperative chemotherapy.<sup>881,882</sup> All 3 studies showed a survival advantage for patients who received preoperative chemotherapy. The 2 earlier phase 3 studies had a small number of patients, while the SWOG study was stopped early because of the positive results of the IALT study. A number of phase 2 studies have evaluated preoperative chemotherapy for stage III NSCLC, with (or without) RT, followed by surgery.<sup>883-885</sup>

### Radiation Therapy

After complete resection of clinical early-stage NSCLC, postoperative RT has been found to be detrimental for pathologic N0 or N1 stage disease in a meta-analysis of small randomized trials using older techniques and

dosing regimens and a population-based analysis of data from SEER.<sup>886</sup> There was an apparent survival benefit of postoperative RT in patients with N2 nodal stage diagnosed surgically.<sup>475</sup> The analysis of the ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received chemotherapy.<sup>382</sup> A review of the National Cancer Database concluded that postoperative RT and chemotherapy provided a survival advantage for patients with completely resected N2 disease when compared with chemotherapy alone.<sup>887</sup> A recent meta-analysis also concluded that postoperative RT improves survival for patients with N2 disease.<sup>888</sup> Postoperative sequential chemotherapy with RT is recommended for patients with T1–3, N2 disease and negative margins (see the NCCN Guidelines for NSCLC). A meta-analysis assessed postoperative chemotherapy with (or without) postoperative RT in patients mainly with stage III disease.<sup>878</sup> In this meta-analysis, 70% of the eligible trials used sequential chemotherapy before RT; 30% used concurrent chemo/RT. Regimens included cisplatin/vinorelbine followed by RT or concurrent cisplatin/etoposide.

The ACR Appropriateness Criteria® provide specific recommendations for postoperative therapy.<sup>889,890</sup> Either concurrent or sequential chemoradiation may be used for postoperative therapy, depending on the type of resection and the setting (eg, N2 disease) (see the NCCN Guidelines for NSCLC). Concurrent chemo/RT is recommended for R2 resections, whereas either sequential or concurrent chemo/RT is recommended for R1 resections. Concurrent chemoradiation is often used for positive margins, but sequential is reasonable in frailer patients.<sup>642</sup> Cisplatin/etoposide, cisplatin/vinorelbine, and carboplatin/paclitaxel are chemoradiation regimens recommended by the NCCN NSCLC Panel for all histologies (see *Chemotherapy Regimens Used with Radiation Therapy* in the NCCN Guidelines for NSCLC).<sup>645</sup> Pemetrexed with either cisplatin or carboplatin may be used for concurrent chemoradiation in patients with nonsquamous NSCLC.<sup>648,891,892</sup> When chemoradiation is recommended in the NCCN

Guidelines, these regimens may be used for stage II to III disease.<sup>383,384,599,600,646,649,650</sup>

A phase 3 trial (PROCLAIM) assessed concurrent thoracic RT with cisplatin/pemetrexed versus cisplatin/etoposide followed by consolidation chemotherapy in patients with unresectable stage III nonsquamous NSCLC.<sup>643</sup> Both regimens were equivalent in terms of survival, but the cisplatin/pemetrexed regimen was associated with less neutropenia (24.4% vs. 44.5%;  $P < .001$ ) and fewer grade 3 to 4 adverse events (64.0% vs. 76.8%;  $P = .001$ ). The NCCN NSCLC Panel recently deleted the cisplatin/etoposide consolidation regimen based on the PROCLAIM trial. In addition, the NCCN NSCLC Panel clarified that the cisplatin/pemetrexed and carboplatin/paclitaxel regimens may be followed by consolidation chemotherapy alone for patients receiving definitive chemoradiation.

### Surveillance

Because recurrence is common after treatment for NSCLC, surveillance with history and physical (H&P) and chest CT (with or without contrast) is recommended in the NCCN Guidelines. Data from randomized phase 3 trials are not available to clarify surveillance recommendations; therefore, the most appropriate schedules are controversial.<sup>893-897</sup> The surveillance guidelines were recently revised by polling the NCCN NSCLC Panel regarding their practice patterns. Details regarding the specific surveillance schedules for patients with no clinical or radiographic evidence of disease after completion of definitive therapy are outlined in the algorithm based on stage (see *Surveillance* in the NCCN Guidelines for NSCLC). A chest CT scan with (or without) contrast and an H&P are recommended for the initial surveillance schedules (2–5 years) followed by an annual low-dose non-contrast-enhanced CT and an H&P.<sup>895,896,898-901</sup> Patients treated with chemotherapy with (or without) RT who have residual abnormalities may require more frequent imaging.

It is important to note that the surveillance recommendations for NSCLC are different from the screening recommendations for individuals at high risk for lung cancer (see the NCCN Guidelines for Lung Cancer Screening). Data show that low-dose CT screening decreased the mortality from lung cancer;<sup>57</sup> low-dose CT may be beneficial for identifying recurrences. FDG PET/CT or brain MRI is not routinely recommended for routine surveillance in patients without symptoms. But, PET may be useful for assessing CT scans that appear to show malignant neoplasms but may be radiation fibrosis, atelectasis, or other benign conditions. Areas previously treated with RT may remain FDG avid for up to 2 years; therefore, histologic confirmation of apparent “recurrent” disease is needed.<sup>902</sup> Information about smoking cessation (eg, advice, counseling, therapy) should be provided for patients undergoing surveillance to improve their quality of life.

The NCCN Guidelines include information about the long-term follow-up care of NSCLC survivors (see *Cancer Survivorship Care* in the NCCN Guidelines for NSCLC). These recommendations include guidelines for routine cancer surveillance, immunizations, health monitoring, counseling for wellness and health promotion, and cancer screening. An analysis suggests that patients who survive lung cancer have a high symptom burden 1 year after diagnosis and therefore need management after treatment.<sup>903</sup>

### Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases. Management of locoregional recurrences or symptomatic local disease (eg, endobronchial obstruction, mediastinal lymph node recurrence, superior vena cava [SVC] obstructions, severe hemoptysis) is described in the NCCN Guidelines (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for NSCLC).<sup>12</sup> For the 2019 update (Version 1), the NCCN NSCLC Panel clarified the recommended

treatment for SVC obstruction and severe hemoptysis. For example, an SVC stent may be used with either concurrent chemoradiation or RT to treat SVC obstruction. For patients with endobronchial obstruction, relieving airway obstruction may increase survival, especially in patients who are severely compromised, and may improve the quality of life.<sup>904</sup> After treatment for the locoregional recurrence, observation or systemic therapy (category 2B for systemic therapy) is recommended if disseminated disease is not evident. Systemic therapy is recommended for disseminated disease. The type of systemic therapy depends on the histologic type, whether genetic alterations are present that can be treated with targeted therapy, and PS (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). The NCCN NSCLC Panel recommends (category 2A) response assessment after 2 cycles of systemic therapy, then after every 2 to 4 cycles of therapy or when clinically indicated; assessment is done using CT with (or without contrast) of known sites of disease.<sup>205,905-907</sup>

Management of distant metastases (eg, localized symptoms; bone, limited, diffuse brain, or disseminated metastases) is described in the NCCN Guidelines (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for NSCLC). Palliation of symptoms throughout the disease course can be achieved with external-beam RT for distant metastases with localized symptoms, diffuse brain metastases, or bone metastases (bisphosphonate or denosumab therapy can be considered).<sup>390,480,908</sup> For patients at risk of fracture in weight-bearing bone, orthopedic stabilization and palliative RT are recommended.

Of note, recurrent and metastatic disease have historically been regarded as incurable. However, selected limited locoregional recurrences may be treated with curative intent therapy (surgery or RT with [or without] chemotherapy) (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for NSCLC). Similarly, patients with limited-site oligometastatic

disease and good PS may benefit from aggressive local therapies to the metastatic and primary sites, with clinical data suggesting the possibility of long-term survival (see *Initial Treatment for Stage IVA, M1b* in the NCCN Guidelines for NSCLC).<sup>515,516,519,548,909-912</sup> In addition, emerging clinical data suggest the feasibility of definitive reirradiation of local recurrences within prior RT fields using highly conformal techniques, although this should be limited to highly selected cases in specialty centers with appropriate expertise because of the potential for severe toxicity with high cumulative radiation doses to critical structures.<sup>387,526-528,913-916</sup>

Denosumab or intravenous bisphosphonate therapy can be considered in patients with bone metastases to decrease bone complications (eg, decrease pain, delay skeletal-related events).<sup>146,917-920</sup> In patients with NSCLC who have bone metastases, data suggest that denosumab increases median overall survival when compared with zoledronic acid (9.5 vs. 8 months).<sup>921</sup> Denosumab and bisphosphonate therapy 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 and denosumab in patients with bone metastases from solid tumors.<sup>922,923</sup>

For patients with recurrent and metastatic disease, the NCCN Guidelines recommend that histologic subtype should be determined before therapy so that the best treatment can be selected (see *Metastatic Disease: Histologic Subtype* in the NCCN Guidelines for NSCLC).<sup>252</sup> In addition, biomarker testing for genetic alterations (ie, oncogenic driver events) is recommended in patients with NSCLC, because targeted therapy has been shown to decrease tumor burden, decrease symptoms, and dramatically improve the quality of life for patients with specific genetic alterations. The number of available targeted agents is increasing. Several targeted agents have category 1 recommendations for first-line therapy based on phase 3 randomized trials such as erlotinib, gefitinib, afatinib,

osimertinib, dacomitinib, alectinib, ceritinib, brigatinib, and crizotinib.<sup>705</sup> Additional targeted therapies for patients with other genetic alterations are also recommended, although there is less evidence for these agents and they have not been FDA approved for lung cancer (see *Emerging Biomarkers to Identify Novel Therapies for Patients With Metastatic NSCLC* in the NCCN Guidelines for NSCLC). Targeted therapies—such as ceritinib, alectinib, brigatinib, and osimertinib—are recommended as subsequent therapies (if not previously given) for patients with the indicated genetic alterations whose disease becomes resistant to first-line targeted therapies; other targeted therapies are being investigated for resistance.<sup>265</sup>

Biomarker testing for genetic alterations is recommended in the NCCN Guidelines. Recently, the NCCN NSCLC Panel added a section describing the details of biomarker testing (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). It is important to note that 1) several different tests may be used to identify the same biomarker, including FDA-approved biomarker tests and validated laboratory tests done in CLIA-approved laboratories; and 2) biomarker testing is rapidly changing and improving. *EGFR* mutation testing (category 1) is recommended in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or NSCLC NOS, because *EGFR* TKIs are recommended for patients who are positive for sensitizing *EGFR* mutations (see *EGFR Mutation Positive/First-Line Therapy* in the NCCN Guidelines for NSCLC).<sup>93,189,207,226,924</sup> Testing for *ALK* rearrangements (category 1) is also recommended in patients with nonsquamous NSCLC, because *ALK* inhibitors are recommended for patients who are positive for *ALK* rearrangements.<sup>148,925</sup> The NCCN NSCLC Panel also recommends testing for *ROS1* rearrangements (category 2A). Testing for *ROS1* has typically been done using FISH; a validated NGS platform that can detect this gene fusion may also be used.<sup>263</sup> The NCCN NSCLC Panel recommends that *EGFR* and *BRAF* mutation testing be done as part of

broad molecular profiling (eg, multiplex mutation screening assays or NGS). Testing for *ALK* gene rearrangements can be done with FISH or with NGS if the platform is validated and can identify gene fusions.<sup>172,186,187</sup> The NCCN NSCLC Panel also recommends upfront PD-L1 expression testing (category 2A) before first-line therapy in patients with metastatic NSCLC to assess whether patients are candidates for pembrolizumab (see *Pembrolizumab* in this Discussion).

The following targeted agents are recommended (category 2A) for patients with specific genetic alterations: 1) crizotinib (for high-level *MET* amplification or *METex14* mutation); 2) cabozantinib or vandetanib (for *RET* rearrangements); and 3) ado-trastuzumab for HER2 mutations.<sup>90,95,139-141,154,155,160-162,166,169,172,224,697,708,731,761,926-938</sup> The NCCN NSCLC Panel recommends crizotinib for high-level *MET* amplification or *METex14* mutation based on data from several studies.<sup>731,939,940</sup> The NCCN NSCLC Panel recommends vandetanib (category 2A) for *RET* rearrangements based on data from a phase 2 study in 18 patients who had received 2 or more previous chemotherapy regimens.<sup>927,930</sup> The overall survival was 11.6 months and the PFS was 4.5 months. Partial remission (18%) was reported in 3 patients; stable disease was reported in another 8 patients. The disease control rate was 65%. Six (33%) patients died within 3 months of enrollment of the study due to rapid tumor progression. The recommendation for cabozantinib for *RET* rearrangements is based on data from a phase II study in 26 patients.<sup>140,926,933</sup> The overall response rate was 28% (95% CI, 12%–49%). Many patients (19 [73%]) needed dose reductions because of adverse events. The most common grade 3 adverse events included lipase elevation (4 patients [15%]), increased ALT (2 [8%]), decreased platelet count (2 [8%]), and hypophosphatemia (2 [8%]).

The NCCN NSCLC Panel recommends ado-trastuzumab emtansine (category 2A) for patients with HER2 mutations based on results from a

phase 2 basket trial.<sup>928,941</sup> The partial response rate was 44% (95% CI, 22%–69%). The median PFS was 5 months (95% CI, 3–9). Minor toxicities (grade 1–2) included infusion reactions, thrombocytopenia, and transaminitis; no treatment-related deaths were reported. Patients (n=18) were mostly women (72%) and nonsmokers, and all had adenocarcinomas. The NCCN NSCLC Panel does not recommend single-agent therapy with trastuzumab or afatinib (both for HER2 mutations), because response rates are lower and treatment is less effective when these agents are used for patients with HER2 mutations.<sup>942,943</sup>

As previously mentioned, recommendations from an international panel suggest that general histologic categories be avoided (eg, NSCLC), because more effective treatment can be selected when the histology is known.<sup>65</sup> Patients with pure squamous cell carcinoma do not seem to have *ALK* rearrangements, *ROS1* rearrangements, sensitizing *EGFR* mutations, or *BRAF* mutations; therefore, routine testing is not recommended in these patients.<sup>149,151,944,945</sup> However, testing for *ALK* rearrangements, *ROS1* rearrangements, *BRAF* mutations, or *EGFR* mutations can be considered in patients with squamous cell carcinomas whose histology was determined using small biopsy specimens or mixed histology specimens.<sup>149</sup> Testing for *EGFR* mutations or *ALK* rearrangements can also be considered in patients who never smoked. Treatment recommendations and eligibility criteria are described in the NCCN Guidelines for patients with nonsquamous NSCLC (or NSCLC NOS) with negative or unknown test results for *ALK* rearrangements or sensitizing *EGFR* mutations and with PD-L1 expression less than 1% or unknown. Treatment recommendations and eligibility criteria for patients with squamous cell carcinoma are also described in the NCCN Guidelines. These recommendations are briefly summarized in the following paragraphs. Data supporting these recommendations are described in the following section (see *Trial Data* in this Discussion).

Chemotherapy/immunotherapy regimens are now recommended for patients without genetic alterations (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). Single-agent targeted therapy is recommended for patients with *ALK* or *ROS1* rearrangements, sensitizing *EGFR* mutations, or other driver mutations (see *Emerging Biomarkers to Identify Novel Therapies for Patients With Metastatic NSCLC* in the NCCN Guidelines for NSCLC). Pembrolizumab is recommended (category 1, preferred) as first-line monotherapy for patients with PD-L1 expression of 50% or more.

Chemotherapy/immunotherapy regimens, such as pembrolizumab/carboplatin (or cisplatin)/pemetrexed, are recommended (category 1, preferred) for patients with nonsquamous NSCLC and negative or unknown test results for *ALK* rearrangements or sensitizing *EGFR* mutations and with PD-L1 expression less than 50% or unknown (also known as wild-type) (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC, the NCCN Drugs & Biologics Compendium [NCCN Compendium®] for NSCLC, and the NCCN Guidelines With Evidence Blocks™ for NSCLC).<sup>252</sup>

For patients with metastatic NSCLC and contraindications to pembrolizumab, other chemotherapy options are recommended (such as carboplatin/paclitaxel), although some regimens may be more appropriate for certain patients, depending on histology, PS, and other factors (see *Trial Data* in this Discussion, *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC, the NCCN Compendium® for NSCLC, and the NCCN Guidelines With Evidence Blocks™ for NSCLC).<sup>705,946</sup> Bevacizumab/chemotherapy is an option if eligibility criteria are met for patients with nonsquamous NSCLC and negative or unknown test results for *ALK* rearrangements or sensitizing *EGFR* mutations and with PD-L1 expression less than 1% or unknown.<sup>947</sup> Previously, patients with brain metastases were excluded from receiving



bevacizumab because of concerns about CNS hemorrhage; however, data suggest that bevacizumab can be used in patients with treated CNS metastases.<sup>948</sup> A phase 3 randomized trial in elderly patients (70–89 years) with advanced NSCLC reported that combined therapy with weekly paclitaxel and monthly carboplatin improved survival when compared with single-agent therapy using either gemcitabine or vinorelbine (10.3 vs. 6.2 months).<sup>949</sup> Systemic therapy for elderly patients with advanced NSCLC needs to be carefully selected to avoid adverse reactions.<sup>950</sup> The NCCN NSCLC Panel previously revised the lists of recommended doublet and single-agent cytotoxic chemotherapy regimens for patients with nonsquamous NSCLC or NSCLC NOS—who are negative or unknown for mutations, rearrangements, or PD-L1 expression—by deleting regimens that are rarely used in the United States. Deleted regimens include carboplatin/vinorelbine, cisplatin/vinorelbine, etoposide, irinotecan, and vinorelbine.

For patients with metastatic squamous cell NSCLC and negative or unknown test results for mutations, rearrangements, or PD-L1 expression, chemotherapy/immunotherapy regimens—such as pembrolizumab/carboplatin/paclitaxel or albumin-bound paclitaxel—are recommended (category 1, preferred) as of the 2019 update. For patients with contraindications to pembrolizumab, cisplatin/gemcitabine (category 1) is a recommended doublet option for patients with squamous cell carcinoma.<sup>252</sup> Carboplatin/paclitaxel, carboplatin/gemcitabine (category 1 for both), and other regimens listed in the NSCLC algorithm are also recommended (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC, the NCCN Compendium® for NSCLC, and the NCCN Guidelines With Evidence Blocks™ for NSCLC). The NCCN NSCLC Panel previously revised the lists of recommended doublet cytotoxic therapy regimens by deleting regimens that are rarely used for patients with metastatic squamous cell carcinoma NSCLC and negative or unknown test results for *ALK* rearrangements or sensitizing *EGFR*

mutations and with PD-L1 expression less than 1% or unknown. Deleted regimens include carboplatin/etoposide, carboplatin/vinorelbine, cisplatin/vinorelbine, cisplatin/gemcitabine/necitumumab, etoposide, irinotecan, and vinorelbine. Regimens containing pemetrexed or bevacizumab are not recommended for squamous cell carcinoma. Currently, there are fewer treatment options for patients with squamous cell carcinoma when compared with nonsquamous NSCLC. Research is ongoing to find newer options.<sup>7,90,187,951,952</sup>

### Trial Data

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 many of the following agents: docetaxel, etoposide, gemcitabine, paclitaxel (and albumin-bound paclitaxel), pemetrexed, and vinorelbine (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).<sup>252,631,653-655,678,679,687</sup> Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.<sup>953</sup> Non-platinum regimens (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine) are reasonable alternatives, because data show they are active and less toxic than platinum-based regimens.<sup>681-684,954</sup>

In a phase 2/3 trial (ECOG 4599), 878 patients were randomly assigned to either 1) bevacizumab in combination with paclitaxel/carboplatin; or 2) paclitaxel/carboplatin alone.<sup>251,955</sup> Both regimens were well tolerated with selected toxicities. Patients receiving bevacizumab/paclitaxel/carboplatin showed an improved median survival (12.3 vs. 10.3 months,  $P = .003$ ) when compared to patients receiving paclitaxel/carboplatin alone.<sup>251</sup> The overall 1-year and 2-year survival was 51% versus 44% and 23% versus 15%, respectively, in favor of the bevacizumab/paclitaxel/carboplatin arm.<sup>251</sup> More significant toxicities were observed with bevacizumab/paclitaxel/carboplatin compared to paclitaxel/carboplatin

(grade 4 neutropenia: 25.5% vs. 16.8%; grade 5 hemoptysis: 1.2% vs. 0%; and grade 3 hypertension: 6.8% vs. 0.5%). Treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (15 patients) than with paclitaxel/carboplatin (2 patients) ( $P = .001$ ). An analysis of ECOG 4599 found that patients with adenocarcinoma histology receiving bevacizumab/paclitaxel/carboplatin had improved survival compared with chemotherapy alone (14.2 vs. 10.3 months).<sup>947</sup> A trial (AVAIL) comparing cisplatin/gemcitabine with (or without) bevacizumab did not show an increase in survival with the addition of bevacizumab.<sup>956,957</sup> For the 2019 update (Version 6), the NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the systemic therapy regimens containing bevacizumab (eg, carboplatin plus paclitaxel plus bevacizumab) that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.<sup>289-293</sup>

A noninferiority trial in 1725 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) assessed cisplatin/gemcitabine compared with cisplatin/pemetrexed.<sup>252</sup> Patients with either adenocarcinoma or large cell carcinoma (ie, nonsquamous NSCLC) had improved survival with cisplatin/pemetrexed (adenocarcinoma: 12.6 vs. 10.9 months). Patients with squamous cell carcinoma had improved survival with the cisplatin/gemcitabine regimen (10.8 vs. 9.4 months). When compared with the cisplatin/gemcitabine regimen, 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%]). An analysis of three phase 3 trials confirmed that pemetrexed improves survival for patients with nonsquamous NSCLC in first-line, subsequent, and maintenance therapy.<sup>958</sup>

### Number of Cycles of First-Line Systemic Therapy

Patients receiving first-line systemic therapy for advanced disease should be evaluated for tumor response with a CT scan. Response assessment should occur after 2 cycles and then every 2 to 4 cycles using CT of known sites of disease (with or without contrast) or when clinically indicated.<sup>205,905-907</sup> Approximately 25% of patients show disease progression after the initial cycle of chemotherapy; subsequent therapy is recommended for these patients (see the NCCN Guidelines for NSCLC). Patients with responsive or stable disease can continue to receive a total of 4 to 6 cycles of systemic therapy.<sup>604,803,959</sup> The NCCN Guidelines do not recommend continuing chemotherapy beyond 4 to 6 cycles.

Data from the PARAMOUNT trial suggest that 4 cycles of platinum-based therapy is not optimal,<sup>795</sup> tumors can shrink between 4 to 6 cycles of chemotherapy. However, patients may not be able to tolerate more than 4 cycles of chemotherapy, and most of the maintenance trials used only 4 cycles of chemotherapy.<sup>661</sup> A meta-analysis suggests that continuing the initial regimen beyond 4 to 6 cycles is associated with increased PFS; patients have more adverse events.<sup>960</sup> A phase 3 randomized trial suggested that continuing chemotherapy beyond 4 to 6 cycles is not beneficial; however, many patients assigned to a longer duration of therapy did not receive the planned number of cycles.<sup>802,803</sup> In this phase 3 trial, taxane-based regimens were used and patients had increasing neurotoxicity as more cycles were used.<sup>803</sup>

Many patients with adenocarcinoma receive pemetrexed-based regimens and not taxane-based regimens. Pemetrexed-based regimens are less toxic than taxane-based regimens. Thus, data suggesting that more than 6 cycles of first-line chemotherapy are not appropriate may only apply to taxane-based regimens.<sup>661</sup> Studies report that 60% of patients were able to receive 6 cycles of pemetrexed-based chemotherapy (and had a low incidence of toxicity), whereas only 42% were able to receive more than 5

cycles of taxane-based chemotherapy and often stopped therapy because of neurotoxicity.<sup>793,803</sup>

### Maintenance Therapy

For patients with nonsquamous NSCLC who are negative or have unknown rearrangements, mutations, or PD-L1 expression, maintenance therapy is another option for those with responsive or stable disease after first-line systemic therapy (see the NCCN Guidelines for NSCLC).

Continuation maintenance therapy includes bevacizumab (category 1), pemetrexed (category 1), bevacizumab/pemetrexed (category 2A), or gemcitabine (category 2B) (see the NCCN Guidelines for NSCLC).<sup>251,663,765,795,797,799,800</sup> For the 2019 update (Version 6), the NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the systemic therapy regimens containing bevacizumab (eg, carboplatin/paclitaxel/bevacizumab) that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.<sup>289-293</sup>

Switch maintenance therapy for these patients includes pemetrexed (category 2A).<sup>799,800,805,806</sup> Recently, the NCCN NSCLC Panel revised the recommendation for switch maintenance therapy with pemetrexed to category 2A (from 2B) based on clinical experience.

A phase 3 randomized trial in 663 patients assessed the effect of best supportive care with (or without) switch maintenance pemetrexed in patients with advanced NSCLC who had received platinum-based chemotherapy but had not progressed.<sup>806</sup> In patients with nonsquamous NSCLC, overall survival was 13.4 months (95% CI, 11.9–15.9) with pemetrexed compared with 10.6 months (8.7–12.0) with placebo (HR, 0.50; 95% CI, 0.42–0.61,  $P < .0001$ ). Close observation is another option. Maintenance therapy is discussed in greater detail earlier in this Discussion (see *Combined Modality Therapy: Maintenance Therapy*).

The NCCN NSCLC Panel recently deleted the recommendation for erlotinib as switch maintenance therapy (and as subsequent therapy) for patients with nonsquamous NSCLC and PS 0 to 2 but without *EGFR* mutations based on results from a randomized trial (IUNO) and revised indication by the FDA.<sup>808</sup> The data showed that overall survival and PFS were not improved in patients receiving erlotinib when compared with placebo. For patients with squamous cell carcinoma, gemcitabine (category 2B) is recommended as continuation maintenance therapy (see the NCCN Guidelines for NSCLC).<sup>800,805</sup> Docetaxel is recommended (category 2B) as switch maintenance therapy for these patients. Close observation is a category 2A option. As previously mentioned, a phase 3 randomized trial compared using maintenance therapy with either gemcitabine or erlotinib after initial cytotoxic therapy with cisplatin-gemcitabine. Continuation maintenance therapy with single-agent gemcitabine increased PFS to a greater extent (3.8 months) than switch maintenance therapy with erlotinib (2.9 months) when compared with observation (1.9 months).<sup>799,800</sup> The benefits of maintenance therapy were very slight; therefore, the recommendation is only category 2B for maintenance therapy with gemcitabine. A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.<sup>810</sup> Switch maintenance therapy with docetaxel is a category 2B recommendation in the NCCN Guidelines, because many patients in the delayed chemotherapy arm did not receive docetaxel.<sup>961</sup>

### Continuation of Targeted Therapy After Progression on Initial Therapy

Patients may continue to derive benefit from EGFR TKIs or ALK inhibitors after disease progression on first-line therapy; discontinuation of these TKIs leads to more rapid progression of disease (symptoms, tumor size, FDG-avidity on PET scan).<sup>962</sup> This strategy mirrors the experience in other oncogene-addicted cancers, such as ALK inhibitors.<sup>963</sup> Because of

previous restrictions on the use of gefitinib, erlotinib was commonly used in the United States in patients with sensitizing *EGFR* mutations. Gefitinib was re-approved by the FDA based on a phase 4 study and is available in the United States.<sup>145</sup> After development of acquired resistance in patients with lung adenocarcinoma and sensitizing *EGFR* mutations, erlotinib, gefitinib, afatinib, dacomitinib, or osimertinib may be continued, but osimertinib as second-line therapy is also an option for select patients; local therapy should be considered (eg, SRS to brain metastases or other sites, SABR for thoracic disease).<sup>553,875,876,964,965</sup>

Accumulating data suggest how cancers become resistant to EGFR inhibitors.<sup>966</sup> The most common known mechanism is the acquisition of T790M (which is a secondary mutation in *EGFR*), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib, or afatinib.<sup>967,968</sup> Therefore, if patients are T790M positive, osimertinib is recommended (category 1) and erlotinib, gefitinib, dacomitinib, or afatinib are discontinued. Amplification of the *MET* oncogene is another validated resistance mechanism. To overcome resistance, EGFR must still be inhibited. In the case of *MET* amplification, new inhibitors must be added to the EGFR inhibitor; EGFR inhibition is still required to induce remission. Furthermore, data by Riely et al show that when cancers start to progress, which were once sensitive to EGFR inhibitors, discontinuation of the EGFR TKI can lead to a much more accelerated progression of the cancer.<sup>962,969</sup> Thus, continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.<sup>965</sup>

The NCCN NSCLC Panel recommends continuing erlotinib, gefitinib, afatinib, dacomitinib, or osimertinib and considering local therapy in patients with asymptomatic progression; however, treatment varies for patients with symptomatic progression (see *Sensitizing EGFR Mutation Positive: Subsequent Therapy* in the NCCN Guidelines for NSCLC).<sup>935,964,970-972</sup> Osimertinib is recommended (category 1) for patients

with symptomatic brain metastases and T790M who have progressed on erlotinib, gefitinib, dacomitinib, or afatinib.<sup>208</sup> Another option is to continue use of erlotinib, gefitinib, dacomitinib, or afatinib for these patients with symptomatic brain metastases; additional therapy may be added or substituted (eg, local therapy, systemic therapy). First-line systemic therapy options are recommended for patients with multiple symptomatic lesions who are negative for T790M; osimertinib is recommended (category 1) as subsequent therapy for patients positive for T790M who have progressed on erlotinib, gefitinib, dacomitinib, or afatinib. After progression on osimertinib, patients with sensitizing *EGFR* mutations may continue to derive benefit from osimertinib; other options are also recommended [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion]. After progression on alectinib, brigatinib, or ceritinib, patients with *ALK* rearrangements may continue to derive benefit from these agents; other options are also recommended [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion].

### Second-Line and Beyond (Subsequent) Systemic Therapy

The phrase *subsequent* therapy was recently substituted for the terms *second-line*, *third-line*, and *beyond* systemic therapy, because the line of therapy may vary depending on previous treatment with targeted agents. Subsequent systemic therapy regimens for patients who have disease progression during or after first-line therapy are described in the NSCLC algorithm and depend on the specific genetic alteration, the histologic subtype, and whether the patient has symptoms (see the NCCN Guidelines for NSCLC).<sup>973-982</sup> The NCCN NSCLC Panel recommends response assessment of known sites of disease with CT (with contrast) every 6 to 12 weeks in patients receiving subsequent therapy. Note that traditional RECIST response criteria (1.1) are used to assess response for most types of systemic therapy, but different response criteria may be

useful for assessing response in patients receiving immunotherapy.<sup>205,905,907,983,984</sup>

The NCCN NSCLC Panel recommends immune checkpoint inhibitors as preferred agents for subsequent therapy in patients with metastatic NSCLC based on improved survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy (see *Nivolumab*, *Pembrolizumab*, and *Atezolizumab* in this Discussion).<sup>279,282,790</sup> Human immune-checkpoint-inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.<sup>279-281</sup> The NCCN NSCLC Panel recommends nivolumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC based on phase 3 randomized trials (CheckMate 017 and CheckMate 057) and FDA approvals.<sup>279,769</sup> The NCCN NSCLC Panel recommends pembrolizumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC and PD-L1 expression based on a phase 2/3 randomized trial (KEYNOTE-010), KEYNOTE-001 trial, and FDA approval.<sup>296,785</sup> The NCCN NSCLC Panel also recommends atezolizumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC based on a phase 3 randomized trial (OAK), data from a phase 2 trial (POPLAR), and FDA approval.<sup>284,295,790</sup> The NCCN NSCLC Panel recommends osimertinib (category 1) as subsequent therapy for patients with metastatic *EGFR* T790M-positive NSCLC who have progressed on erlotinib, gefitinib, dacomitinib, or afatinib therapy based on recent data and on the FDA approval (see *Osimertinib* in this Discussion).<sup>208,212</sup>

For patients with sensitizing *EGFR* mutations who progress during or after first-line erlotinib, afatinib, gefitinib, dacomitinib, or osimertinib therapy, recommended subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes: 1) considering local therapy;

2) continuing erlotinib, afatinib, gefitinib, dacomitinib, or osimertinib; 3) taking osimertinib if not previously given and T790M positive; or 4) taking a first-line systemic therapy regimen for nonsquamous NSCLC (such as cisplatin/pemetrexed). The NCCN NSCLC Panel recommends osimertinib (category 1) for patients with T790M who have brain metastases and have progressed on erlotinib, afatinib, dacomitinib, or gefitinib.<sup>208,719-721</sup> Data suggest that an afatinib/cetuximab regimen may be useful for patients who have progressed after receiving erlotinib, afatinib, or gefitinib and after chemotherapy.<sup>985</sup> Patients with T790M-positive and T790M-negative tumors had a similar response rate to an afatinib/cetuximab regimen (32% vs. 25%;  $P = .341$ ). The NCCN NSCLC Panel recommends (category 2A) considering an afatinib/cetuximab regimen for patients who have progressed after receiving erlotinib, afatinib, dacomitinib, or gefitinib and chemotherapy based on these data.

The NCCN NSCLC Panel recently added a new subsequent therapy algorithm for patients with advanced NSCLC and sensitizing *EGFR* mutations who progress during or after first-line therapy with osimertinib. Recommended subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes: 1) considering local therapy; and/or 2) continuing osimertinib or switching to a first-line systemic therapy regimen for nonsquamous NSCLC (such as cisplatin/pemetrexed). There are no data to support using erlotinib, gefitinib, dacomitinib, or afatinib after progression on osimertinib.

Among patients with sensitizing *EGFR* mutations, no improvement in overall survival has been noted in the phase 3 trials assessing subsequent therapy with pembrolizumab, nivolumab, or atezolizumab compared to docetaxel, but there were not enough patients with these mutations to determine whether there were statistically significant differences.<sup>279,296,297,790</sup> Immunotherapy was not worse than chemotherapy and was better tolerated. In the phase 3 trials for pembrolizumab, nivolumab, or

atezolizumab versus docetaxel as subsequent therapy for patients with metastatic NSCLC, subset analyses were done in patients with *EGFR* mutations to determine the best subsequent therapy.<sup>279,296,790</sup> The HRs for overall survival do not favor docetaxel over nivolumab (HR, 1.18; CI, 0.69–2.0), pembrolizumab (HR, 0.88; CI, 0.45–1.7), or atezolizumab (HR, 1.24; CI, 0.7–2.2); the CIs for the HRs are wide probably because there were so few patients with *EGFR* mutations. The HRs for PFS do favor docetaxel for patients with *EGFR* mutations when compared with either pembrolizumab (HR, 1.79; CI, 0.94–3.42) or nivolumab (HR, 1.46; CI, 0.90–2.37). But again, the CIs are wide. The evidence is weak for recommending docetaxel, pembrolizumab, nivolumab, or atezolizumab as subsequent therapy for patients with *EGFR* mutations. Data suggest that patients with *EGFR* mutations or *ALK* rearrangements have a low response rate to PD-1 or PD-L1 inhibitors when compared with patients without these genetic alterations (response rate, 3.6% vs. 23%, respectively).<sup>297</sup> Therefore, the NCCN NSCLC Panel recently deleted the recommendation for pembrolizumab as subsequent therapy for patients with PD-L1 expression of 50% or more and genetic alterations such as *EGFR* mutations or *ALK* rearrangements.

For the 2019 update (Version 2), the NCCN NSCLC Panel now recommends lorlatinib (category 2A) as a subsequent therapy option for select patients with *ALK*-positive NSCLC who have progressed after treatment with *ALK* inhibitors (see *Lorlatinib* in this Discussion). For patients with *ALK* rearrangements who progress during or after first-line targeted therapy, recommended subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes: 1) considering local therapy (eg, SABR, SRS, surgery); 2) continuing alectinib, brigatinib, crizotinib, or ceritinib; 3) taking alectinib, brigatinib, or ceritinib (if all were not previously given) or lorlatinib; or 4) taking a first-line systemic therapy regimen for nonsquamous NSCLC. After further progression on subsequent targeted therapy, options include: 1)

lorlatinib; or 2) first-line combination chemotherapy options for NSCLC (eg, carboplatin/paclitaxel), which are recommended for patients with PS of 0 to 1.<sup>146,986</sup>

Other chemotherapy options are also recommended for patients with PS 2, such as docetaxel (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). Patients with *ALK*-positive NSCLC and very high PD-L1 expression do not respond to pembrolizumab.<sup>297</sup> In addition, those with *MET* exon 14 mutations and high PD-L1 expression also do not respond to immunotherapy.<sup>987</sup> For the 2019 update (Version 2), the NCCN NSCLC Panel also recommends lorlatinib (category 2A) as a subsequent therapy option for select patients with *ROS1*-positive NSCLC who have progressed after treatment with crizotinib or ceritinib. Most patients with NSCLC do not have *ALK* rearrangements, *ROS1* rearrangements, *BRAF* V600E mutations, or sensitizing *EGFR* mutations. For patients with all histologic subtypes and PS of 0 to 2 but without these genetic alterations who have disease progression during or after initial cytotoxic therapy, recommended subsequent systemic therapy options include immunotherapy (nivolumab, pembrolizumab, or atezolizumab [category 1 for all] if any were not previously given) or chemotherapy (docetaxel with or without ramucirumab, or gemcitabine if not already given; pemetrexed is recommended for patients with nonsquamous NSCLC) if not already given. The NCCN NSCLC Panel recommends immune checkpoint inhibitors—nivolumab, pembrolizumab, or atezolizumab if not already given—as preferred options for subsequent therapy for all histologic subtypes based on improved survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy (see *Nivolumab*, *Pembrolizumab*, and *Atezolizumab* in this Discussion).<sup>279,282,790</sup>

Immunotherapy is superior to docetaxel; however, some patients cannot tolerate immunotherapy. Ramucirumab/docetaxel is an option for all histologic subtypes for subsequent therapy based on a phase 3 randomized trial (see *Ramucirumab* in this Discussion).<sup>692</sup> Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.<sup>979,980</sup> When compared with docetaxel, pemetrexed has similar median survival but less toxicity.<sup>981,988</sup> Pemetrexed is recommended in patients with nonsquamous NSCLC.<sup>806</sup> Docetaxel is recommended for patients with wild-type *EGFR* tumors based on 2 randomized trials comparing erlotinib versus docetaxel.<sup>989,990</sup> In patients with PS of 3 to 4, best supportive care is recommended (see the NCCN Guidelines for NSCLC).<sup>12,611,612</sup> Patients often have a limited response to subsequent chemotherapy other than immune checkpoint inhibitors, although chemotherapy may serve a useful palliative role.<sup>991</sup>

The NCCN NSCLC Panel recently deleted the recommendation for erlotinib as subsequent therapy (and as switch maintenance therapy) for patients with nonsquamous NSCLC and PS of 0 to 2 but without *EGFR* mutations based on results from a randomized trial (IUNO) and revised indication by the FDA.<sup>808</sup> Data showed that overall survival and PFS were not improved in patients receiving erlotinib when compared with placebo. Recently, the NCCN NSCLC Panel deleted erlotinib as an option for subsequent therapy for patients with squamous cell NSCLC based on a study comparing afatinib with erlotinib; this study was statistically significant but not clinically significant.<sup>711</sup> Overall survival was slightly better in the afatinib group than in the erlotinib group (median overall survival, 7.9 months [95% CI, 7.2–8.7] vs. 6.8 months [95% CI, 5.9–7.8]; HR, 0.81 [95% CI, 0.69–0.95],  $P=0.0077$ ); however, almost 60% of patients in each arm had grade 3 or higher adverse events. In contrast, the median overall survival was 9.2 months with nivolumab compared with 6.0 months for docetaxel for patients with squamous cell NSCLC.<sup>282</sup> In addition, only 7% of patients receiving nivolumab had grade 3 or higher adverse events.

Erlotinib and afatinib are not recommended as second-line therapy for squamous cell carcinoma based on a phase 3 randomized trial showing low response rates; they are less efficacious and safe compared to other available options.<sup>711</sup>

Doublet chemotherapy options used for initial cytotoxic therapy are recommended for patients with metastatic NSCLC (eg, carboplatin/paclitaxel) and genetic alterations who progress with symptomatic systemic multiple lesions after first-line targeted therapy.<sup>251</sup> Recent data (IMPRESS) indicate that chemotherapy should be used alone and not be combined with EGFR inhibitors such as gefitinib in patients who have progressed on gefitinib.<sup>992</sup> Erlotinib, gefitinib, afatinib, dacomitinib, or osimertinib may be continued in patients with sensitizing *EGFR* mutations who have progressed after first-line therapy, depending on the type of progression.<sup>189,935,971,972</sup> Osimertinib is recommended for patients with T790M whose disease becomes resistant to erlotinib, afatinib, or gefitinib.<sup>212</sup> Afatinib/cetuximab may be considered for patients with sensitizing *EGFR* mutations who have progressed after erlotinib, gefitinib, dacomitinib, or afatinib and after doublet chemotherapy.<sup>985</sup> Ceritinib, alectinib, or brigatinib are recommended in patients with *ALK*-positive NSCLC who have progressed after first-line therapy with crizotinib or for patients who are intolerant to crizotinib.<sup>144,250,752</sup> Flare phenomenon may occur in some patients who discontinue *ALK* inhibitors. If disease flare occurs, then *ALK* inhibitors should be restarted.<sup>963,993</sup> Subsequent therapy is recommended after second disease progression in patients with advanced NSCLC and a PS of 0 to 2 if the following agents have not already been given: 1) immune checkpoint inhibitors including nivolumab, pembrolizumab, and atezolizumab if none have been previously given (all are category 2A); 2) docetaxel with or without ramucirumab (category 2B for both); 3) gemcitabine (category 2B); or 4) pemetrexed (nonsquamous only) (category 2B).<sup>974,990,994,995</sup>



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

For patients with metastatic NSCLC who have progressed after first-line therapy with pembrolizumab, platinum-based doublet therapy is recommended (eg, carboplatin/paclitaxel). For patients with metastatic NSCLC who have progressed after first-line therapy with PD-1/PD-L1 inhibitors/chemotherapy, subsequent therapy with docetaxel (with or without ramucirumab), pemetrexed (for nonsquamous only), or gemcitabine is recommended. Clinical trials are also recommended in these settings.

### Summary

The NCCN Guidelines for NSCLC are updated at least once a year by the NCCN NSCLC Panel; there have been 7 updates for the 2019 guidelines. The *Summary of the Guidelines Updates* describes the most recent revisions to the algorithms, which have been incorporated into this updated Discussion text (see the NCCN Guidelines for NSCLC). A brief summary of some of the recent updates is as follows: For the 2019 update (Version 1), the NCCN NSCLC Panel recommends several new regimens for patients with metastatic NSCLC, including: 1) dacomitinib (category 1) as a first-line treatment option for sensitizing *EGFR*-mutation–positive disease;<sup>729</sup> 2) brigatinib (category 1) as a first-line treatment option for *ALK*-positive disease;<sup>756</sup> and 3) nivolumab with or without ipilimumab (category 2A) as first-line therapy for high TMB.<sup>170</sup> For the Version 2 update, lorlatinib (category 2A) is recommended as a subsequent therapy option for certain patients with *ALK*-positive or *ROS1*-positive NSCLC who have progressed after treatment with *ALK* inhibitors.<sup>245</sup> For the Version 3 update, larotrectinib is recommended as either a first-line or subsequent therapy option for patients with *NTRK* gene–fusion positive metastatic NSCLC.<sup>270,271</sup> For the Version 6 update, the NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the systemic therapy regimens containing bevacizumab (eg, carboplatin plus paclitaxel plus bevacizumab) that are used for eligible patients with metastatic NSCLC.<sup>289-293</sup> For the Version 7 update, the NCCN NSCLC

Panel recommends entrectinib as a first-line option for patients with *ROS1* positive metastatic NSCLC (category 2A, preferred) and also recommends entrectinib as either a first-line or subsequent therapy option for *NTRK* gene fusion–positive metastatic NSCLC (category 2A).<sup>259-261</sup>

In addition, several regimens are now preferred as first-line therapy for patients with metastatic NSCLC, including: 1) osimertinib monotherapy for sensitizing *EGFR* mutation–positive disease (preferred, category 1);<sup>713</sup> 2) pembrolizumab monotherapy (preferred, category 1) for patients with PD-L1 expression levels of 50% or more and with negative or unknown test results for *EGFR* mutations or *ALK* rearrangements, regardless of histology;<sup>9,104</sup> 3) pembrolizumab/carboplatin (or cisplatin)/pemetrexed (preferred, category 1) for patients with nonsquamous NSCLC, negative or unknown test results for *EGFR* mutations or *ALK* rearrangements, and PD-L1 expression levels less than 50% or unknown; and 4) pembrolizumab/carboplatin/paclitaxel (or albumin-bound paclitaxel) for patients with metastatic squamous cell carcinoma NSCLC (preferred, category 1).<sup>287</sup> The NCCN NSCLC Panel clarified the recommendations for pembrolizumab/chemotherapy in patients with metastatic nonsquamous NSCLC and PD-L1 expression levels of 1% to 49% for the 2019 update (Version 5); all of the regimens are *preferred* category 1 recommendations in this setting. Thus, the pembrolizumab/carboplatin (or cisplatin)/pemetrexed regimens are category 1 recommended options for patients with metastatic nonsquamous NSCLC regardless of PD-L1 expression levels; however, these regimens are preferred for those whose PD-L1 levels are less than 50% or unknown.<sup>287</sup> In addition, the NCCN NSCLC Panel also clarified the recommendations for pembrolizumab/carboplatin/paclitaxel (or albumin-bound paclitaxel) in patients with metastatic squamous cell carcinoma NSCLC and PD-L1 expression levels of 1% to 49% for the 2019 update (Version 5); these regimens are *preferred* category 1 recommendations in this setting. The pembrolizumab/carboplatin/paclitaxel (or albumin-bound paclitaxel)





regimens are category 1 recommended options for patients with metastatic squamous cell carcinoma NSCLC regardless of PD-L1 expression levels; however, these regimens are preferred for those whose PD-L1 levels are less than 50% or unknown.<sup>294</sup>

Other recent updates for 2019 (Version 1) include: 1) new algorithms were added for sequencing systemic therapy with first-line PD-1 or PD-L1 inhibitors with or without chemotherapy in patients with metastatic NSCLC based on their PD-L1 expression levels and with negative or unknown test results for *EGFR* mutations or *ALK* rearrangements; and 2) the RT section in the algorithm was extensively revised; for example, some of the normal tissue dose constraints for conventionally fractionated RT were revised (see Table 5 in the *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC). Also, panel members voted to upgrade several regimens to category 1 recommendations (from category 2A) based on recent trial data, including: 1) durvalumab as consolidation immunotherapy after concurrent chemoradiation for patients with unresectable stage III NSCLC;<sup>652</sup> and 2) pembrolizumab/carboplatin/paclitaxel (or albumin-bound paclitaxel) for patients with metastatic squamous cell carcinoma NSCLC (preferred).<sup>294</sup> For the 2019 update (Version 4), the NCCN NSCLC Panel added another recommendation for single-agent pembrolizumab as first-line therapy in patients with metastatic NSCLC regardless of histology, PD-L1 levels of 1% to 49% (category 2B), and negative or unknown test results for *EGFR* mutations and *ALK* rearrangements.<sup>286</sup> Based on clinical trial data, the NCCN NSCLC Panel retained the category 1 preferred recommendation for single-agent pembrolizumab as first-line therapy in a similar setting but in patients with PD-L1 levels of 50% or more.<sup>104,286</sup>

### References

1. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. *Adv Exp Med Biol* 2016;893:1-19. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26667336>.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7-34. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30620402>.
3. Noone AM, Howlander N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2015, based on November 2017 SEER data submission, posted to the SEER web site, April 2018. Bethesda, MD: National Cancer Institute; 2018. Available at: [https://seer.cancer.gov/csr/1975\\_2015/](https://seer.cancer.gov/csr/1975_2015/).
4. Brahmer JR, Govindan R, Anders RA, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). *J Immunother Cancer* 2018;6:75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30012210>.
5. Johnson DH, Schiller JH, Bunn PA, Jr. Recent clinical advances in lung cancer management. *J Clin Oncol* 2014;32:973-982. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24567433>.
6. Reck M, Heigener DF, Mok T, et al. Management of non-small-cell lung cancer: recent developments. *Lancet* 2013;382:709-719. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23972814>.
7. Forde PM, Ettinger DS. Targeted therapy for non-small-cell lung cancer: past, present and future. *Expert Rev Anticancer Ther* 2013;13:745-758. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23773106>.
8. Ettinger DS. Ten years of progress in non-small cell lung cancer. *J Natl Compr Canc Netw* 2012;10:292-295. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22393190>.
9. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol* 2019;37:537-546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30620668>.
10. Zhao D, Chen X, Qin N, et al. The prognostic role of EGFR-TKIs for patients with advanced non-small cell lung cancer. *Sci Rep* 2017;7:40374. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28079142>.
11. Johung KL, Yeh N, Desai NB, et al. Extended survival and prognostic factors for patients with ALK-rearranged non-small-cell lung cancer and brain metastasis. *J Clin Oncol* 2016;34:123-129. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26438117>.
12. Simoff MJ, Lally B, Slade MG, et al. Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e455S-e497S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649452>.
13. Ettinger DS, Cox JD, Ginsberg RJ, et al. NCCN Non-Small-Cell Lung Cancer Practice Guidelines. The National Comprehensive Cancer Network. *Oncology (Williston Park)* 1996;10:81-111. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8953597>.
14. Alberg AJ, Brock MV, Ford JG, et al. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e1S-e29S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649439>.
15. Subramanian J, Govindan R. Lung cancer in never smokers: a review. *J Clin Oncol* 2007;25:561-570. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17290066>.
16. The Health Consequences of Smoking: A Report of the Surgeon General. (ed 2010/07/30). Atlanta (GA): U.S. Department of Health and Human Services. Centers for Disease Control and Prevention (US); 2004.
17. Secretan B, Straif K, Baan R, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

fish. *Lancet Oncol* 2009;10:1033-1034. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/19891056>.

18. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *Br Med J* 1976;2:1525-1536. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/1009386>.

19. Taylor R, Najafi F, Dobson A. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. *Int J Epidemiol* 2007;36:1048-1059. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/17690135>.

20. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. (ed 2010/07/30). Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2006.

21. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ* 1997;315:980-988. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/9365295>.

22. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS. Does breathing other people's tobacco smoke cause lung cancer? *Br Med J (Clin Res Ed)* 1986;293:1217-1222. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/3096439>.

23. Fraumeni JF, Jr. Respiratory carcinogenesis: an epidemiologic appraisal. *J Natl Cancer Inst* 1975;55:1039-1046. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/1107567>.

24. Janerich DT, Thompson WD, Varela LR, et al. Lung cancer and exposure to tobacco smoke in the household. *N Engl J Med* 1990;323:632-636. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/2385268>.

25. Straif K, Benbrahim-Tallaa L, Baan R, et al. A review of human carcinogens--Part C: metals, arsenic, dusts, and fibres. *Lancet Oncol* 2009;10:453-454. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/19418618>.

26. Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. *Am J Ind Med* 2005;48:419-431. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/16299703>.

27. Humans IWGotEoCRt. Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risks Hum 2012;100:11-465. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/23189751>.

28. Omenn GS, Merchant J, Boatman E, et al. Contribution of environmental fibers to respiratory cancer. *Environ Health Perspect* 1986;70:51-56. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/3830113>.

29. Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. *Lancet* 2009;374:1243-1251. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/19767090>.

30. Chlebowski RT, Anderson GL, Manson JE, et al. Lung cancer among postmenopausal women treated with estrogen alone in the women's health initiative randomized trial. *J Natl Cancer Inst* 2010;102:1413-1421. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/20709992>.

31. Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. *N Engl J Med* 2013;368:351-364. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/23343064>.

32. Shiels MS, Gibson T, Sampson J, et al. Cigarette smoking prior to first cancer and risk of second smoking-associated cancers among survivors of bladder, kidney, head and neck, and stage I lung cancers. *J Clin Oncol* 2014;32:3989-3995. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25385740>.

33. Leone FT, Evers-Casey S, Toll BA, Vachani A. Treatment of tobacco use in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice

guidelines. Chest 2013;143:e61S-e77S. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/23649454>.

34. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013;368:341-350. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/23343063>.

35. Rigotti NA. Strategies to help a smoker who is struggling to quit. JAMA 2012;308:1573-1580. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/23073954>.

36. Five Major Steps to Intervention (The "5 A's"). Vol. December. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Available at: <https://bit.ly/1jXzEvC>.

37. Tao L, Wang R, Gao YT, Yuan JM. Impact of postdiagnosis smoking on long-term survival of cancer patients: the Shanghai cohort study. Cancer Epidemiol Biomarkers Prev 2013;22:2404-2411. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/24319070>.

38. Marino KA, Little MA, Bursac Z, et al. Operating on Patients Who Smoke: A Survey of Thoracic Surgeons in the United States. Ann Thorac Surg 2016;102:911-916. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/27474514>.

39. Treating Tobacco Use and Dependence. Vol. April. Rockville, MD: Agency for Healthcare Research and Quality; 2013. Available at:  
<https://bit.ly/28KMo4K>.

40. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;5:CD009329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23728690>.

41. Koegelenberg CF, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. JAMA 2014;312:155-161. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25005652>.

42. Walker N, Howe C, Glover M, et al. Cytisine versus nicotine for smoking cessation. N Engl J Med 2014;371:2353-2362. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25517706>.

43. Aubin HJ, Bobak A, Britton JR, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax 2008;63:717-724. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/18263663>.

44. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006;296:56-63. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/16820547>.

45. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006;296:47-55. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/16820546>.

46. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2011:CD006103. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21328282>.

47. Ware JH, Vetrovec GW, Miller AB, et al. Cardiovascular safety of varenicline: patient-level meta-analysis of randomized, blinded, placebo-controlled trials. Am J Ther 2013;20:235-246. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/23615317>.

48. Haber SL, Boomershine V, Raney E. Safety of varenicline in patients with cardiovascular disease. Journal of Pharmacy Practice 2013;27:65-70. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24080536>.

49. Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. Circulation 2014;129:28-41. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/24323793>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

50. Xi ZX. Preclinical pharmacology, efficacy and safety of varenicline in smoking cessation and clinical utility in high risk patients. *Drug Healthc Patient Saf* 2010;2010:39-48. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21278851>.
51. Gonzales D, Hajek P, Pliamm L, et al. Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. *Clin Pharmacol Ther* 2014;96:390-396. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24911368>.
52. Garrison GD, Dugan SE. Varenicline: a first-line treatment option for smoking cessation. *Clin Ther* 2009;31:463-491. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19393839>.
53. Hays JT, Ebbert JO. Adverse effects and tolerability of medications for the treatment of tobacco use and dependence. *Drugs* 2010;70:2357-2372. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21142259>.
54. Carney DN. Lung cancer--time to move on from chemotherapy. *N Engl J Med* 2002;346:126-128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11784881>.
55. Chute JP, Chen T, Feigal E, et al. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. *J Clin Oncol* 1999;17:1794-1801. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10561217>.
56. National Lung Screening Trial Research T, Aberle DR, Berg CD, et al. The National Lung Screening Trial: overview and study design. *Radiology* 2011;258:243-253. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21045183>.
57. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395-409. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21714641>.
58. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Baseline characteristics of participants in the randomized national lung screening trial. *J Natl Cancer Inst* 2010;102:1771-1779. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21119104>.
59. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e78S-e92S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649455>.
60. Vansteenkiste J, Crino L, Dooms C, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Ann Oncol* 2014;25:1462-1474. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24562446>.
61. Smith RA, Brooks D, Cokkinides V, et al. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. *CA Cancer J Clin* 2013;63:88-105. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23378235>.
62. Moyer VA, Force USPST. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014;160:330-338. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24378917>.
63. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. *J Thorac Oncol* 2015;10:1243-1260. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26291008>.
64. Travis WD, Brambilla E, Burke AP, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, Volume 7. Lyon: International Agency for Research on Cancer; 2015:412.

65. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244-285. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21252716>.
66. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group Study. *J Clin Oncol* 1986;4:702-709. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3701389>.
67. Tammemagi MC, Church TR, Hocking WG, et al. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. *PLoS Med* 2014;11:e1001764. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25460915>.
68. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e93S-e120S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649456>.
69. American College of Radiology. Lung CT screening reporting and data system (Lung-RADS); 2016. Available at: <https://www.acr.org/Quality-Safety/Resources/LungRADS>.
70. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology* 2017;284:228-243. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28240562>.
71. MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005;237:395-400. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16244247>.
72. Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. *Radiology* 2013;266:304-317. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23070270>.
73. Blagev DP, Lloyd JF, Conner K, et al. Follow-up of incidental pulmonary nodules and the radiology report. *J Am Coll Radiol* 2014;11:378-383. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24316231>.
74. Gould MK, Tang T, Liu IL, et al. Recent trends in the identification of incidental pulmonary nodules. *Am J Respir Crit Care Med* 2015;192:1208-1214. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26214244>.
75. Gardiner N, Jogai S, Wallis A. The revised lung adenocarcinoma classification-an imaging guide. *J Thorac Dis* 2014;6:S537-546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25349704>.
76. Seidelman JL, Myers JL, Quint LE. Incidental, subsolid pulmonary nodules at CT: etiology and management. *Cancer Imaging* 2013;13:365-373. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24061063>.
77. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008;246:697-722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18195376>.
78. Yankelevitz DF, Yip R, Smith JP, et al. CT screening for lung cancer: nonsolid nodules in baseline and annual repeat rounds. *Radiology* 2015;277:555-564. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26101879>.
79. Travis WD, Brambilla E, Noguchi M, et al. Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. *Arch Pathol Lab Med* 2013;137:668-684. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22970842>.

80. Kim HY, Shim YM, Lee KS, et al. Persistent pulmonary nodular ground-glass opacity at thin-section CT: histopathologic comparisons. *Radiology* 2007;245:267-275. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17885195>.

81. Marshall HM, Bowman RV, Yang IA, et al. Screening for lung cancer with low-dose computed tomography: a review of current status. *J Thorac Dis* 2013;5 Suppl 5:S524-539. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24163745>.

82. Brawley OW, Flenaugh EL. Low-dose spiral CT screening and evaluation of the solitary pulmonary nodule. *Oncology (Williston Park)* 2014;28:441-446. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25004661>.

83. Pinsky PF, Gierada DS, Black W, et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. *Ann Intern Med* 2015;162:485-491. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25664444>.

84. McKee BJ, Regis SM, McKee AB, et al. Performance of ACR Lung-RADS in a clinical CT lung screening program. *J Am Coll Radiol* 2015;12:273-276. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25176499>.

85. Kazerooni EA, Austin JH, Black WC, et al. ACR-STR practice parameter for the performance and reporting of lung cancer screening thoracic computed tomography (CT): 2014 (Resolution 4). *J Thorac Imaging* 2014;29:310-316. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24992501>.

86. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e142S-e165S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649436>.

87. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer,

3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e211S-e250S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649440>.

88. Schwartz AM, Rezaei MK. Diagnostic surgical pathology in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e251S-e262S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649441>.

89. Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov* 2017;7:596-609. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28336552>.

90. Oxnard GR, Binder A, Janne PA. New targetable oncogenes in non-small-cell lung cancer. *J Clin Oncol* 2013;31:1097-1104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23401445>.

91. Cooper WA, O'Toole S, Boyer M, et al. What's new in non-small cell lung cancer for pathologists: the importance of accurate subtyping, EGFR mutations and ALK rearrangements. *Pathology* 2011;43:103-115. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21233671>.

92. Fossella FV, Putnam JB, Komaki R, eds. *Lung Cancer*. M.D. Anderson Cancer Care Series. New York: Springer; 2003:316.

93. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005;23:5900-5909. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16043828>.

94. Cappuzzo F, Ligorio C, Toschi L, et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2007;2:423-429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17473658>.

95. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363:1693-1703. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20979469>.
96. Travis WD, Brambilla E, Noguchi M, et al. Diagnosis of lung adenocarcinoma in resected specimens: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. *Arch Pathol Lab Med* 2013;137:685-705. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22913371>.
97. Cameron SE, Andrade RS, Pambuccian SE. Endobronchial ultrasound-guided transbronchial needle aspiration cytology: a state of the art review. *Cytopathology* 2010;21:6-26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20015257>.
98. Moreira AL, Thornton RH. Personalized medicine for non-small-cell lung cancer: implications of recent advances in tissue acquisition for molecular and histologic testing. *Clin Lung Cancer* 2012;13:334-339. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22424871>.
99. Thompson GR, 3rd. Pulmonary coccidioidomycosis. *Semin Respir Crit Care Med* 2011;32:754-763. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22167403>.
100. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA* 2011;305:391-399. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21266686>.
101. Centers for Disease C, Prevention. CDC Grand Rounds: the TB/HIV syndemic. *MMWR Morb Mortal Wkly Rep* 2012;61:484-489. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22763886>.
102. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. Pathology and genetics of tumours of the lung, pleura, thymus and heart, World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2004.
103. Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J Clin Oncol* 2013;31:992-1001. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23401443>.
104. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016;375:1823-1833. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27718847>.
105. Dugay F, Llamas-Gutierrez F, Gournay M, et al. Clinicopathological characteristics of ROS1- and RET-rearranged NSCLC in caucasian patients: Data from a cohort of 713 non-squamous NSCLC lacking KRAS/EGFR/HER2/BRAF/PIK3CA/ALK alterations. *Oncotarget* 2017;8:53336-53351. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28881815>.
106. Ou SI, Horn L, Cruz M, et al. Emergence of FGFR3-TACC3 fusions as a potential by-pass resistance mechanism to EGFR tyrosine kinase inhibitors in EGFR mutated NSCLC patients. *Lung Cancer* 2017;111:61-64. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28838400>.
107. Hyman DM, Laetsch TW, Kummar S, et al. The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers [abstract]. *J Clin Oncol* 2017;35:Abstract LBA2501. Available at: <https://meetinglibrary.asco.org/record/144598/abstract>.
108. Travis WD, Rekhtman N. Pathological diagnosis and classification of lung cancer in small biopsies and cytology: strategic management of tissue for molecular testing. *Semin Respir Crit Care Med* 2011;32:22-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21500121>.
109. Zakowski MF, Rekhtman N, Auger M, et al. Morphologic accuracy in differentiating primary lung adenocarcinoma from squamous cell carcinoma in cytology specimens. *Arch Pathol Lab Med* 2016;140:1116-1120. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27552093>.



110. Rekhtman N, Ang DC, Sima CS, et al. Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. *Mod Pathol* 2011;24:1348-1359. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21623384>.
111. Mukhopadhyay S, Katzenstein AL. Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: Utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6. *Am J Surg Pathol* 2011;35:15-25. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21164283>.
112. Terry J, Leung S, Laskin J, et al. Optimal immunohistochemical markers for distinguishing lung adenocarcinomas from squamous cell carcinomas in small tumor samples. *Am J Surg Pathol* 2010;34:1805-1811. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21107086>.
113. Ordonez NG. Thyroid transcription factor-1 is a marker of lung and thyroid carcinomas. *Adv Anat Pathol* 2000;7:123-127. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10721419>.
114. Husain AN, Colby T, Ordonez N, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2013;137:647-667. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22929121>.
115. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2009;133:1317-1331. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19653732>.
116. Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. *Hum Pathol* 2005;36:372-380. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15891998>.
117. Rivera MP, Mehta AC, Physicians ACoC. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:131S-148S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17873165>.
118. Tan D, Zander DS. Immunohistochemistry for assessment of pulmonary and pleural neoplasms: a review and update. *Int J Clin Exp Pathol* 2008;1:19-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18784820>.
119. Zhang H, Liu J, Cagle PT, et al. Distinction of pulmonary small cell carcinoma from poorly differentiated squamous cell carcinoma: an immunohistochemical approach. *Mod Pathol* 2005;18:111-118. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15309021>.
120. Amin MB, Greene FL, Edge SB, et al. *AJCC Staging Manual*, 8th ed: Springer International Publishing; 2017:1-1024.
121. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*, 7th ed. New York: Springer; 2010.
122. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017;67:138-155. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28140453>.
123. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016;11:39-51. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26762738>.
124. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007;2:706-714. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17762336>.

125. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest* 2009;136:260-271. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19584208>.

126. Rami-Porta R, Bolejack V, Goldstraw P. The new tumor, node, and metastasis staging system. *Semin Respir Crit Care Med* 2011;32:44-51. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21500123>.

127. Rami-Porta R, Crowley JJ, Goldstraw P. The revised TNM staging system for lung cancer. *Ann Thorac Cardiovasc Surg* 2009;15:4-9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19262443>.

128. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;28:iv1-iv21. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28881918>.

129. Ou SH, Zell JA, Ziogas A, Anton-Culver H. Prognostic factors for survival of stage I nonsmall cell lung cancer patients : a population-based analysis of 19,702 stage I patients in the California Cancer Registry from 1989 to 2003. *Cancer* 2007;110:1532-1541. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17702091>.

130. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. *Chest* 2007;132:193-199. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17505036>.

131. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *Arch Pathol Lab Med* 2018;142:321-346. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29355391>.

132. Mitchell RL, Kosche C, Burgess K, et al. Misdiagnosis of Li-Fraumeni syndrome in a patient with clonal hematopoiesis and a somatic TP53 mutation. *J Natl Compr Canc Netw* 2018;16:461-466. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29752319>.

133. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014;371:2488-2498. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25426837>.

134. Coombs CC, Zehir A, Devlin SM, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and associated with adverse clinical outcomes. *Cell Stem Cell* 2017;21:374-382 e374. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28803919>.

135. Miller VA, Riely GJ, Zakowski MF, et al. Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. *J Clin Oncol* 2008;26:1472-1478. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18349398>.

136. Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. *J Clin Oncol* 2008;26:2442-2449. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18458038>.

137. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer - molecular and clinical predictors of outcome. *N Engl J Med* 2005;353:133-144. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16014883>.

138. Mazieres J, Zalcman G, Crino L, et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. *J Clin Oncol* 2015;33:992-999. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25667280>.

139. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;371:1963-1971. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25264305>.

140. Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov*

2013;3:630-635. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23533264>.

141. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol* 2012;30:863-870.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22215748>.

142. Ou SH, Tan J, Yen Y, Soo RA. ROS1 as a 'druggable' receptor tyrosine kinase: lessons learned from inhibiting the ALK pathway. *Expert Rev Anticancer Ther* 2012;12:447-456. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22500682>.

143. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. *Nat Med* 2012;18:378-381. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22327623>.

144. Ou SH, Ahn JS, De Petris L, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. *J Clin Oncol* 2016;34:661-668. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26598747>.

145. Douillard JY, Ostoros G, Cobo M, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. *Br J Cancer* 2014;110:55-62. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24263064>.

146. Besse B, Adjei A, Baas P, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. *Ann Oncol* 2014;25:1475-1484.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24669016>.

147. Kerr KM, Bubendorf L, Edelman MJ, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. *Ann Oncol* 2014;25:1681-1690. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24718890>.

148. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists,

International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013;8:823-859. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23552377>.

149. Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with EGFR mutant advanced non-small cell lung cancers with a squamous or squamous-like component. *Mol Cancer Ther* 2012;11:2535-2540. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22896669>.

150. Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. *Cancer* 2009;115:1723-1733. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19170230>.

151. Forbes SA, Bhamra G, Bamford S, et al. The Catalogue of Somatic Mutations in Cancer (COSMIC). *Curr Protoc Hum Genet* 2008;Chapter 10:Unit 10 11. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18428421>.

152. Sholl LM, Aisner DL, Varella-Garcia M, et al. Multi-institutional Oncogenic Driver Mutation Analysis in Lung Adenocarcinoma: The Lung Cancer Mutation Consortium Experience. *J Thorac Oncol* 2015;10:768-777. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25738220>.

153. Ali G, Proietti A, Pelliccioni S, et al. ALK rearrangement in a large series of consecutive non-small cell lung cancers: comparison between a new immunohistochemical approach and fluorescence in situ hybridization for the screening of patients eligible for crizotinib treatment. *Arch Pathol Lab Med* 2014;138:1449-1458. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24885803>.

154. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol* 2016;17:984-993. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27283860>.

155. Gautschi O, Milia J, Cabarro B, et al. Targeted Therapy for Patients with BRAF-Mutant Lung Cancer: Results from the European EURAF Cohort. *J Thorac Oncol* 2015;10:1451-1457. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26200454>.

156. Shaw AT, Forcione DG, Digumarthy SR, Iafrate AJ. Case records of the Massachusetts General Hospital. Case 21-2011. A 31-year-old man with ALK-positive adenocarcinoma of the lung. *N Engl J Med* 2011;365:158-167. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21751909>.

157. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009;27:4247-4253. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19667264>.

158. Kim AS, Bartley AN, Bridge JA, et al. Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing. *JAMA Oncol* 2018;4:838-841. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29242895>.

159. Klempner SJ, Borghei A, Hakimian B, et al. Intracranial Activity of Cabozantinib in MET Exon 14-Positive NSCLC with Brain Metastases. *J Thorac Oncol* 2017;12:152-156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27693535>.

160. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016;17:642-650. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27080216>.

161. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov* 2015;5:850-859. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25971938>.

162. Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations

causing exon 14 skipping. *Cancer Discov* 2015;5:842-849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25971939>.

163. Villaruz LC, Socinski MA, Abberbock S, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. *Cancer* 2015;121:448-456. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25273224>.

164. Cardarella S, Ogino A, Nishino M, et al. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. *Clin Cancer Res* 2013;19:4532-4540. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23833300>.

165. Kelly RJ, Carter CA, Giaccone G. HER2 mutations in non-small-cell lung cancer can be continually targeted. *J Clin Oncol* 2012;30:3318-3319. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22649146>.

166. Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. *J Thorac Oncol* 2012;7:e23-24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22743296>.

167. Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. *J Clin Oncol* 2011;29:2046-2051. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21483012>.

168. Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat Med* 2012;18:382-384. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22327622>.

169. Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. *J Thorac Oncol* 2011;6:942-946. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21623265>.

170. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N Engl J Med* 2018;378:2093-2104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29658845>.

171. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;376:2415-2426. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28636851>.

172. Cardarella S, Ortiz TM, Joshi VA, et al. The introduction of systematic genomic testing for patients with non-small-cell lung cancer. *J Thorac Oncol* 2012;7:1767-1774. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23154547>.

173. Sequist LV, Heist RS, Shaw AT, et al. Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice. *Ann Oncol* 2011;22:2616-2624. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22071650>.

174. Lovly CM, Horn L. Molecular profiling of lung cancer. *My Cancer Genome*; 2016. Available at: <https://www.mycancergenome.org/content/disease/lung-cancer/>.

175. Pao W, Girard N. New driver mutations in non-small-cell lung cancer. *Lancet Oncol* 2011;12:175-180. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21277552>.

176. Slebos RJ, Kibbelaar RE, Dalesio O, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *N Engl J Med* 1990;323:561-565. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2199829>.

177. Roberts PJ, Stinchcombe TE. KRAS mutation: should we test for it, and does it matter? *J Clin Oncol* 2013;31:1112-1121. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23401440>.

178. Tsao MS, Aviel-Ronen S, Ding K, et al. Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell

lung cancer. *J Clin Oncol* 2007;25:5240-5247. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18024870>.

179. Kim HR, Lim SM, Kim HJ, et al. The frequency and impact of ROS1 rearrangement on clinical outcomes in never smokers with lung adenocarcinoma. *Ann Oncol* 2013;24:2364-2370. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23788756>.

180. Jennings LJ, Arcila ME, Corless C, et al. Guidelines for Validation of Next-Generation Sequencing-Based Oncology Panels: A Joint Consensus Recommendation of the Association for Molecular Pathology and College of American Pathologists. *J Mol Diagn* 2017;19:341-365. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28341590>.

181. Aziz N, Zhao Q, Bry L, et al. College of American Pathologists' laboratory standards for next-generation sequencing clinical tests. *Arch Pathol Lab Med* 2015;139:481-493. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25152313>.

182. Luthra R, Chen H, Roy-Chowdhuri S, Singh RR. Next-Generation Sequencing in Clinical Molecular Diagnostics of Cancer: Advantages and Challenges. *Cancers (Basel)* 2015;7:2023-2036. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26473927>.

183. Drilon A, Wang L, Arcila ME, et al. Broad, Hybrid Capture-Based Next-Generation Sequencing Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches. *Clin Cancer Res* 2015;21:3631-3639. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25567908>.

184. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol* 2015;33:3660-3667. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26324357>.

185. Yu PP, Vose JM, Hayes DF. Genetic Cancer Susceptibility Testing: Increased Technology, Increased Complexity. *J Clin Oncol* 2015;33:3533-3534. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26324366>.

186. Li T, Kung HJ, Mack PC, Gandara DR. Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies. *J Clin Oncol* 2013;31:1039-1049. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23401433>.

187. Planchard D. Identification of driver mutations in lung cancer: first step in personalized cancer. *Target Oncol* 2013;8:3-14. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23371030>.

188. Dias-Santagata D, Akhavanfard S, David SS, et al. Rapid targeted mutational analysis of human tumours: a clinical platform to guide personalized cancer medicine. *EMBO Mol Med* 2010;2:146-158. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20432502>.

189. Langer CJ. Epidermal growth factor receptor inhibition in mutation-positive non-small-cell lung cancer: is afatinib better or simply newer? *J Clin Oncol* 2013;31:3303-3306. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23980079>.

190. Riely GJ, Politi KA, Miller VA, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. *Clin Cancer Res* 2006;12:7232-7241. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17189394>.

191. O'Kane GM, Bradbury PA, Feld R, et al. Uncommon EGFR mutations in advanced non-small cell lung cancer. *Lung Cancer* 2017;109:137-144. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28577943>.

192. Hirsch FR, Bunn PA, Jr. EGFR testing in lung cancer is ready for prime time. *Lancet Oncol* 2009;10:432-433. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19410185>.

193. Yasuda H, Park E, Yun CH, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sci Transl Med* 2013;5:216ra177. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24353160>.

194. Arcila ME, Nafa K, Chaft JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and

clinicopathologic characteristics. *Mol Cancer Ther* 2013;12:220-229. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23371856>.

195. Oxnard GR, Lo PC, Nishino M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. *J Thorac Oncol* 2013;8:179-184. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23328547>.

196. Lund-Iversen M, Kleinberg L, Fjellbirkeland L, et al. Clinicopathological characteristics of 11 NSCLC patients with EGFR-exon 20 mutations. *J Thorac Oncol* 2012;7:1471-1473. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22895145>.

197. Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. *Lancet Oncol* 2012;13:e23-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21764376>.

198. Riely GJ, Yu HA. EGFR: The Paradigm of an Oncogene-Driven Lung Cancer. *Clin Cancer Res* 2015;21:2221-2226. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25979928>.

199. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013;19:2240-2247. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23470965>.

200. Finlay MR, Anderton M, Ashton S, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. *J Med Chem* 2014;57:8249-8267. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25271963>.

201. Gainor JF, Shaw AT. Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer. *J Clin Oncol* 2013;31:3987-3996. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24101047>.

202. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med* 2005;2:e73. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15737014>.

203. Kosaka T, Yatabe Y, Endoh H, et al. Analysis of epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer and acquired resistance to gefitinib. *Clin Cancer Res* 2006;12:5764-5769. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17020982>.

204. Onitsuka T, Uramoto H, Nose N, et al. Acquired resistance to gefitinib: the contribution of mechanisms other than the T790M, MET, and HGF status. *Lung Cancer* 2010;68:198-203. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19589612>.

205. Nishino M, Cardarella S, Jackman DM, et al. RECIST 1.1 in NSCLC patients with EGFR mutations treated with EGFR tyrosine kinase inhibitors: comparison with RECIST 1.0. *AJR Am J Roentgenol* 2013;201:W64-71. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23789698>.

206. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239-246. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22285168>.

207. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-957. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19692680>.

208. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. *N Engl J Med* 2017;376:629-640. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27959700>.

209. Rosell R, Molina MA, Costa C, et al. Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced

non-small-cell lung cancer patients with EGFR mutations. *Clin Cancer Res* 2011;17:1160-1168. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21233402>.

210. Oxnard GR, Miller VA, Robson ME, et al. Screening for germline EGFR T790M mutations through lung cancer genotyping. *J Thorac Oncol* 2012;7:1049-1052. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22588155>.

211. Gazdar A, Robinson L, Oliver D, et al. Hereditary lung cancer syndrome targets never smokers with germline EGFR gene T790M mutations. *J Thorac Oncol* 2014;9:456-463. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24736066>.

212. Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015;372:1689-1699. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25923549>.

213. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011;3:75ra26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21430269>.

214. Oxnard GR. Strategies for overcoming acquired resistance to epidermal growth factor receptor: targeted therapies in lung cancer. *Arch Pathol Lab Med* 2012;136:1205-1209. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23020725>.

215. Suda K, Mizuuchi H, Maehara Y, Mitsudomi T. Acquired resistance mechanisms to tyrosine kinase inhibitors in lung cancer with activating epidermal growth factor receptor mutation--diversity, ductility, and destiny. *Cancer Metastasis Rev* 2012;31:807-814. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22736441>.

216. Yu HA, Suzawa K, Jordan E, et al. Concurrent Alterations in EGFR-Mutant Lung Cancers Associated with Resistance to EGFR Kinase Inhibitors and Characterization of MTOR as a Mediator of Resistance. *Clin*



Cancer Res 2018;24:3108-3118. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/29530932>.

217. Sholl LM, Cagle PT, Lindeman NI, et al. Template for reporting results of biomarker testing of specimens from patients with non-small cell carcinoma of the lung; Version: LungBiomarkers 1.3.0.0: College of American Pathologists; 2016. Available at: <https://www.cap.org>.

218. Han SW, Kim TY, Jeon YK, et al. Optimization of patient selection for gefitinib in non-small cell lung cancer by combined analysis of epidermal growth factor receptor mutation, K-ras mutation, and Akt phosphorylation. Clin Cancer Res 2006;12:2538-2544. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16638863>.

219. Dacic S. EGFR assays in lung cancer. Adv Anat Pathol 2008;15:241-247. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18580100>.

220. Sholl LM, Xiao Y, Joshi V, et al. EGFR mutation is a better predictor of response to tyrosine kinase inhibitors in non-small cell lung carcinoma than FISH, CISH, and immunohistochemistry. Am J Clin Pathol 2010;133:922-934. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20472851>.

221. Eberhard DA, Giaccone G, Johnson BE, Non-Small-Cell Lung Cancer Working G. Biomarkers of response to epidermal growth factor receptor inhibitors in Non-Small-Cell Lung Cancer Working Group: standardization for use in the clinical trial setting. J Clin Oncol 2008;26:983-994. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18281673>.

222. Pao W, Ladanyi M. Epidermal growth factor receptor mutation testing in lung cancer: searching for the ideal method. Clin Cancer Res 2007;13:4954-4955. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17785543>.

223. Shepherd FA, Tsao MS. Epidermal growth factor receptor biomarkers in non-small-cell lung cancer: a riddle, wrapped in a mystery, inside an

enigma. J Clin Oncol 2010;28:903-905. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20100955>.

224. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-3334. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23816960>.

225. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20022809>.

226. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-2388. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20573926>.

227. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-742. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21783417>.

228. Zhou C, Wu YL, Chen G, et al. Updated efficacy and quality-of-life (QoL) analyses in OPTIMAL, a phase III, randomized, open-label study of first-line erlotinib versus gemcitabine/carboplatin in patients with EGFR-activating mutation-positive (EGFR Act Mut+) advanced non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 7520. Available at: [https://meeting.ascopubs.org/cqi/content/abstract/29/15\\_suppl/7520](https://meeting.ascopubs.org/cqi/content/abstract/29/15_suppl/7520).

229. Yang JC, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3342-3350. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23816967>.



230. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015;16:141-151. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25589191>.

231. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature* 2002;417:949-954. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12068308>.

232. Borczuk AC. Keeping Up With Testing Guidelines in Lung Cancer. *Arch Pathol Lab Med* 2018;142:783-784. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29939779>.

233. Rogers TM, Russell PA, Wright G, et al. Comparison of methods in the detection of ALK and ROS1 rearrangements in lung cancer. *J Thorac Oncol* 2015;10:611-618. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25789833>.

234. von Laffert M, Warth A, Penzel R, et al. Multicenter immunohistochemical ALK-testing of non-small-cell lung cancer shows high concordance after harmonization of techniques and interpretation criteria. *J Thorac Oncol* 2014;9:1685-1692. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25436802>.

235. Wynes MW, Sholl LM, Dietel M, et al. An international interpretation study using the ALK IHC antibody D5F3 and a sensitive detection kit demonstrates high concordance between ALK IHC and ALK FISH and between evaluators. *J Thorac Oncol* 2014;9:631-638. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24722153>.

236. Zhou J, Zhao J, Sun K, et al. Accurate and economical detection of ALK positive lung adenocarcinoma with semiquantitative immunohistochemical screening. *PLoS One* 2014;9:e92828. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24667320>.

237. Thunnissen E, Bubendorf L, Dietel M, et al. EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations.

*Virchows Arch* 2012;461:245-257. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22825000>.

238. Kim H, Yoo SB, Choe JY, et al. Detection of ALK gene rearrangement in non-small cell lung cancer: a comparison of fluorescence in situ hybridization and chromogenic in situ hybridization with correlation of ALK protein expression. *J Thorac Oncol* 2011;6:1359-1366. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21587085>.

239. Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. *Clin Cancer Res* 2009;15:5216-5223. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19671850>.

240. Mino-Kenudson M, Chirieac LR, Law K, et al. A novel, highly sensitive antibody allows for the routine detection of ALK-rearranged lung adenocarcinomas by standard immunohistochemistry. *Clin Cancer Res* 2010;16:1561-1571. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20179225>.

241. Ali SM, Hensing T, Schrock AB, et al. Comprehensive Genomic Profiling Identifies a Subset of Crizotinib-Responsive ALK-Rearranged Non-Small Cell Lung Cancer Not Detected by Fluorescence In Situ Hybridization. *Oncologist* 2016;21:762-770. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27245569>.

242. Wallander ML, Geiersbach KB, Tripp SR, Layfield LJ. Comparison of reverse transcription-polymerase chain reaction, immunohistochemistry, and fluorescence in situ hybridization methodologies for detection of echinoderm microtubule-associated proteinlike 4-anaplastic lymphoma kinase fusion-positive non-small cell lung carcinoma: implications for optimal clinical testing. *Arch Pathol Lab Med* 2012;136:796-803. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22742552>.

243. Weickhardt AJ, Aisner DL, Franklin WA, et al. Diagnostic assays for identification of anaplastic lymphoma kinase-positive non-small cell lung cancer. *Cancer* 2013;119:1467-1477. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23280244>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

244. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;377:829-838. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28586279>.

245. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol* 2018;19:1654-1667. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30413378>.

246. Besse B, Solomon BJ, Felip E, et al. Lorlatinib in patients (Pts) with previously treated ALK+ advanced non-small cell lung cancer (NSCLC): Updated efficacy and safety [abstract]. *J Clin Oncol* 2018;36(15\_suppl):Abstract 9032. Available at: [https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15\\_suppl.9032](https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.9032).

247. Browning ET, Weickhardt AJ, Camidge DR. Response to crizotinib rechallenge after initial progression and intervening chemotherapy in ALK lung cancer. *J Thorac Oncol* 2013;8:e21. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23407562>.

248. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 2012;13:1011-1019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22954507>.

249. West H, Oxnard GR, Doebele RC. Acquired resistance to targeted therapies in advanced non-small cell lung cancer: new strategies and new agents. *Am Soc Clin Oncol Educ Book* 2013:272-278. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23714521>.

250. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. *J Clin Oncol* 2017;35:2490-2498. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28475456>.

251. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*

2006;355:2542-2550. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17167137>.

252. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543-3551. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18506025>.

253. Ou SH, Janne PA, Bartlett CH, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. *Ann Oncol* 2014;25:415-422. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24478318>.

254. Gainor JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. *Clin Cancer Res* 2013;19:4273-4281. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23729361>.

255. Takahashi T, Sonobe M, Kobayashi M, et al. Clinicopathologic features of non-small-cell lung cancer with EML4-ALK fusion gene. *Ann Surg Oncol* 2010;17:889-897. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20183914>.

256. Robinson DR, Wu YM, Lin SF. The protein tyrosine kinase family of the human genome. *Oncogene* 2000;19:5548-5557. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11114734>.

257. Wu YL, Yang JC, Kim DW, et al. Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2018;36:1405-1411. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29596029>.

258. Kazandjian D, Blumenthal GM, Luo L, et al. Benefit-Risk Summary of Crizotinib for the Treatment of Patients With ROS1 Alteration-Positive, Metastatic Non-Small Cell Lung Cancer. *Oncologist* 2016;21:974-980. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27328934>.

259. Doebele RC, Paz-Ares L, Farago AF, et al. Entrectinib in NTRK fusion-positive non-small cell lung cancer (NSCLC): integrated analysis of patients enrolled in three trials (STARTRK-2, STARTRK-1 and ALKA-372-001) [abstract]. AACR Annual Meeting. Atlanta, GA:Abstract CT131. Available at:

[https://cancerres.aacrjournals.org/content/79/13\\_Supplement/CT131](https://cancerres.aacrjournals.org/content/79/13_Supplement/CT131).

260. Drilon A, Barlesi F, De Braud F, et al. Entrectinib in locally advanced or metastatic ROS1 fusion positive non-small cell lung cancer (NSCLC): Integrated analysis of STARTRK-2, STARTRK-1, and ALKA-372-001 [abstract]. Cancer Research 2019;79:Abstract CT192. Available at:

[https://cancerres.aacrjournals.org/content/79/13\\_Supplement/CT192](https://cancerres.aacrjournals.org/content/79/13_Supplement/CT192).

261. Drilon A, Siena S, Ou SI, et al. Safety and antitumor activity of the multitargeted Pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). Cancer Discov 2017;7:400-409. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28183697>.

262. Clave S, Gimeno J, Munoz-Marmol AM, et al. ROS1 copy number alterations are frequent in non-small cell lung cancer. Oncotarget 2016;7:8019-8028. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26783962>.

263. Bubendorf L, Buttner R, Al-Dayel F, et al. Testing for ROS1 in non-small cell lung cancer: a review with recommendations. Virchows Arch 2016;469:489-503. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27535289>.

264. Davies KD, Le AT, Theodoro MF, et al. Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. Clin Cancer Res 2012;18:4570-4579. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22919003>.

265. Solomon BJ, Bauer TM, Felip E, et al. Safety and efficacy of lorlatinib (PF-06463922) from the dose-escalation component of a study in patients with advanced ALK+ or ROS1+ non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2016;34:Abstract 9009. Available at:

<https://meetinglibrary.asco.org/content/161846-176>.

266. Farago AF, Le LP, Zheng Z, et al. Durable Clinical Response to Entrectinib in NTRK1-Rearranged Non-Small Cell Lung Cancer. J Thorac Oncol 2015;10:1670-1674. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26565381>.

267. Zou HY, Li Q, Engstrom LD, et al. PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking crizotinib-resistant ROS1 mutations. Proc Natl Acad Sci U S A 2015;112:3493-3498. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25733882>.

268. Katayama R, Kobayashi Y, Friboulet L, et al. Cabozantinib overcomes crizotinib resistance in ROS1 fusion-positive cancer. Clin Cancer Res 2015;21:166-174. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25351743>.

269. Farago AF, Taylor MS, Doebele RC, et al. Clinicopathologic Features of Non-Small-Cell Lung Cancer Harboring an NTRK Gene Fusion. JCO Precis Oncol 2018;2018. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30215037>.

270. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29466156>.

271. Lassen U, Albert CM, Kummar S, et al. Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach [abstract] [abstract]. Presented at the ESMO Congress; October 19-23; Munich, Germany. Abstract 409O.

272. Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumors: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001 [abstract]. Ann Oncol 2018;29:LBA17. Available at: <https://tinyurl.com/y6mqmhx8>.

273. Slebos RJ, Hruban RH, Dalesio O, et al. Relationship between K-ras oncogene activation and smoking in adenocarcinoma of the human lung. J



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

Natl Cancer Inst 1991;83:1024-1027. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/2072410>.

274. Mitsudomi T, Steinberg SM, Oie HK, et al. ras gene mutations in non-small cell lung cancers are associated with shortened survival irrespective of treatment intent. Cancer Res 1991;51:4999-5002. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1654209>.

275. Febbo PG, Ladanyi M, Aldape KD, et al. NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 2011;9 Suppl 5:S1-32; quiz S33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22138009>.

276. Calles A, Liao X, Sholl LM, et al. Expression of PD-1 and Its Ligands, PD-L1 and PD-L2, in Smokers and Never Smokers with KRAS-Mutant Lung Cancer. J Thorac Oncol 2015;10:1726-1735. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26473645>.

277. Stinchcombe TE. Novel agents in development for advanced non-small cell lung cancer. Ther Adv Med Oncol 2014;6:240-253. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25342991>.

278. Janne PA, Shaw AT, Pereira JR, et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. Lancet Oncol 2013;14:38-47. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23200175>.

279. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-1639. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26412456>.

280. Ribas A. Releasing the Brakes on Cancer Immunotherapy. N Engl J Med 2015;373:1490-1492. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26348216>.

281. Brahmer JR, Hammers H, Lipson EJ. Nivolumab: targeting PD-1 to bolster antitumor immunity. Future Oncol 2015;11:1307-1326. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25798726>.

282. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-135. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26028407>.

283. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:1919-1929. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28885881>.

284. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-1846. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26970723>.

285. Gadgeel SM, Stevenson J, Langer C, et al. Pembrolizumab (pembro) plus chemotherapy as front-line therapy for advanced NSCLC: KEYNOTE-021 cohorts A-C [abstract]. J Clin Oncol 2016;34:Abstract 9016. Available at: <https://meetinglibrary.asco.org/content/167088-176>.

286. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819-1830. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30955977>.

287. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078-2092. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29658856>.

288. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med



2018;378:2288-2301. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29863955>.

289. Thatcher N, Goldschmidt JH, Thomas M, et al. Efficacy and Safety of the Biosimilar ABP 215 Compared with Bevacizumab in Patients with Advanced Nonsquamous Non-small Cell Lung Cancer (MAPLE): A Randomized, Double-blind, Phase III Study. *Clin Cancer Res* 2019;25:2088-2095. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30617139>.

290. Reinmuth N, Bryl M, Bondarenko I, et al. PF-06439535 (a bevacizumab biosimilar) compared with reference bevacizumab (avastin((r))), both plus paclitaxel and carboplatin, as first-line treatment for advanced non-squamous non-small-cell lung cancer: a randomized, double-blind study. *BioDrugs* 2019. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/31338773>.

291. Melosky B, Reardon DA, Nixon AB, et al. Bevacizumab biosimilars: scientific justification for extrapolation of indications. *Future Oncol* 2018;14:2507-2520. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29690784>.

292. Weise M, Kurki P, Wolff-Holz E, et al. Biosimilars: the science of extrapolation. *Blood* 2014;124:3191-3196. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25298038>.

293. Weise M, Bielsky MC, De Smet K, et al. Biosimilars: what clinicians should know. *Blood* 2012;120:5111-5117. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23093622>.

294. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018;379:2040-2051. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30280635>.

295. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial.

*Lancet* 2017;389:255-265. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27979383>.

296. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540-1550. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26712084>.

297. Gainor JF, Shaw AT, Sequist LV, et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis. *Clin Cancer Res* 2016;22:4585-4593. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27225694>.

298. Lisberg A, Cummings A, Goldman JW, et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naive patients with advanced NSCLC. *J Thorac Oncol* 2018;13:1138-1145. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29874546>.

299. Kerr KM, Nicolson MC. Non-Small Cell Lung Cancer, PD-L1, and the Pathologist. *Arch Pathol Lab Med* 2016;140:249-254. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26927720>.

300. Kerr KM, Hirsch FR. Programmed Death Ligand-1 Immunohistochemistry: Friend or Foe? *Arch Pathol Lab Med* 2016;140:326-331. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26756647>.

301. Rimm DL, Han G, Taube JM, et al. A Prospective, Multi-institutional, Pathologist-Based Assessment of 4 Immunohistochemistry Assays for PD-L1 Expression in Non-Small Cell Lung Cancer. *JAMA Oncol* 2017;3:1051-1058. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28278348>.

302. Buttner R, Gosney JR, Skov BG, et al. Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer. *J Clin Oncol*



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

2017;35:3867-3876. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29053400>.

303. Kerr KM, Tsao MS, Nicholson AG, et al. Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer: In what state is this art? J Thorac Oncol 2015;10:985-989. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26134220>.

304. Chow WB, Rosenthal RA, Merkow RP, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. J Am Coll Surg 2012;215:453-466. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22917646>.

305. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e278S-e313S. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23649443>.

306. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol 2015;26:1091-1101. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25403592>.

307. Caillet P, Laurent M, Bastuji-Garin S, et al. Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment. Clin Interv Aging 2014;9:1645-1660. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25302022>.

308. Pallis AG, Gridelli C, Wedding U, et al. Management of elderly patients with NSCLC; updated expert's opinion paper: EORTC Elderly Task Force, Lung Cancer Group and International Society for Geriatric Oncology. Ann Oncol 2014;25:1270-1283. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24638905>.

309. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional

surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e166S-e190S. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23649437>.

310. Turner G, Clegg A, British Geriatrics S, et al. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. Age Ageing 2014;43:744-747. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25336440>.

311. Vairaktarakis C, Tsiamis V, Soursou G, et al. A computer-aided diagnosis system for geriatrics assessment and frailty evaluation. Adv Exp Med Biol 2015;820:69-77. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25417017>.

312. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32:2595-2603. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25071125>.

313. Kozower BD, Lerner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e369S-e399S. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23649447>.

314. Boffa DJ, Allen MS, Grab JD, et al. Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. J Thorac Cardiovasc Surg 2008;135:247-254. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18242243>.

315. Scott WJ, Howington J, Feigenberg S, et al. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:234S-242S. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17873171>.

316. Villamizar N, Swanson SJ. Lobectomy vs. segmentectomy for NSCLC (T<2 cm). *Ann Cardiothorac Surg* 2014;3:160-166. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24790839>.

317. Landreneau RJ, Normolle DP, Christie NA, et al. Recurrence and Survival Outcomes After Anatomic Segmentectomy Versus Lobectomy for Clinical Stage I Non-Small-Cell Lung Cancer: A Propensity-Matched Analysis. *Journal of Clinical Oncology* 2014;32:2449-2455. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24982447>.

318. Altorki NK, Yip R, Hanaoka T, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. *J Thorac Cardiovasc Surg* 2014;147:754-762; Discussion 762-754. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24280722>.

319. Sienel W, Dango S, Kirschbaum A, et al. Sublobar resections in stage IA non-small cell lung cancer: segmentectomies result in significantly better cancer-related survival than wedge resections. *Eur J Cardiothorac Surg* 2008;33:728-734. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18261918>.

320. Sienel W, Stremmel C, Kirschbaum A, et al. Frequency of local recurrence following segmentectomy of stage IA non-small cell lung cancer is influenced by segment localisation and width of resection margins--implications for patient selection for segmentectomy. *Eur J Cardiothorac Surg* 2007;31:522-527; discussion 527-528. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17229574>.

321. Narsule CK, Ebright MI, Fernando HC. Sublobar versus lobar resection: current status. *Cancer J* 2011;17:23-27. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21263263>.

322. Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* 2017;7:295-301. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28596092>.

323. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070-1076. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20233825>.

324. Woody NM, Stephans KL, Marwaha G, et al. Stereotactic Body Radiation Therapy for Non-Small Cell Lung Cancer Tumors Greater Than 5 cm: Safety and Efficacy. *Int J Radiat Oncol Biol Phys* 2015;92:325-331. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25841625>.

325. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol* 2010;28:928-935. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20065181>.

326. Donington J, Ferguson M, Mazzone P, et al. American College of Chest Physicians and Society of Thoracic Surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. *Chest* 2012;142:1620-1635. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23208335>.

327. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *J Thorac Cardiovasc Surg* 2011;141:662-670. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21335122>.

328. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006;81:1013-1019; discussion 1019-1020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16488712>.

329. Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J*

Thorac Oncol 2009;4:568-577. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/19357537>.

330. Martins RG, D'Amico TA, Loo BW, Jr., et al. The management of patients with stage IIIA non-small cell lung cancer with N2 mediastinal node involvement. J Natl Compr Canc Netw 2012;10:599-613. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22570291>.

331. Farjah F, Flum DR, Varghese TK, Jr., et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. Ann Thorac Surg 2009;87:995-1004; discussion 1005-1006. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19324119>.

332. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-386. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19632716>.

333. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442-450. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17374834>.

334. Cerfolio RJ, Bryant AS. Survival of patients with unsuspected N2 (stage IIIA) nonsmall-cell lung cancer. Ann Thorac Surg 2008;86:362-366; discussion 366-367. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18640297>.

335. Sher DJ, Fidler MJ, Liptay MJ, Koshy M. Comparative effectiveness of neoadjuvant chemoradiotherapy versus chemotherapy alone followed by surgery for patients with stage IIIA non-small cell lung cancer. Lung Cancer 2015;88:267-274. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25862147>.

336. Shah AA, Berry MF, Tzao C, et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. Ann

Thorac Surg 2012;93:1807-1812. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/22632486>.

337. Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. Lancet Oncol 2008;9:636-648. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18583190>.

338. Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;75:1462-1467. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19467798>.

339. Stefani A, Alifano M, Bobbio A, et al. Which patients should be operated on after induction chemotherapy for N2 non-small cell lung cancer? Analysis of a 7-year experience in 175 patients. J Thorac Cardiovasc Surg 2010;140:356-363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20381815>.

340. Gopal RS, Dubey S, Rosenzweig KE, et al. ACR Appropriateness Criteria(R) on Induction and Adjuvant Therapy for Stage N2 Non-Small-Cell Lung Cancer: expert panel on radiation oncology-lung. Int J Radiat Oncol Biol Phys 2010;78:969-974. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20813465>.

341. Evans NR, 3rd, Li S, Wright CD, et al. The impact of induction therapy on morbidity and operative mortality after resection of primary lung cancer. J Thorac Cardiovasc Surg 2010;139:991-996 e991-992. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20304144>.

342. Gaissert HA, Keum DY, Wright CD, et al. POINT: Operative risk of pneumonectomy--influence of preoperative induction therapy. J Thorac Cardiovasc Surg 2009;138:289-294. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19619768>.

343. Mansour Z, Kochetkova EA, Ducrocq X, et al. Induction chemotherapy does not increase the operative risk of pneumonectomy! Eur J Cardiothorac Surg 2007;31:181-185. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17141515>.



344. Weder W, Collaud S, Eberhardt WE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 2010;139:1424-1430. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20416887>.

345. Kappers I, van Sandick JW, Burgers SA, et al. Surgery after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer: why pneumonectomy should be avoided. *Lung Cancer* 2010;68:222-227. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19664843>.

346. Decaluwe H, De Leyn P, Vansteenkiste J, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. *Eur J Cardiothorac Surg* 2009;36:433-439. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19502079>.

347. Swanson SJ, Batirel HF. Video-assisted thoracic surgery (VATS) resection for lung cancer. *Surg Clin North Am* 2002;82:541-559. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12371584>.

348. Mahtabifard A, Fuller CB, McKenna RJ, Jr. Video-assisted thoracic surgery sleeve lobectomy: a case series. *Ann Thorac Surg* 2008;85:S729-732. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18222205>.

349. Shaw JP, Dembitzer FR, Wisnivesky JP, et al. Video-assisted thoracoscopic lobectomy: state of the art and future directions. *Ann Thorac Surg* 2008;85:S705-709. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18222201>.

350. Cheng D, Downey RJ, Kernstine K, et al. Video-assisted thoracic surgery in lung cancer resection: a meta-analysis and systematic review of controlled trials. *Innovations (Phila)* 2007;2:261-292. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22437196>.

351. Alam N, Flores RM. Video-assisted thoracic surgery (VATS) lobectomy: the evidence base. *JSLC* 2007;11:368-374. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17931521>.

352. Whitson BA, Andrade RS, Boettcher A, et al. Video-assisted thoracoscopic surgery is more favorable than thoracotomy for resection of clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2007;83:1965-1970. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17532379>.

353. Whitson BA, Groth SS, Duval SJ, et al. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. *Ann Thorac Surg* 2008;86:2008-2016; discussion 2016-2008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19022040>.

354. Scott WJ, Allen MS, Darling G, et al. Video-assisted thoracic surgery versus open lobectomy for lung cancer: a secondary analysis of data from the American College of Surgeons Oncology Group Z0030 randomized clinical trial. *J Thorac Cardiovasc Surg* 2010;139:976-981; discussion 981-973. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20172539>.

355. Atkins BZ, Harpole DH, Jr., Mangum JH, et al. Pulmonary segmentectomy by thoracotomy or thoracoscopy: reduced hospital length of stay with a minimally-invasive approach. *Ann Thorac Surg* 2007;84:1107-1112; discussion 1112-1103. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17888955>.

356. Swanson SJ, Herndon JE, D'Amico TA, et al. Video-Assisted Thoracic Surgery Lobectomy: Report of CALGB 39802—A Prospective, Multi-Institution Feasibility Study. *Journal of Clinical Oncology* 2007;25:4993-4997. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17971599>.

357. Ohtsuka T, Nomori H, Horio H, et al. Is major pulmonary resection by video-assisted thoracic surgery an adequate procedure in clinical stage I lung cancer? *Chest* 2004;125:1742-1746. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15136385>.

358. McKenna RJ, Jr. New approaches to the minimally invasive treatment of lung cancer. *Cancer J* 2005;11:73-76. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15831227>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

359. Demmy TL, Nwogu C. Is video-assisted thoracic surgery lobectomy better? Quality of life considerations. *Ann Thorac Surg* 2008;85:S719-728. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18222204>.

360. Cattaneo SM, Park BJ, Wilton AS, et al. Use of video-assisted thoracic surgery for lobectomy in the elderly results in fewer complications. *Ann Thorac Surg* 2008;85:231-235; discussion 235-236. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18154816>.

361. Cao C, Manganas C, Ang SC, et al. Video-assisted thoracic surgery versus open thoracotomy for non-small cell lung cancer: a meta-analysis of propensity score-matched patients. *Interact Cardiovasc Thorac Surg* 2013;16:244-249. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23169877>.

362. Ilonen IK, Rasanen JV, Knuutila A, et al. Anatomic thoracoscopic lung resection for non-small cell lung cancer in stage I is associated with less morbidity and shorter hospitalization than thoracotomy. *Acta Oncol* 2011;50:1126-1132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21314296>.

363. Villamizar NR, Darrabie MD, Burfeind WR, et al. Thoracoscopic lobectomy is associated with lower morbidity compared with thoracotomy. *J Thorac Cardiovasc Surg* 2009;138:419-425. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19619789>.

364. Paul S, Altorki NK, Sheng S, et al. Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. *J Thorac Cardiovasc Surg* 2010;139:366-378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20106398>.

365. Su S, Scott WJ, Allen MS, et al. Patterns of survival and recurrence after surgical treatment of early stage non-small cell lung carcinoma in the ACOSOG Z0030 (ALLIANCE) trial. *J Thorac Cardiovasc Surg* 2014;147:747-752; Discussion 752-743. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24290575>.

366. Lee PC, Nasar A, Port JL, et al. Long-term survival after lobectomy for non-small cell lung cancer by video-assisted thoracic surgery versus thoracotomy. *Ann Thorac Surg* 2013;96:951-960; discussion 960-951. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23866808>.

367. Thomas P, Doddoli C, Yena S, et al. VATS is an adequate oncological operation for stage I non-small cell lung cancer. *Eur J Cardiothorac Surg* 2002;21:1094-1099. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12048091>.

368. Roviario G, Varoli F, Vergani C, et al. Long-term survival after videothoracoscopic lobectomy for stage I lung cancer. *Chest* 2004;126:725-732. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15364748>.

369. Solaini L, Prusciano F, Bagioni P, Poddie DB. Long-term results of video-assisted thoracic surgery lobectomy for stage I non-small cell lung cancer: a single-centre study of 104 cases. *Interact Cardiovasc Thorac Surg* 2004;3:57-62. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17670176>.

370. Demmy TL, Plante AJ, Nwogu CE, et al. Discharge independence with minimally invasive lobectomy. *Am J Surg* 2004;188:698-702. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15619486>.

371. Demmy TL. VATS lobectomy for frail or complex patients. *Chest Meeting Abstracts* 2003;124:234S. Available at: <https://meeting.chestpubs.org/cgi/reprint/124/4/234S.pdf>.

372. Nicastrì DG, Wisnivesky JP, Litle VR, et al. Thoracoscopic lobectomy: report on safety, discharge independence, pain, and chemotherapy tolerance. *J Thorac Cardiovasc Surg* 2008;135:642-647. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18329487>.

373. Petersen RP, Pham D, Burfeind WR, et al. Thoracoscopic lobectomy facilitates the delivery of chemotherapy after resection for lung cancer. *Ann Thorac Surg* 2007;83:1245-1249; discussion 1250. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17383320>.

374. Hanna JM, Berry MF, D'Amico TA. Contraindications of video-assisted thoracoscopic surgical lobectomy and determinants of conversion to open. *J Thorac Dis* 2013;5 Suppl 3:S182-189. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24040521>.

375. Yan TD, Cao C, D'Amico TA, et al. Video-assisted thoracoscopic surgery lobectomy at 20 years: a consensus statement. *Eur J Cardiothorac Surg* 2014;45:633-639. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24130372>.

376. Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. *J Clin Oncol* 2009;27:2553-2562. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19289625>.

377. Cao C, Manganas C, Ang SC, Yan TD. A meta-analysis of unmatched and matched patients comparing video-assisted thoracoscopic lobectomy and conventional open lobectomy. *Ann Cardiothorac Surg* 2012;1:16-23. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23977459>.

378. Nakamura H. Systematic review of published studies on safety and efficacy of thoracoscopic and robot-assisted lobectomy for lung cancer. *Ann Thorac Cardiovasc Surg* 2014;20:93-98. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24583699>.

379. Swanson SJ, Miller DL, McKenna RJ, et al. Comparing robot-assisted thoracic surgical lobectomy with conventional video-assisted thoracic surgical lobectomy and wedge resection: Results from a multihospital database (Premier). *The Journal of Thoracic and Cardiovascular Surgery* 2014;147:929-937. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24210834>.

380. Lung Cancer Study G. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. *N Engl J Med* 1986;315:1377-1381. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2877397>.

381. Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. *N Engl J Med* 2000;343:1217-1222. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11071672>.

382. Douillard JY, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys* 2008;72:695-701. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18439766>.

383. Bradley JD, Paulus R, Graham MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group--RTOG 9705. *J Clin Oncol* 2005;23:3480-3487. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15908657>.

384. Feigenberg SJ, Hanlon AL, Langer C, et al. A phase II study of concurrent carboplatin and paclitaxel and thoracic radiotherapy for completely resected stage II and IIIA non-small cell lung cancer. *J Thorac Oncol* 2007;2:287-292. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17409799>.

385. Jaklitsch MT, Herndon JE, 2nd, DeCamp MM, Jr., et al. Nodal downstaging predicts survival following induction chemotherapy for stage IIIA (N2) non-small cell lung cancer in CALGB protocol #8935. *J Surg Oncol* 2006;94:599-606. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17039491>.

386. Lutz ST, Jones J, Chow E. Role of radiation therapy in palliative care of the patient with cancer. *J Clin Oncol* 2014;32:2913-2919. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25113773>.

387. McAvoy S, Ciura K, Wei C, et al. Definitive reirradiation for locoregionally recurrent non-small cell lung cancer with proton beam therapy or intensity modulated radiation therapy: predictors of high-grade



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

toxicity and survival outcomes. *Int J Radiat Oncol Biol Phys* 2014;90:819-827. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25220718>.

388. Expert Panel on Radiation Oncology-Brain M, Lo SS, Gore EM, et al. ACR Appropriateness Criteria(R) pre-irradiation evaluation and management of brain metastases. *J Palliat Med* 2014;17:880-886. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24971478>.

389. Expert Panel on Radiation Oncology-Bone M, Lo SS, Lutz ST, et al. ACR Appropriateness Criteria (R) spinal bone metastases. *J Palliat Med* 2013;16:9-19. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23167547>.

390. Expert Panel On Radiation Oncology-Bone M, Lutz ST, Lo SS, et al. ACR Appropriateness Criteria(R) non-spine bone metastases. *J Palliat Med* 2012;15:521-526. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22536988>.

391. Patel SH, Robbins JR, Gore EM, et al. ACR Appropriateness Criteria(R) follow-up and retreatment of brain metastases. *Am J Clin Oncol* 2012;35:302-306. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22609733>.

392. Chang JY, Kestin LL, Barriger RB, et al. ACR Appropriateness Criteria(R) nonsurgical treatment for locally advanced non-small-cell lung cancer: good performance status/definitive intent. *Oncology (Williston Park)* 2014;28:706-710, 712, 714 passim. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25140629>.

393. Rosenzweig KE, Chang JY, Chetty IJ, et al. ACR appropriateness criteria nonsurgical treatment for non-small-cell lung cancer: poor performance status or palliative intent. *J Am Coll Radiol* 2013;10:654-664. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23890874>.

394. Sejpal S, Komaki R, Tsao A, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer. *Cancer* 2011;117:3004-3013. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21264827>.

395. Chang JY, Verma V, Li M, et al. Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer: Final Results of a Phase 2 Study. *JAMA Oncol* 2017;3:e172032. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28727865>.

396. Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). *Cancer Radiother* 2011;15:555-559. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21802333>.

397. Teoh M, Clark CH, Wood K, et al. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. *Br J Radiol* 2011;84:967-996. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22011829>.

398. Chen AB, Neville BA, Sher DJ, et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. *J Clin Oncol* 2011;29:2305-2311. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21537034>.

399. Liao ZX, Komaki RR, Thames HD, Jr., et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2010;76:775-781. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19515503>.

400. Terasawa T, Dvorak T, Ip S, et al. Systematic review: charged-particle radiation therapy for cancer. *Ann Intern Med* 2009;151:556-565. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19755348>.

401. Chun SG, Hu C, Choy H, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. *J Clin Oncol* 2017;35:56-62. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28034064>.

402. Ung Y, Gu C-S, Cline K, et al. An Ontario Clinical Oncology Group (COG) randomized trial (PET SMART) of FDG PET/CT in patients with



stage 3 non-small cell lung cancer (NSCLC): impact of PET on radiation treatment volumes [Abstract O35.01]. *J Thorac Oncol* 2011;6:S428.

Available at: <https://journals.lww.com/jto/toc/2011/06001>.

403. MacManus M, Nestle U, Rosenzweig KE, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. *Radiother Oncol* 2009;91:85-94. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19100641>.

404. Everitt S, Herschtal A, Callahan J, et al. High rates of tumor growth and disease progression detected on serial pretreatment fluorodeoxyglucose-positron emission tomography/computed tomography scans in radical radiotherapy candidates with nonsmall cell lung cancer. *Cancer* 2010;116:5030-5037. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20623786>.

405. Mohammed N, Kestin LL, Grills IS, et al. Rapid disease progression with delay in treatment of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;79:466-472. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20471184>.

406. Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1087-1096. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16682145>.

407. Bush DA, Slater JD, Shin BB, et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest* 2004;126:1198-1203. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15486383>.

408. Nihei K, Ogino T, Ishikura S, Nishimura H. High-dose proton beam therapy for Stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;65:107-111. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16458447>.

409. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions

for non-small cell lung cancer: a meta-analysis. *Radiother Oncol* 2010;95:32-40. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19733410>.

410. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. *Med Phys* 2006;33:3874-3900. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17089851>.

411. Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. *Semin Radiat Oncol* 2007;17:108-120. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17395041>.

412. Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol* 2008;18:215-222. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18725106>.

413. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol* 2007;25:313-318. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17235046>.

414. Cerfolio RJ, Bryant AS, Jones VL, Cerfolio RM. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. *Eur J Cardiothorac Surg* 2009;35:718-723; discussion 723. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19233668>.

415. Kwong KF, Edelman MJ, Suntharalingam M, et al. High-dose radiotherapy in trimodality treatment of Pancoast tumors results in high pathologic complete response rates and excellent long-term survival. *J Thorac Cardiovasc Surg* 2005;129:1250-1257. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15942564>.

416. Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent

chemotherapy in non-small-cell lung cancer. *Ann Thorac Surg* 2004;78:1200-1205; discussion 1206. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15464470>.

417. ICRU. ICRU Report 50. Prescribing, Recording and Reporting Photon Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements; 1993.

418. ICRU. Prescribing, Recording and Reporting Photon Beam Therapy (Report 62) (Supplement to ICRU Report 50). Bethesda, MD: ICRU; 1999.

419. ICRU Report 83: Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy (IMRT). Bethesda, MD: International Commission on Radiation Units and Measurements; 2010. Available at: <https://bit.ly/2pBwGkl>.

420. Group IDW, Holmes T, Das R, et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. *Int J Radiat Oncol Biol Phys* 2009;74:1311-1318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19616738>.

421. Kong FM, Ritter T, Quint DJ, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat Oncol Biol Phys* 2011;81:1442-1457. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20934273>.

422. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010;76:S10-19. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20171502>.

423. Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;76:S70-76. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20171521>.

424. Werner-Wasik M, Yorke E, Deasy J, et al. Radiation dose-volume effects in the esophagus. *Int J Radiat Oncol Biol Phys* 2010;76:S86-93. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20171523>.

425. Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys* 2010;76:S77-85. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20171522>.

426. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. *Int J Radiat Oncol Biol Phys* 2010;76:S42-49. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20171517>.

427. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999;45:323-329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10487552>.

428. Kong FM, Hayman JA, Griffith KA, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. *Int J Radiat Oncol Biol Phys* 2006;65:1075-1086. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16647222>.

429. Hernando ML, Marks LB, Bentel GC, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. *Int J Radiat Oncol Biol Phys* 2001;51:650-659. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11597805>.

430. Kim TH, Cho KH, Pyo HR, et al. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. *Radiology* 2005;235:208-215. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15703313>.

431. Wang S, Liao Z, Wei X, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). *Int J Radiat Oncol Biol Phys* 2006;66:1399-1407. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16997503>.

432. Rose J, Rodrigues G, Yaremko B, et al. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic



radiotherapy. *Radiother Oncol* 2009;91:282-287. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/18950881>.

433. Hall WH, Guiou M, Lee NY, et al. Development and validation of a standardized method for contouring the brachial plexus: preliminary dosimetric analysis among patients treated with IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2008;72:1362-1367. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/18448267>.

434. Bezjak A, Temin S, Franklin G, et al. Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. *J Clin Oncol* 2015;33:2100-2105. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25944914>.

435. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2005;61:318-328. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/15667949>.

436. Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005;63:324-333. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/16168827>.

437. Zhao L, West BT, Hayman JA, et al. High radiation dose may reduce the negative effect of large gross tumor volume in patients with medically inoperable early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2007;68:103-110. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/17363189>.

438. Wang L, Correa CR, Zhao L, et al. The effect of radiation dose and chemotherapy on overall survival in 237 patients with Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*

2009;73:1383-1390. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/18929449>.

439. Rosenman JG, Halle JS, Socinski MA, et al. High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: technical issues and results of a phase I/II trial. *Int J Radiat Oncol Biol Phys* 2002;54:348-356. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/12243807>.

440. Schild SE, McGinnis WL, Graham D, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1106-1111. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/16730134>.

441. Bradley JD, Moughan J, Graham MV, et al. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell lung cancer: phase I results of RTOG 0117. *Int J Radiat Oncol Biol Phys* 2010;77:367-372. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/20457350>.

442. Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. *J Clin Oncol* 2008;26:2457-2463. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/18487565>.

443. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *The Lancet Oncology* 2015;16:187-199. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25601342>.

444. Stinchcombe TE, Lee CB, Moore DT, et al. Long-term follow-up of a phase I/II trial of dose escalating three-dimensional conformal thoracic radiation therapy with induction and concurrent carboplatin and paclitaxel



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

in unresectable stage IIIA/B non-small cell lung cancer. *J Thorac Oncol* 2008;3:1279-1285. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18978563>.

445. Bradley JD, Bae K, Graham MV, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. *J Clin Oncol* 2010;28:2475-2480. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20368547>.

446. Machtay M, Bae K, Movsas B, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 2012;82:425-434. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20980108>.

447. Wang K, Eblan MJ, Deal AM, et al. Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. *J Clin Oncol* 2017;35:1387-1394. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28113017>.

448. Dess RT, Sun Y, Matuszak MM, et al. Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2017;35:1395-1402. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28301264>.

449. Cox JD. Are the results of RTOG 0617 mysterious? *Int J Radiat Oncol Biol Phys* 2012;82:1042-1044. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22284026>.

450. Sun B, Brooks ED, Komaki RU, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. *Cancer* 2017;123:3031-3039. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28346656>.

451. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. *Int J Radiat Oncol Biol Phys* 2012;82:967-973. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21377293>.

452. Ambrogi MC, Fanucchi O, Cioni R, et al. Long-term results of radiofrequency ablation treatment of stage I non-small cell lung cancer: a prospective intention-to-treat study. *J Thorac Oncol* 2011;6:2044-2051. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22052222>.

453. Bilal H, Mahmood S, Rajashanker B, Shah R. Is radiofrequency ablation more effective than stereotactic ablative radiotherapy in patients with early stage medically inoperable non-small cell lung cancer? *Interact Cardiovasc Thorac Surg* 2012;15:258-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22581864>.

454. Allibhai Z, Taremi M, Bezjak A, et al. The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013;87:1064-1070. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24210082>.

455. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys* 2012;84:1060-1070. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22975611>.

456. Burdett S, Stewart L, Group PM-a. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. *Lung Cancer* 2005;47:81-83. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15603857>.

457. Gewanter RM, Rosenzweig KE, Chang JY, et al. ACR Appropriateness Criteria: nonsurgical treatment for non-small-cell lung cancer: good performance status/definitive intent. *Curr Probl Cancer* 2010;34:228-249. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20541060>.



458. Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987;59:1874-1881. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3032394>.

459. Rengan R, Rosenzweig KE, Venkatraman E, et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;60:741-747. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15465190>.

460. Mauguén A, Le Pechoux C, Saunders MI, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:2788-2797. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22753901>.

461. Bradley J, Bae K, Choi N, et al. A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of Radiation Therapy Oncology Group (RTOG) 0515. *Int J Radiat Oncol Biol Phys* 2012;82:435-441 e431. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21075551>.

462. Belderbos JS, Kepka L, Spring Kong FM, et al. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small-Cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2008;72:335-342. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18793953>.

463. Sanuki-Fujimoto N, Sumi M, Ito Y, et al. Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. *Radiother Oncol* 2009;91:433-437. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19167118>.

464. Sulman EP, Komaki R, Klopp AH, et al. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. *Radiat Oncol* 2009;4:5. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19183471>.

465. Rosenzweig KE, Sura S, Jackson A, Yorke E. Involved-field radiation therapy for inoperable non small-cell lung cancer. *J Clin Oncol* 2007;25:5557-5561. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17984185>.

466. Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *Am J Clin Oncol* 2007;30:239-244. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17551299>.

467. Fernandes AT, Shen J, Finlay J, et al. Elective nodal irradiation (ENI) vs. involved field radiotherapy (IFRT) for locally advanced non-small cell lung cancer (NSCLC): A comparative analysis of toxicities and clinical outcomes. *Radiother Oncol* 2010;95:178-184. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20356642>.

468. Chen M, Bao Y, Ma HL, et al. Involved-field radiotherapy versus elective nodal irradiation in combination with concurrent chemotherapy for locally advanced non-small cell lung cancer: a prospective randomized study. *Biomed Res Int* 2013;2013:371819. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23762840>.

469. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 1995;13:1880-1892. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7636530>.

470. Francis S, Orton A, Stoddard G, et al. Sequencing of Postoperative Radiotherapy and Chemotherapy for Locally Advanced or Incompletely Resected Non-Small-Cell Lung Cancer. *J Clin Oncol* 2018;36:333-341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29236592>.

471. Sher DJ, Fidler MJ, Seder CW, et al. Relationship Between Radiation Therapy Dose and Outcome in Patients Treated With Neoadjuvant Chemoradiation Therapy and Surgery for Stage IIIA Non-Small Cell Lung Cancer: A Population-Based, Comparative Effectiveness Analysis. *Int J*

Radiat Oncol Biol Phys 2015;92:307-316. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25838187>.

472. Suntharalingam M, Paulus R, Edelman MJ, et al. Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 2012;84:456-463. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/22543206>.

473. Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. Int J Radiat Oncol Biol Phys 2006;65:1097-1105. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/16682136>.

474. Corso CD, Rutter CE, Wilson LD, et al. Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the National Cancer Database. J Thorac Oncol 2015;10:148-155. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25325781>.

475. Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 2006;24:2998-3006. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/16769986>.

476. Spoelstra FO, Senan S, Le Pechoux C, et al. Variations in target volume definition for postoperative radiotherapy in stage III non-small-cell lung cancer: analysis of an international contouring study. Int J Radiat Oncol Biol Phys 2010;76:1106-1113. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/19560881>.

477. Rodrigues G, Videtic GM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. Pract Radiat Oncol 2011;1:60-71. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25740118>.

478. Rodrigues G, Macbeth F, Burmeister B, et al. Consensus statement on palliative lung radiotherapy: third international consensus workshop on palliative radiotherapy and symptom control. Clin Lung Cancer 2012;13:1-5. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/21729656>.

479. Chen AB, Cronin A, Weeks JC, et al. Palliative radiation therapy practice in patients with metastatic non-small-cell lung cancer: a Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) Study. J Clin Oncol 2013;31:558-564. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/23295799>.

480. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423-1436. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17416863>.

481. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 2011;79:965-976. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/21277118>.

482. Cross CK, Berman S, Buswell L, et al. Prospective study of palliative hypofractionated radiotherapy (8.5 Gy x 2) for patients with symptomatic non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2004;58:1098-1105. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/15001250>.

483. A Medical Research Council (MRC) randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Medical Research Council Lung Cancer Working Party. Br J Cancer 1992;65:934-941. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/1377484>.

484. Koshy M, Malik R, Mahmood U, et al. Comparative effectiveness of aggressive thoracic radiation therapy and concurrent chemoradiation therapy in metastatic lung cancer. Pract Radiat Oncol 2015;5:374-382. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26412340>.

485. Gomez DR, Blumenschein GR, Jr., Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016;17:1672-1682. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27789196>.

486. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol* 2018;4:e173501. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28973074>.

487. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014;15:346-355. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24894943>.

488. Milano MT, Katz AW, Okunieff P. Patterns of recurrence after curative-intent radiation for oligometastases confined to one organ. *Am J Clin Oncol* 2010;33:157-163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19770627>.

489. Salama JK, Chmura SJ, Mehta N, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. *Clin Cancer Res* 2008;14:5255-5259. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18698045>.

490. Falkson CB, Vella ET, Yu E, et al. Guideline for radiotherapy with curative intent in patients with early-stage medically inoperable non-small-cell lung cancer. *Curr Oncol* 2017;24:e44-e49. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28270731>.

491. Dahele M, Senan S. The role of stereotactic ablative radiotherapy for early-stage and oligometastatic non-small cell lung cancer: evidence for changing paradigms. *Cancer Res Treat* 2011;43:75-82. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21811422>.

492. Heinzerling JH, Kavanagh B, Timmerman RD. Stereotactic ablative radiation therapy for primary lung tumors. *Cancer J* 2011;17:28-32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21263264>.

493. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2010;76:326-332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20117285>.

494. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2010;140:377-386. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20400121>.

495. Guckenberger M, Andratschke N, Alheit H, et al. Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. *Strahlenther Onkol* 2014;190:26-33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24052011>.

496. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011;81:1352-1358. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20638194>.

497. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;27:3290-3296. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19414667>.

498. Iyengar P, Westover K, Timmerman RD. Stereotactic ablative radiotherapy (SABR) for non-small cell lung cancer. *Semin Respir Crit Care Med* 2013;34:845-854. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24258574>.

499. Nagata Y, Hiraoka M, Shibata T, et al. Stereotactic Body Radiation Therapy For T1N0M0 Non-small Cell Lung Cancer: First Report for Inoperable Population of a Phase II Trial by Japan Clinical Oncology

Group (JCOG 0403). International Journal of Radiation Oncology\*Biophysics 2012;84:S46. Available at: [https://www.redjournal.org/article/S0360-3016\(12\)01274-6/abstract](https://www.redjournal.org/article/S0360-3016(12)01274-6/abstract).

500. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 2010;28:5153-5159. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21041709>.

501. Widder J, Postmus D, Ubbels JF, et al. Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys 2011;81:e291-297. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21640503>.

502. Bradley JD, El Naqa I, Drzymala RE, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the pattern of failure is distant. Int J Radiat Oncol Biol Phys 2010;77:1146-1150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19800181>.

503. Senti S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802-809. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22727222>.

504. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-682. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19251380>.

505. van den Berg LL, Klinkenberg TJ, Groen HJ, Widder J. Patterns of Recurrence and Survival after Surgery or Stereotactic Radiotherapy for Early Stage NSCLC. J Thorac Oncol 2015;10:826-831. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25629639>.

506. Versteegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative

radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-1548. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23425947>.

507. Nagata Y, Hiraoka M, Shibata T, et al. A Phase II Trial of Stereotactic Body Radiation Therapy for Operable T1N0M0 Non-small Cell Lung Cancer: Japan Clinical Oncology Group (JCOG0403). International Journal of Radiation Oncology\*Biophysics 2010;78:S27-S28. Available at: [https://www.redjournal.org/article/S0360-3016\(10\)01078-3/abstract](https://www.redjournal.org/article/S0360-3016(10)01078-3/abstract).

508. Lagerwaard FJ, Versteegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348-353. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22104360>.

509. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 2014;149:1244-1253. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25321323>.

510. Timmerman RD, Paulus R, Pass HI, et al. RTOG 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients [abstract]. J Clin Oncol 2013;31(Suppl 15):Abstract 7523. Available at:

511. Matsuo Y, Shibuya K, Nagata Y, et al. Preliminary report of late recurrences, at 5 years or more, after stereotactic body radiation therapy for non-small cell lung cancer. J Thorac Oncol 2012;7:453-456. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22252562>.

512. Rusthoven CG, Kavanagh BD, Karam SD. Improved survival with stereotactic ablative radiotherapy (SABR) over lobectomy for early stage non-small cell lung cancer (NSCLC): addressing the fallout of disruptive randomized data. Ann Transl Med 2015;3:149. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26244136>.

513. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;16:630-637. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25981812>.

514. Kunkler IH, Audisio R, Belkacemi Y, et al. Review of current best practice and priorities for research in radiation oncology for elderly patients with cancer: the International Society of Geriatric Oncology (SIOG) task force. *Ann Oncol* 2014;25:2134-2146. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24625455>.

515. Shultz DB, Filippi AR, Thariat J, et al. Stereotactic ablative radiotherapy for pulmonary oligometastases and oligometastatic lung cancer. *J Thorac Oncol* 2014;9:1426-1433. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25170641>.

516. Filippi AR, Badellino S, Guarneri A, et al. Outcomes of single fraction stereotactic ablative radiotherapy for lung metastases. *Technol Cancer Res Treat* 2014;13:37-45. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23819496>.

517. Chan NK, Abdullah KG, Lubelski D, et al. Stereotactic radiosurgery for metastatic spine tumors. *J Neurosurg Sci* 2014;58:37-44. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24614791>.

518. Ojerholm E, Lee JY, Kolker J, et al. Gamma Knife radiosurgery to four or more brain metastases in patients without prior intracranial radiation or surgery. *Cancer Med* 2014;3:565-571. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24510602>.

519. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. *J Clin Oncol* 2014;32:2847-2854. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25113761>.

520. Salazar OM, Sandhu TS, Lattin PB, et al. Once-weekly, high-dose stereotactic body radiotherapy for lung cancer: 6-year analysis of 60 early-stage, 42 locally advanced, and 7 metastatic lung cancers. *Int J*

*Radiat Oncol Biol Phys* 2008;72:707-715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18455322>.

521. Guckenberger M, Wulf J, Mueller G, et al. Dose-response relationship for image-guided stereotactic body radiotherapy of pulmonary tumors: relevance of 4D dose calculation. *Int J Radiat Oncol Biol Phys* 2009;74:47-54. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18977095>.

522. Zhang X, Liu H, Balter P, et al. Positron emission tomography for assessing local failure after stereotactic body radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012;83:1558-1565. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22572078>.

523. Hoopes DJ, Tann M, Fletcher JW, et al. FDG-PET and stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer. *Lung Cancer* 2007;56:229-234. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17353064>.

524. Chen F, Matsuo Y, Yoshizawa A, et al. Salvage lung resection for non-small cell lung cancer after stereotactic body radiotherapy in initially operable patients. *J Thorac Oncol* 2010;5:1999-2002. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21102261>.

525. Neri S, Takahashi Y, Terashi T, et al. Surgical treatment of local recurrence after stereotactic body radiotherapy for primary and metastatic lung cancers. *J Thorac Oncol* 2010;5:2003-2007. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21102262>.

526. Hearn JW, Videtic GM, Djemil T, Stephans KL. Salvage stereotactic body radiation therapy (SBRT) for local failure after primary lung SBRT. *Int J Radiat Oncol Biol Phys* 2014;90:402-406. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25017480>.

527. Trakul N, Harris JP, Le QT, et al. Stereotactic ablative radiotherapy for reirradiation of locally recurrent lung tumors. *J Thorac Oncol* 2012;7:1462-1465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22895143>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

528. Kilburn JM, Kuremsky JG, Blackstock AW, et al. Thoracic re-irradiation using stereotactic body radiotherapy (SBRT) techniques as first or second course of treatment. *Radiother Oncol* 2014;110:505-510. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24444530>.

529. Zhao L, Zhou S, Balter P, et al. Planning Target Volume D95 and Mean Dose Should Be Considered for Optimal Local Control for Stereotactic Ablative Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2016;95:1226-1235. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27209498>.

530. Baker R, Han G, Sarangkasiri S, et al. Clinical and dosimetric predictors of radiation pneumonitis in a large series of patients treated with stereotactic body radiation therapy to the lung. *Int J Radiat Oncol Biol Phys* 2013;85:190-195. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22929858>.

531. Chang JY, Bezjak A, Mornex F, Committee IART. Stereotactic ablative radiotherapy for centrally located early stage non-small-cell lung cancer: what we have learned. *J Thorac Oncol* 2015;10:577-585. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25514807>.

532. Chang JY, Li QQ, Xu QY, et al. Stereotactic ablative radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: how to fly in a "no fly zone". *Int J Radiat Oncol Biol Phys* 2014;88:1120-1128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24661665>.

533. Hadziahmetovic M, Loo BW, Timmerman RD, et al. Stereotactic body radiation therapy (stereotactic ablative radiotherapy) for stage I non-small cell lung cancer--updates of radiobiology, techniques, and clinical outcomes. *Discov Med* 2010;9:411-417. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20515609>.

534. Hara R, Itami J, Kondo T, et al. Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors. *Cancer* 2006;106:1347-1352. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16475150>.

535. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;72:967-971. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18954709>.

536. Takeda A, Sanuki N, Kunieda E, et al. Stereotactic body radiotherapy for primary lung cancer at a dose of 50 Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm. *Int J Radiat Oncol Biol Phys* 2009;73:442-448. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18990507>.

537. Stephans KL, Djemil T, Reddy CA, et al. A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience. *J Thorac Oncol* 2009;4:976-982. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19633473>.

538. Jin JY, Kong FM, Chetty IJ, et al. Impact of fraction size on lung radiation toxicity: hypofractionation may be beneficial in dose escalation of radiotherapy for lung cancers. *Int J Radiat Oncol Biol Phys* 2010;76:782-788. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19577855>.

539. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2:S94-100. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17603311>.

540. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;70:685-692. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18164849>.

541. Liu MB, Eclov NC, Trakul N, et al. Clinical impact of dose overestimation by effective path length calculation in stereotactic ablative radiation therapy of lung tumors. *Pract Radiat Oncol* 2013;3:294-300. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24674401>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

542. Xiao Y, Papiez L, Paulus R, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;73:1235-1242. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19251095>.

543. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833-4839. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17050868>.

544. Chaudhuri AA, Tang C, Binkley MS, et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. *Lung Cancer* 2015;89:50-56. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25997421>.

545. Haseltine JM, Rimner A, Gelblum DY, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. *Pract Radiat Oncol* 2016;6:e27-33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26577006>.

546. Bezjak A, Paulus R, Gaspar LE, et al. Primary Study Endpoint Analysis for NRG Oncology/RTOG 0813 Trial of Stereotactic Body Radiation Therapy (SBRT) for Centrally Located Non-Small Cell Lung Cancer (NSCLC). *International Journal of Radiation Oncology\*Biophysics\*Physics* 2016;94:5-6. Available at: <https://dx.doi.org/10.1016/j.ijrobp.2015.10.040>.

547. Fleckenstein J, Petroff A, Schafers HJ, et al. Long-term outcomes in radically treated synchronous vs. metachronous oligometastatic non-small-cell lung cancer. *BMC Cancer* 2016;16:348. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27255302>.

548. De Ruyscher D, Wanders R, van Baardwijk A, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). *J Thorac Oncol* 2012;7:1547-1555. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22982655>.

549. Chawla S, Chen Y, Katz AW, et al. Stereotactic body radiotherapy for treatment of adrenal metastases. *Int J Radiat Oncol Biol Phys* 2009;75:71-75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19250766>.

550. Scorsetti M, Alongi F, Filippi AR, et al. Long-term local control achieved after hypofractionated stereotactic body radiotherapy for adrenal gland metastases: a retrospective analysis of 34 patients. *Acta Oncol* 2012;51:618-623. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22263925>.

551. Weickhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* 2012;7:1807-1814. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23154552>.

552. Gan GN, Weickhardt AJ, Scheier B, et al. Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. *Int J Radiat Oncol Biol Phys* 2014;88:892-898. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24462383>.

553. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J Clin Oncol* 2014;32:3824-3830. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25349291>.

554. Takeda M, Okamoto I, Nakagawa K. Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement. *J Thorac Oncol* 2013;8:654-657. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23584297>.

555. Bogart JA, Hodgson L, Seagren SL, et al. Phase I study of accelerated conformal radiotherapy for stage I non-small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904. *J Clin Oncol*

2010;28:202-206. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19933904>.

556. Cheung P, Faria S, Ahmed S, et al. Phase II study of accelerated hypofractionated three-dimensional conformal radiotherapy for stage T1-3 N0 M0 non-small cell lung cancer: NCIC CTG BR.25. J Natl Cancer Inst 2014;106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25074417>.

557. Sura S, Yorke E, Jackson A, Rosenzweig KE. High-Dose Radiotherapy for the Treatment of Inoperable Non-Small Cell Lung Cancer. The Cancer Journal 2007;13:238-242. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17762758>.

558. Hu C, Chang EL, Hassenbusch SJ, 3rd, et al. Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. Cancer 2006;106:1998-2004. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16572401>.

559. Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA 2016;316:401-409. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27458945>.

560. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:33-43. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19960230>.

561. Gaspar LE, Mehta MP, Patchell RA, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:17-32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19960231>.

562. Mintz A, Perry J, Spithoff K, et al. Management of single brain metastasis: a practice guideline. Curr Oncol 2007;14:131-143. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17710205>.

563. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990;322:494-500. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2405271>.

564. Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:45-68. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19960227>.

565. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483-2491. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16757720>.

566. Abe E, Aoyama H. The role of whole brain radiation therapy for the management of brain metastases in the era of stereotactic radiosurgery. Curr Oncol Rep 2012;14:79-84. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22006098>.

567. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of Brain Metastases in Tyrosine Kinase Inhibitor-Naive Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis. J Clin Oncol 2017;35:1070-1077. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28113019>.

568. Mehta MP, Paleologos NA, Mikkelsen T, et al. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:71-83. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19960229>.

569. Ellis TL, Neal MT, Chan MD. The role of surgery, radiosurgery and whole brain radiation therapy in the management of patients with metastatic brain tumors. Int J Surg Oncol 2012;2012:952345. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22312545>.



570. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998;280:1485-1489. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/9809728>.

571. Ammirati M, Cobbs CS, Linskey ME, et al. The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;96:85-96. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19957016>.

572. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014;15:387-395. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24621620>.

573. Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25 Suppl 3:iii27-39. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25115305>.

574. Tsao MN, Lloyd N, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev* 2012;4:CD003869. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22513917>.

575. Chang WS, Kim HY, Chang JW, et al. Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: is stereotactic radiosurgery effective for multiple brain metastases? *J Neurosurg* 2010;113 Suppl:73-78. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21121789>.

576. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;81:77-84. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20800380>.

577. Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. *J Clin Oncol* 2011;29:279-286. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21135267>.

578. Tallet AV, Azria D, Barlesi F, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. *Radiat Oncol* 2012;7:77. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22640600>.

579. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol* 2007;25:1260-1266. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17401015>.

580. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 2007;68:1388-1395. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17674975>.

581. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009;10:1037-1044. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19801201>.

582. Suh JH, Videtic GM, Aref AM, et al. ACR Appropriateness Criteria: single brain metastasis. *Curr Probl Cancer* 2010;34:162-174. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20541055>.

583. Marsh JC, Giolda BT, Herskovic AM, Abrams RA. Cognitive Sparing during the Administration of Whole Brain Radiotherapy and Prophylactic Cranial Irradiation: Current Concepts and Approaches. *J Oncol* 2010;2010:198208. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20671962>.

584. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* 2014;32:3810-3816. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25349290>.

585. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* 2016;388:2004-2014. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27604504>.

586. Bradbury P, Sivajohanathan D, Chan A, et al. Postoperative Adjuvant Systemic Therapy in Completely Resected Non-Small-Cell Lung Cancer: A Systematic Review. *Clin Lung Cancer* 2017;18:259-273 e258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28162945>.

587. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351-360. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14736927>.

588. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;352:2589-2597. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15972865>.

589. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006;7:719-727. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16945766>.

590. Song WA, Zhou NK, Wang W, et al. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer: an updated meta-analysis of 13 randomized control trials. *J Thorac Oncol* 2010;5:510-516. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20107424>.

591. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIa non-small-cell lung cancer. *J Clin Oncol* 2012;30:172-178. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22124104>.

592. Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol* 2002;20:247-253. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11773176>.

593. Rosell R, Gomez-Codina J, Camps C, et al. Preresectional chemotherapy in stage IIIa non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. *Lung Cancer* 1999;26:7-14. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10574676>.

594. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIa non-small-cell lung cancer. *J Natl Cancer Inst* 1994;86:673-680. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8158698>.

595. Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol* 2010;28:3138-3145. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20516435>.

596. Pisters KM, Vallieres E, Crowley JJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. *J Clin Oncol* 2010;28:1843-1849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20231678>.

597. Westeel V, Quoix E, Puyraveau M, et al. A randomised trial comparing preoperative to perioperative chemotherapy in early-stage non-small-cell lung cancer (IFCT 0002 trial). *Eur J Cancer* 2013;49:2654-2664. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23735703>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

598. Group NM-aC. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet* 2014;383:1561-1571. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24576776>.

599. Curran WJ, Jr., Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 2011;103:1452-1460. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21903745>.

600. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181-2190. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20351327>.

601. Socinski MA, Rosenman JG, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B nonsmall cell lung carcinoma: a modified phase I/II trial. *Cancer* 2001;92:1213-1223. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11571735>.

602. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692-2699. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10561343>.

603. Socinski MA, Evans T, Gettinger S, et al. Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e341S-e368S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649446>.

604. Azzoli CG, Temin S, Aliff T, et al. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. *J Clin Oncol* 2011;29:3825-3831. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21900105>.

605. Azzoli CG, Baker S, Jr., Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009;27:6251-6266. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19917871>.

606. Group NM-AC. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *J Clin Oncol* 2008;26:4617-4625. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18678835>.

607. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. *Lancet* 1993;342:19-21. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8100290>.

608. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ* 1995;311:899-909. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7580546>.

609. Bakitas MA, El-Jawahri A, Farquhar M, et al. The TEAM Approach to Improving Oncology Outcomes by Incorporating Palliative Care in Practice. *J Oncol Pract* 2017;13:557-566. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28898605>.

610. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733-742. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20818875>.

611. Yates P, Schofield P, Zhao I, Currow D. Supportive and palliative care for lung cancer patients. *J Thorac Dis* 2013;5 Suppl 5:S623-628. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24163753>.

612. Ford DW, Koch KA, Ray DE, Selecky PA. Palliative and end-of-life care in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice

guidelines. Chest 2013;143:e498S-e512S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649453>.

613. Aizer AA, Chen MH, McCarthy EP, et al. Marital status and survival in patients with cancer. J Clin Oncol 2013;31:3869-3876. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24062405>.

614. Basch EM, Deal AM, Dueck AC, et al. Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment [abstract]. J Clin Oncol 2017;35:Abstract LBA2. Available at: <https://meetinglibrary.asco.org/record/147027/abstract>.

615. Magilligan DJ, Jr., Duvernoy C, Malik G, et al. Surgical approach to lung cancer with solitary cerebral metastasis: twenty-five years' experience. Ann Thorac Surg 1986;42:360-364. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3767508>.

616. Kris MG, Gaspar LE, Chaft JE, et al. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non-Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. J Clin Oncol 2017;35:2960-2974. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28437162>.

617. Usami N, Yokoi K, Hasegawa Y, et al. Phase II study of carboplatin and gemcitabine as adjuvant chemotherapy in patients with completely resected non-small cell lung cancer: a report from the Central Japan Lung Study Group, CJLSG 0503 trial. Int J Clin Oncol 2010;15:583-587. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20714770>.

618. Zhang L, Ou W, Liu Q, et al. Pemetrexed plus carboplatin as adjuvant chemotherapy in patients with curative resected non-squamous non-small cell lung cancer. Thorac Cancer 2014;5:50-56. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26766972>.

619. Schmid-Bindert G, Engel-Riedel W, Reck M, et al. A randomized Phase 2 study of pemetrexed in combination with cisplatin or carboplatin as adjuvant chemotherapy in patients with completely resected stage IB or

II Non-Small-Cell Lung Cancer. Lung Cancer 2015;90:397-404. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26791798>.

620. Kim YH, Hirabayashi M, Togashi Y, et al. Phase II study of carboplatin and pemetrexed in advanced non-squamous, non-small-cell lung cancer: Kyoto Thoracic Oncology Research Group Trial 0902. Cancer Chemother Pharmacol 2012;70:271-276. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22752216>.

621. Arriagada R, Dunant A, Pignon JP, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 2010;28:35-42. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19933916>.

622. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol 2010;28:29-34. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19933915>.

623. Douillard JY, Tribodet H, Aubert D, et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol 2010;5:220-228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20027124>.

624. Kreuter M, Vansteenkiste J, Fischer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. Ann Oncol 2013;24:986-992. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23161898>.

625. Petrelli F, Barni S. Non-cancer-related mortality after cisplatin-based adjuvant chemotherapy for non-small cell lung cancer: a study-level meta-analysis of 16 randomized trials. Med Oncol 2013;30:641. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23813019>.

626. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin

Oncol 2008;26:3552-3559. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18506026>.

627. Wisnivesky JP, Smith CB, Packer S, et al. Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIa lung cancer: observational cohort study. *BMJ* 2011;343:d4013. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21757436>.

628. Strauss GM, Herndon J, Maddaus MA, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633 [abstract]. *J Clin Oncol* 2004;22 (Suppl 14):Abstract 7019. Available at:

[https://meeting.ascopubs.org/cgi/content/abstract/22/14\\_suppl/7019](https://meeting.ascopubs.org/cgi/content/abstract/22/14_suppl/7019).

629. Strauss GM, Herndon JE, II, Maddaus MA, et al. Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): Update of Cancer and Leukemia Group B (CALGB) protocol 9633 [abstract]. *J Clin Oncol* 2006;24 (Suppl 18):Abstract 7007. Available at:

[https://meeting.ascopubs.org/cgi/content/abstract/24/18\\_suppl/7007](https://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7007).

630. Strauss GM, Herndon JE, 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;26:5043-5051.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18809614>.

631. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007;18:317-323. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17079694>.

632. Katz A, Saad ED. CALGB 9633: an underpowered trial with a methodologically questionable conclusion. *J Clin Oncol*

2009;27:2300-2301; author reply 2301-2302. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19332712>.

633. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* 1990;323:940-945.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2169587>.

634. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* 1991;83:417-423. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/1847977>.

635. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;326:524-530. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/1310160>.

636. Dillman RO, Seagren SL, Herndon J, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer: Five-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Clin Oncol (Meeting Abstracts)* 1993;12:329. Available at:

637. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;88:1210-1215. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8780630>.

638. Sause W, Kolesar P, Taylor SI, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest* 2000;117:358-364. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10669675>.

639. O'Rourke N, Roque IFM, Farre Bernado N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database*



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

Syst Rev 2010;CD002140. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20556756>.

640. Baumann M, Herrmann T, Koch R, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). *Radiother Oncol* 2011;100:76-85. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21757247>.

641. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e314S-e340S. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23649445>.

642. Hancock JG, Rosen JE, Antonicelli A, et al. Impact of adjuvant treatment for microscopic residual disease after non-small cell lung cancer surgery. *Ann Thorac Surg* 2015;99:406-413. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25528723>.

643. Senan S, Brade A, Wang LH, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol* 2016;34:953-962. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26811519>.

644. Ezer N, Smith CB, Galsky MD, et al. Cisplatin vs. carboplatin-based chemoradiotherapy in patients >65 years of age with stage III non-small cell lung cancer. *Radiother Oncol* 2014;112:272-278. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25150635>.

645. Albain KS, Crowley JJ, Turrisi AT, 3rd, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol* 2002;20:3454-3460. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12177106>.

646. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2005;23:5883-5891. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16087941>.

647. Santana-Davila R, Devisetty K, Szabo A, et al. Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiotherapy for stage III non-small-cell lung cancer: an analysis of Veterans Health Administration data. *J Clin Oncol* 2015;33:567-574. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25422491>.

648. Choy H, Gerber DE, Bradley JD, et al. Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a systematic review of completed and ongoing studies. *Lung Cancer* 2015;87:232-240. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25650301>.

649. Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol* 2011;29:3120-3125. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21747084>.

650. Vokes EE, Senan S, Treat JA, Iscoe NA. PROCLAIM: A phase III study of pemetrexed, cisplatin, and radiation therapy followed by consolidation pemetrexed versus etoposide, cisplatin, and radiation therapy followed by consolidation cytotoxic chemotherapy of choice in locally advanced stage III non-small-cell lung cancer of other than predominantly squamous cell histology. *Clin Lung Cancer* 2009;10:193-198. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19443340>.

651. Senan S, Brade AM, Wang L, et al. Final overall survival results of the phase III PROCLAIM trial: pemetrexed, cisplatin or etoposide, cisplatin plus thoracic radiation therapy followed by consolidation cytotoxic chemotherapy in locally advanced nonsquamous non-small cell lung



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

cancer [abstract]. J Clin Oncol 2015;33:Abstract 7506. Available at: <https://meetinglibrary.asco.org/content/144034-156>.

652. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med 2018;379:2342-2350. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30280658>.

653. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-3024. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12837811>.

654. Smit EF, van Meerbeeck JP, Lianes P, et al. Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group--EORTC 08975. J Clin Oncol 2003;21:3909-3917. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14581415>.

655. Zatloukal P, Petruzalka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 2004;46:87-98. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15364136>.

656. Zornosa C, Vandergrift JL, Kalemkerian GP, et al. First-line systemic therapy practice patterns and concordance with NCCN guidelines for patients diagnosed with metastatic NSCLC treated at NCCN institutions. J Natl Compr Canc Netw 2012;10:847-856. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22773800>.

657. Pennell NA. Selection of chemotherapy for patients with advanced non-small cell lung cancer. Cleve Clin J Med 2012;79 Electronic Suppl 1:eS46-50. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22614966>.

658. Leighl NB. Treatment paradigms for patients with metastatic non-small-cell lung cancer: first-, second-, and third-line. Curr Oncol

2012;19:S52-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22787411>.

659. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol 2015;16:763-774. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26045340>.

660. Goldstein DA, Chen Q, Ayer T, et al. Necitumumab in Metastatic Squamous Cell Lung Cancer: Establishing a Value-Based Cost. JAMA Oncol 2015;1:1293-1300. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26313558>.

661. Edelman MJ, Le Chevalier T, Soria JC. Maintenance therapy and advanced non-small-cell lung cancer: a skeptic's view. J Thorac Oncol 2012;7:1331-1336. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22895137>.

662. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:1941-1967. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24733808>.

663. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:4349-4357. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24145346>.

664. Zhu J, Sharma DB, Gray SW, et al. Carboplatin and paclitaxel with vs without bevacizumab in older patients with advanced non-small cell lung cancer. JAMA 2012;307:1593-1601. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22511687>.

665. Langer C, Ravelo A, Hazard SJ, et al. Comparison of survival and hospitalization rates between Medicare patients with advanced NSCLC treated with bevacizumab-carboplatin-paclitaxel and carboplatin-paclitaxel: a retrospective cohort study. *Lung Cancer* 2014;86:350-357. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25439437>.

666. Langer CJ, Socinski MA, Patel JD, et al. Isolating the Role of Bevacizumab in Elderly Patients With Previously Untreated Nonsquamous Non-Small Cell Lung Cancer: Secondary Analyses of the ECOG 4599 and PointBreak Trials. *Am J Clin Oncol* 2016;39:441-447. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25628268>.

667. Felip E, Gridelli C, Baas P, et al. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy: 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. *Ann Oncol* 2011;22:1507-1519. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21536661>.

668. Lilenbaum R, Zukin M, Pereira JR, et al. A randomized phase III trial of single-agent pemetrexed (P) versus carboplatin and pemetrexed (CP) in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) of 2 [abstract]. *J Clin Oncol* 2012;30(Suppl 15):Abstract 7506. Available at: [https://meeting.ascopubs.org/cgi/content/abstract/30/15\\_suppl/7506](https://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/7506).

669. Langer CJ, O'Byrne KJ, Socinski MA, et al. Phase III trial comparing paclitaxel poliglumex (CT-2103, PPX) in combination with carboplatin versus standard paclitaxel and carboplatin in the treatment of PS 2 patients with chemotherapy-naïve advanced non-small cell lung cancer. *J Thorac Oncol* 2008;3:623-630. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18520802>.

670. Lilenbaum R, Villalflor VM, Langer C, et al. Single-agent versus combination chemotherapy in patients with advanced non-small cell lung cancer and a performance status of 2: prognostic factors and treatment selection based on two large randomized clinical trials. *J Thorac Oncol* 2009;4:869-874. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19487960>.

671. Roth BJ, Krilov L, Adams S, et al. Clinical cancer advances 2012: annual report on progress against cancer from the American Society of Clinical Oncology. *J Clin Oncol* 2013;31:131-161. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23213095>.

672. Zukin M, Barrios CH, Pereira JR, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. *J Clin Oncol* 2013;31:2849-2853. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23775961>.

673. Kelly K, Crowley J, Bunn PA, Jr., et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol* 2001;19:3210-3218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11432888>.

674. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92-98. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11784875>.

675. Santana-Davila R, Szabo A, Arce-Lara C, et al. Cisplatin versus carboplatin-based regimens for the treatment of patients with metastatic lung cancer. An analysis of Veterans Health Administration data. *J Thorac Oncol* 2014;9:702-709. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24662458>.

676. Grossi F, Kubota K, Cappuzzo F, et al. Future scenarios for the treatment of advanced non-small cell lung cancer: focus on taxane-containing regimens. *Oncologist* 2010;15:1102-1112. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20930102>.

677. de Marinis F, Rossi A, Di Maio M, et al. Treatment of advanced non-small-cell lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines. *Lung Cancer* 2011;73:1-10. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21440325>.



678. Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. *Cancer* 2003;98:542-553. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12879472>.

679. Booton R, Lorigan P, Anderson H, et al. A phase III trial of docetaxel/carboplatin versus mitomycin C/ifosfamide/cisplatin (MIC) or mitomycin C/vinblastine/cisplatin (MVP) in patients with advanced non-small-cell lung cancer: a randomised multicentre trial of the British Thoracic Oncology Group (BTOG1). *Ann Oncol* 2006;17:1111-1119. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16603599>.

680. Gronberg BH, Bremnes RM, Flotten O, et al. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:3217-3224. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19433683>.

681. D'Addario G, Pintilie M, Leigh NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol* 2005;23:2926-2936. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15728229>.

682. Greco FA, Spigel DR, Kuzur ME, et al. Paclitaxel/Carboplatin/gemcitabine versus gemcitabine/vinorelbine in advanced non-small-cell lung cancer: a phase II/III study of the Minnie Pearl Cancer Research Network. *Clin Lung Cancer* 2007;8:483-487. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17922972>.

683. Herbst RS, Khuri FR, Lu C, et al. The novel and effective nonplatinum, nontaxane combination of gemcitabine and vinorelbine in advanced nonsmall cell lung carcinoma: potential for decreased toxicity and combination with biological therapy. *Cancer* 2002;95:340-353. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12124835>.

684. Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer:

a phase III study addressing the case for cisplatin. *Ann Oncol* 2005;16:602-610. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15741225>.

685. Rizvi NA, Riely GJ, Azzoli CG, et al. Phase I/II trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage IV non-small-cell lung cancer. *J Clin Oncol* 2008;26:639-643. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18235124>.

686. Green MR, Manikhas GM, Orlov S, et al. Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann Oncol* 2006;17:1263-1268. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16740598>.

687. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012;30:2055-2062. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22547591>.

688. Sandler AB, Johnson DH, Herbst RS. Anti-vascular endothelial growth factor monoclonals in non-small cell lung cancer. *Clin Cancer Res* 2004;10:4258s-4262s. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15217970>.

689. Giaccone G. Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer. *J Clin Oncol* 2005;23:3235-3242. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15886311>.

690. Sabari JK, Santini FC, Schram AM, et al. The activity, safety, and evolving role of brigatinib in patients with ALK-rearranged non-small cell lung cancers. *Onco Targets Ther* 2017;10:1983-1992. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28435288>.

691. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) plus Carboplatin and Paclitaxel as

first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. *Oncologist* 2007;12:713-718. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17602060>.

692. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014;384:665-673. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24933332>.

693. Larkins E, Scepura B, Blumenthal GM, et al. U.S. Food and Drug Administration Approval Summary: Ramucirumab for the Treatment of Metastatic Non-Small Cell Lung Cancer Following Disease Progression On or After Platinum-Based Chemotherapy. *Oncologist* 2015;20:1320-1325. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26446239>.

694. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol* 2011;29:2866-2874. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21670455>.

695. Khozin S, Blumenthal GM, Jiang X, et al. U.S. Food and Drug Administration approval summary: Erlotinib for the first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations. *Oncologist* 2014;19:774-779. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24868098>.

696. Kazandjian D, Blumenthal GM, Yuan W, et al. FDA Approval of Gefitinib for the Treatment of Patients with Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer. *Clin Cancer Res* 2016;22:1307-1312. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26980062>.

697. Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. *Oncologist* 2007;12:90-98. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17285735>.

698. Inoue A, Kobayashi K, Usui K, et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. *J Clin Oncol* 2009;27:1394-1400. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19224850>.

699. Burotto M, Manasanch EE, Wilkerson J, Fojo T. Gefitinib and erlotinib in metastatic non-small cell lung cancer: a meta-analysis of toxicity and efficacy of randomized clinical trials. *Oncologist* 2015;20:400-410. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25795635>.

700. Haspinger ER, Agustoni F, Torri V, et al. Is there evidence for different effects among EGFR-TKIs? Systematic review and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs) versus chemotherapy as first-line treatment for patients harboring EGFR mutations. *Crit Rev Oncol Hematol* 2015;94:213-227. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25523487>.

701. Jackman DM, Miller VA, Cioffredi LA, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. *Clin Cancer Res* 2009;15:5267-5273. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19671843>.

702. Gridelli C, Ciardiello F, Gallo C, et al. First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial. *J Clin Oncol* 2012;30:3002-3011. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22778317>.

703. Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) Mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase



inhibitor therapy. *J Clin Oncol* 2011;29:2121-2127. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21482992>.

704. Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J Clin Oncol* 2012;30:2063-2069. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22547605>.

705. Masters GA, Temin S, Azzoli CG, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2015;33:3488-3515. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26324367>.

706. Urata Y, Katakami N, Morita S, et al. Randomized Phase III Study Comparing Gefitinib With Erlotinib in Patients With Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L. *J Clin Oncol* 2016;34:3248-3257. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27022112>.

707. Nelson V, Ziehr J, Agulnik M, Johnson M. Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC. *Onco Targets Ther* 2013;6:135-143. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23493883>.

708. De Greve J, Teugels E, Geers C, et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. *Lung Cancer* 2012;76:123-127. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22325357>.

709. FDA approves afatinib for advanced lung cancer. *Oncology (Williston Park)* 2013;27:813-814. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24133833>.

710. Dungo RT, Keating GM. Afatinib: first global approval. *Drugs* 2013;73:1503-1515. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23982599>.

711. Soria JC, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2015;16:897-907. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26156651>.

712. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol* 2016;17:577-589. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27083334>.

713. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018;378:113-125. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29151359>.

714. Ramalingam SS, Reungwetwattana T, Chewaskulyong B, et al. Osimertinib versus standard-of-care EGFR-TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA [abstract] [abstract]. Presented at the ESMO Congress; Madrid. Abstract LBA2\_PR.

715. Ramalingam SS, Yang JC, Lee CK, et al. Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2018;36:841-849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28841389>.

716. Merker JD, Oxnard GR, Compton C, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol* 2018;36:1631-1641. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29504847>.

717. Oxnard GR, Thress KS, Alden RS, et al. Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2016;34:3375-3382. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27354477>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

718. Sacher AG, Paweletz C, Dahlberg SE, et al. Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer. *JAMA Oncol* 2016;2:1014-1022. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27055085>.
719. Hochmair MJ, Holzer S, Filipits M, et al. EGFR T790M resistance mutation in NSCLC: Real-life data of patients treated with osimertinib [abstract]. *J Clin Oncol* 2016;34:Abstract e20572. Available at:
720. Ricciuti B, Chiari R, Chiarini P, et al. Osimertinib (AZD9291) and CNS Response in Two Radiotherapy-Naive Patients with EGFR-Mutant and T790M-Positive Advanced Non-Small Cell Lung Cancer. *Clin Drug Invest* 2016;36:683-686. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27177916>.
721. Reichegger H, Jochum W, Forbs D, et al. Rapid Intracranial Response to Osimertinib in a Patient with Epidermal Growth Factor Receptor T790M-Positive Adenocarcinoma of the Lung. *Oncol Res Treat* 2016;39:461-463. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27486808>.
722. Ballard P, Yates JW, Yang Z, et al. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. *Clin Cancer Res* 2016;22:5130-5140. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27435396>.
723. How J, Mann J, Lacznia AN, Baggstrom MQ. Pulsatile Erlotinib in EGFR-Positive Non-Small-Cell Lung Cancer Patients With Leptomeningeal and Brain Metastases: Review of the Literature. *Clin Lung Cancer* 2017;18:354-363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28245967>.
724. Grommes C, Oxnard GR, Kris MG, et al. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. *Neuro Oncol* 2011;13:1364-1369. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21865399>.
725. Kawamura T, Hata A, Takeshita J, et al. High-dose erlotinib for refractory leptomeningeal metastases after failure of standard-dose EGFR-TKIs. *Cancer Chemother Pharmacol* 2015;75:1261-1266. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25921002>.
726. Yang JC-H, Cho BC, Kim D-W, et al. Osimertinib for patients (pts) with leptomeningeal metastases (LM) from EGFR-mutant non-small cell lung cancer (NSCLC): Updated results from the BLOOM study [abstract]. *J Clin Oncol* 2017;35(15):Abstract 2020. Available at: [https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15\\_suppl.2020](https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.2020).
727. Tamiya A, Tamiya M, Nishihara T, et al. Cerebrospinal Fluid Penetration Rate and Efficacy of Afatinib in Patients with EGFR Mutation-positive Non-small Cell Lung Cancer with Leptomeningeal Carcinomatosis: A Multicenter Prospective Study. *Anticancer Res* 2017;37:4177-4182. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28739703>.
728. Hoffknecht P, Tufman A, Wehler T, et al. Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. *J Thorac Oncol* 2015;10:156-163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25247337>.
729. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2017;18:1454-1466. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28958502>.
730. Kazandjian D, Blumenthal GM, Chen HY, et al. FDA approval summary: crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. *Oncologist* 2014;19:e5-11. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25170012>.
731. Awad MM, Oxnard GR, Jackman DM, et al. MET Exon 14 Mutations in Non-Small-Cell Lung Cancer Are Associated With Advanced Age and

Stage-Dependent MET Genomic Amplification and c-Met Overexpression. J Clin Oncol 2016;34:721-730. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26729443>.

732. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-2177. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25470694>.

733. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-2394. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23724913>.

734. Crino L, Kim D, Riely GJ, et al. Initial phase II results with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC): PROFILE 1005 [abstract]. J Clin Oncol 2011;29 (Suppl 15):Abstract 7514. Available at: [https://meeting.ascopubs.org/cgi/content/abstract/29/15\\_suppl/7514](https://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7514).

735. Camidge DR, Bang Y, Kwak EL, et al. Progression-free survival (PFS) from a phase I study of crizotinib (PF-02341066) in patients with ALK-positive non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 2501. Available at: [https://meeting.ascopubs.org/cgi/content/abstract/29/15\\_suppl/2501](https://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/2501).

736. Rodig SJ, Shapiro GI. Crizotinib, a small-molecule dual inhibitor of the c-Met and ALK receptor tyrosine kinases. Curr Opin Investig Drugs 2010;11:1477-1490. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21154129>.

737. Costa DB, Shaw AT, Ou SH, et al. Clinical Experience With Crizotinib in Patients With Advanced ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastases. J Clin Oncol 2015;33:1881-1888. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25624436>.

738. Shaw AT, Yeap BY, Solomon BJ, et al. Impact of crizotinib on survival in patients with advanced, ALK-positive NSCLC compared with historical controls [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract

7507. Available at: [https://meeting.ascopubs.org/cgi/content/abstract/29/15\\_suppl/7507](https://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7507).

739. Bang YJ. Treatment of ALK-positive non-small cell lung cancer. Arch Pathol Lab Med 2012;136:1201-1204. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23020724>.

740. Choi YL, Soda M, Yamashita Y, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med 2010;363:1734-1739. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20979473>.

741. Rothenstein JM, Letarte N. Managing treatment-related adverse events associated with Alk inhibitors. Curr Oncol 2014;21:19-26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24523601>.

742. Brosnan EM, Weickhardt AJ, Lu X, et al. Drug-induced reduction in estimated glomerular filtration rate in patients with ALK-positive non-small cell lung cancer treated with the ALK inhibitor crizotinib. Cancer 2014;120:664-674. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24258622>.

743. Frampton JE. Crizotinib: a review of its use in the treatment of anaplastic lymphoma kinase-positive, advanced non-small cell lung cancer. Drugs 2013;73:2031-2051. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24288180>.

744. Gandhi L, Ou SI, Shaw AT, et al. Efficacy of alectinib in central nervous system metastases in crizotinib-resistant ALK-positive non-small-cell lung cancer: Comparison of RECIST 1.1 and RANO-HGG criteria. Eur J Cancer 2017;82:27-33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28646771>.

745. Crino L, Ahn MJ, De Marinis F, et al. Multicenter Phase II Study of Whole-Body and Intracranial Activity With Ceritinib in Patients With ALK-Rearranged Non-Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2. J Clin Oncol 2016;34:2866-2873. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27432917>.

746. Shaw AT, Kim TM, Crino L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 2017;18:874-886. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28602779>.

747. Camidge DR, Kim DW, Tiseo M, et al. Exploratory Analysis of Brigatinib Activity in Patients With Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer and Brain Metastases in Two Clinical Trials. *J Clin Oncol* 2018;36:2693-2701. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29768119>.

748. Lim SM, Kim HR, Lee JS, et al. Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. *J Clin Oncol* 2017;35:2613-2618. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28520527>.

749. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet* 2017;389:917-929. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28126333>.

750. Khozin S, Blumenthal GM, Zhang L, et al. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. *Clin Cancer Res* 2015;21:2436-2439. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25754348>.

751. Kim DW, Mehra R, Tan DSW, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. *Lancet Oncol* 2016;17:452-463. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26973324>.

752. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;370:1189-1197. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24670165>.

753. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* 2017;390:29-39. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28501140>.

754. Larkins E, Blumenthal GM, Chen H, et al. FDA Approval: Alectinib for the Treatment of Metastatic, ALK-Positive Non-Small Cell Lung Cancer Following Crizotinib. *Clin Cancer Res* 2016;22:5171-5176. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27413075>.

755. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol* 2016;17:234-242. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26708155>.

756. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;379:2027-2039. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30280657>.

757. Camidge DR, Tiseo M, Ahn M-J, et al. P3.02a-013 Brigatinib in crizotinib-refractory ALK+ NSCLC: central assessment and updates from ALTA, a pivotal randomized phase 2 trial [abstract]. *J Thorac Oncol* 2017;12:S1167-S1169. Available at: <https://bit.ly/2pCxxKu>.

758. Lin JJ, Zhu VW, Schoenfeld AJ, et al. Brigatinib in Patients With Alectinib-Refractory ALK-Positive NSCLC. *J Thorac Oncol* 2018;13:1530-1538. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29935304>.

759. Odogwu L, Mathieu L, Blumenthal G, et al. FDA Approval Summary: Dabrafenib and Trametinib for the Treatment of Metastatic Non-Small Cell Lung Cancers Harboring BRAF V600E Mutations. *Oncologist* 2018;23:740-745. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29438093>.

760. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*

2017;18:1307-1316. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28919011>.

761. Planchard D, Groen HJM, Kim TM, et al. Interim results of a phase II study of the BRAF inhibitor (BRAFi) dabrafenib (D) in combination with the MEK inhibitor trametinib (T) in patients (pts) with BRAF V600E mutated (mut) metastatic non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2015;33:Abstract 8006. Available at:

<https://meetinglibrary.asco.org/content/147124-156>.

762. Planchard D, Besse B, Kim TM. Updated survival of patients (pts) with previously treated BRAF V600E–mutant advanced non-small cell lung cancer (NSCLC) who received dabrafenib (D) or D + trametinib (T) in the phase II BRF113928 study [abstract]. J Clin Oncol 2017;35:Abstract 9075. Available at:

[https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15\\_suppl.9075](https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9075).

763. Liu D, Offin M, Harnicar S, et al. Entrectinib: an orally available, selective tyrosine kinase inhibitor for the treatment of NTRK, ROS1, and ALK fusion-positive solid tumors. Ther Clin Risk Manag 2018;14:1247-1252. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30050303>.

764. Doebele RC, Ahn M-J, Siena S, et al. OA02.01: Efficacy and safety of entrectinib in locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) [abstract]. J Thorac Oncol 2018;13:S321–S322. Available at:

[https://www.jto.org/article/S1556-0864\(18\)31197-3/fulltext](https://www.jto.org/article/S1556-0864(18)31197-3/fulltext).

765. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-1531. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19410716>.

766. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714-1768. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29442540>.

767. Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. Immunotargets Ther 2017;6:51-71. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28894725>.

768. Chiou VL, Burotto M. Pseudoprogression and Immune-Related Response in Solid Tumors. J Clin Oncol 2015;33:3541-3543. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26261262>.

769. Horn L, Spigel DR, Vokes EE, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol 2017;35:3924-3933. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29023213>.

770. Kazandjian D, Suzman DL, Blumenthal G, et al. FDA Approval Summary: Nivolumab for the Treatment of Metastatic Non-Small Cell Lung Cancer With Progression On or After Platinum-Based Chemotherapy. Oncologist 2016;21:634-642. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26984449>.

771. Melosky B, Chu Q, Juergens R, et al. Pointed Progress in Second-Line Advanced Non-Small-Cell Lung Cancer: The Rapidly Evolving Field of Checkpoint Inhibition. J Clin Oncol 2016;34:1676-1688. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26884577>.

772. Phillips T, Simmons P, Inzunza HD, et al. Development of an automated PD-L1 immunohistochemistry (IHC) assay for non-small cell lung cancer. Appl Immunohistochem Mol Morphol 2015;23:541-549. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26317305>.

773. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-413. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28596308>.

774. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-2520. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26028255>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

775. Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol* 2015;16:257-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25704439>.

776. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol* 2016;2:1607-1616. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27540850>.

777. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol* 2017;35:709-717. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27646942>.

778. Sgambato A, Casaluce F, Sacco PC, et al. Anti PD-1 and PDL-1 Immunotherapy in the Treatment of Advanced Non- Small Cell Lung Cancer (NSCLC): A Review on Toxicity Profile and its Management. *Curr Drug Saf* 2016;11:62-68. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26412670>.

779. Gettinger SN, Horn L, Gandhi L, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* 2015;33:2004-2012. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25897158>.

780. Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. *J Clin Oncol* 2015;33:1974-1982. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25605845>.

781. Chapman PB, D'Angelo SP, Wolchok JD. Rapid eradication of a bulky melanoma mass with one dose of immunotherapy. *N Engl J Med* 2015;372:2073-2074. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25891305>.

782. Pai-Scherf L, Blumenthal GM, Li H, et al. FDA Approval Summary: Pembrolizumab for Treatment of Metastatic Non-Small Cell Lung Cancer: First-Line Therapy and Beyond. *Oncologist* 2017;22:1392-1399. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28835513>.

783. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* 2016;17:1497-1508. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27745820>.

784. Paz-Ares LG, Luft A, Tafreshi A, et al. Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab for patients with metastatic squamous non-small cell lung cancer [abstract]. *J Clin Oncol* 2018;36:Abstract 105. Available at: [https://abstracts.asco.org/214/AbstView\\_214\\_228023.html](https://abstracts.asco.org/214/AbstView_214_228023.html).

785. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018-2028. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25891174>.

786. Sul J, Blumenthal GM, Jiang X, et al. FDA Approval Summary: Pembrolizumab for the Treatment of Patients With Metastatic Non-Small Cell Lung Cancer Whose Tumors Express Programmed Death-Ligand 1. *Oncologist* 2016;21:643-650. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27026676>.

787. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol* 2016;17:883-895. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27269741>.

788. Antonia SJ, Kim S-W, Spira AI, et al. Safety and clinical activity of durvalumab (MEDI4736), an anti-PD-L1 antibody, in treatment-naïve patients with advanced non-small-cell lung cancer [abstract]. *J Clin Oncol* 2016;34:Abstract 9029. Available at: <https://meetinglibrary.asco.org/content/163695-176>.



789. Khoja L, Butler MO, Kang SP, et al. Pembrolizumab. J Immunother Cancer 2015;3:36. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26288737>.

790. Barlesi F, Park K, Ciardiello F. Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC [abstract] [abstract]. Presented at the 2016 Annual Meeting European Society for Medical Oncology (ESMO) Copenhagen, Denmark. Abstract LBA44.

791. Gridelli C, de Marinis F, Di Maio M, et al. Maintenance treatment of advanced non-small-cell lung cancer: results of an international expert panel meeting of the Italian association of thoracic oncology. Lung Cancer 2012;76:269-279. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22266040>.

792. Hashemi-Sadraei N, Pennell NA. Advanced non-small cell lung cancer (NSCLC): maintenance therapy for all? Curr Treat Options Oncol 2012;13:478-490. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22972369>.

793. Patel JD, Hensing TA, Rademaker A, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. J Clin Oncol 2009;27:3284-3289. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19433684>.

794. Nadler E, Yu E, Ravelo A, et al. Bevacizumab treatment to progression after chemotherapy: outcomes from a U.S. community practice network. Oncologist 2011;16:486-496. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21441299>.

795. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012;13:247-255. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22341744>.

796. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:2895-2902. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23835707>.

797. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). J Clin Oncol 2013;31:3004-3011. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23835708>.

798. Barlesi F, Scherpereel A, Gorbunova V, et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous non-small-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. Ann Oncol 2014;25:1044-1052. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24585722>.

799. Perol M, Chouaid C, Perol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012;30:3516-3524. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22949150>.

800. Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 7507. Available at:

[https://meeting.ascopubs.org/cqi/content/abstract/28/15\\_suppl/7507](https://meeting.ascopubs.org/cqi/content/abstract/28/15_suppl/7507).

801. Brodowicz T, Krzakowski M, Zwitter M, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

trial. Lung Cancer 2006;52:155-163. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/16569462>.

802. Fidias P, Novello S. Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. J Clin Oncol 2010;28:5116-5123. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21041704>.

803. Socinski MA, Schell MJ, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 2002;20:1335-1343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11870177>.

804. Gerber DE, Schiller JH. Maintenance chemotherapy for advanced non-small-cell lung cancer: new life for an old idea. J Clin Oncol 2013;31:1009-1020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23401441>.

805. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521-529. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20493771>.

806. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-1440. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19767093>.

807. Cohen MH, Cortazar P, Justice R, Pazdur R. Approval summary: pemetrexed maintenance therapy of advanced/metastatic nonsquamous, non-small cell lung cancer (NSCLC). Oncologist 2010;15:1352-1358. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21148615>.

808. Cicones S, Geater SL, Petrov P, et al. Maintenance erlotinib versus erlotinib at disease progression in patients with advanced non-small-cell lung cancer who have not progressed following platinum-based

chemotherapy (IUNO study). Lung Cancer 2016;102:30-37. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27987585>.

809. Rittmeyer A. Quality of Life in Patients with NSCLC Receiving Maintenance Therapy. Cancers (Basel) 2015;7:950-962. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26035509>.

810. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009;27:591-598. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19075278>.

811. Rigotti NA, Regan S, Levy DE, et al. Sustained care intervention and postdischarge smoking cessation among hospitalized adults: a randomized clinical trial. JAMA 2014;312:719-728. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25138333>.

812. Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. Cochrane Database Syst Rev 2013;8:CD002850. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23934971>.

813. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2012;10:CD008286. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23076944>.

814. Patterson GA, Ginsberg RJ, Poon PY, et al. A prospective evaluation of magnetic resonance imaging, computed tomography, and mediastinoscopy in the preoperative assessment of mediastinal node status in bronchogenic carcinoma. J Thorac Cardiovasc Surg 1987;94:679-684. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3669696>.

815. Gonzalez-Stawinski GV, Lemaire A, Merchant F, et al. A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. J Thorac Cardiovasc Surg

2003;126:1900-1905. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14688703>.

816. Tournoy KG, Maddens S, Gosselin R, et al. Integrated FDG-PET/CT does not make invasive staging of the intrathoracic lymph nodes in non-small cell lung cancer redundant: a prospective study. *Thorax* 2007;62:696-701. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17687098>.

817. Meyers BF, Haddad F, Siegel BA, et al. Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. *J Thorac Cardiovasc Surg* 2006;131:822-829; discussion 822-829. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16580440>.

818. Dillemans B, Deneffe G, Verschakelen J, Decramer M. Value of computed tomography and mediastinoscopy in preoperative evaluation of mediastinal nodes in non-small cell lung cancer. A study of 569 patients. *Eur J Cardiothorac Surg* 1994;8:37-42. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8136168>.

819. Arita T, Kuramitsu T, Kawamura M, et al. Bronchogenic carcinoma: incidence of metastases to normal sized lymph nodes. *Thorax* 1995;50:1267-1269. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8553299>.

820. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med* 2000;343:254-261. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10911007>.

821. Manente P, Vicario G, Piazza F, et al. Does PET/CT modify the therapeutic approach in medical oncology [abstract]? . *J Clin Oncol* 2008;26(Suppl 15):Abstract 17525. Available at:

[https://meeting.ascopubs.org/cgi/content/abstract/26/15\\_suppl/17525](https://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/17525).

822. Maziak DE, Darling GE, Inculet RI, et al. Positron emission tomography in staging early lung cancer: a randomized trial. *Ann Intern*

*Med* 2009;151:221-228, W-248. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19581636>.

823. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med* 2009;361:32-39. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19571281>.

824. De Wever W, Stroobants S, Coolen J, Verschakelen JA. Integrated PET/CT in the staging of nonsmall cell lung cancer: technical aspects and clinical integration. *Eur Respir J* 2009;33:201-212. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19118231>.

825. McCloud TC, Bourgouin PM, Greenberg RW, et al. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. *Radiology* 1992;182:319-323.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1732943>.

826. Seely JM, Mayo JR, Miller RR, Muller NL. T1 lung cancer: prevalence of mediastinal nodal metastases and diagnostic accuracy of CT. *Radiology* 1993;186:129-132. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8416552>.

827. Kerr KM, Lamb D, Wathen CG, et al. Pathological assessment of mediastinal lymph nodes in lung cancer: implications for non-invasive mediastinal staging. *Thorax* 1992;47:337-341. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/1609375>.

828. Chin R, Jr., Ward R, Keyes JW, et al. Mediastinal staging of non-small-cell lung cancer with positron emission tomography. *Am J Respir Crit Care Med* 1995;152:2090-2096. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8520780>.

829. Kernstine KH, Stanford W, Mullan BF, et al. PET, CT, and MRI with Combidex for mediastinal staging in non-small cell lung carcinoma. *Ann Thorac Surg* 1999;68:1022-1028. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10510001>.

830. De Leyn P, Stroobants S, De Wever W, et al. Prospective comparative study of integrated positron emission tomography-computed

tomography scan compared with mediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy for mediastinoscopy-proven stage IIIA-N2 Non-small-cell lung cancer: a Leuven Lung Cancer Group Study. *J Clin Oncol* 2006;24:3333-3339. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16849747>.

831. Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. *J Thorac Cardiovasc Surg* 2006;131:1229-1235. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16733150>.

832. Darling GE, Maziak DE, Incullet RI, et al. Positron emission tomography-computed tomography compared with invasive mediastinal staging in non-small cell lung cancer: results of mediastinal staging in the early lung positron emission tomography trial. *J Thorac Oncol* 2011;6:1367-1372. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21587082>.

833. Yasufuku K, Pierre A, Darling G, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. *J Thorac Cardiovasc Surg* 2011;142:1393-1400 e1391. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21963329>.

834. Annema JT, van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA* 2010;304:2245-2252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21098770>.

835. Tournoy KG, Keller SM, Annema JT. Mediastinal staging of lung cancer: novel concepts. *Lancet Oncol* 2012;13:e221-229. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22554550>.

836. Vilmann P, Krasnik M, Larsen SS, et al. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. *Endoscopy* 2005;37:833-839. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16116534>.

837. Yasufuku K, Nakajima T, Motoori K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest* 2006;130:710-718. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16963667>.

838. Ernst A, Eberhardt R, Krasnik M, Herth FJ. Efficacy of endobronchial ultrasound-guided transbronchial needle aspiration of hilar lymph nodes for diagnosing and staging cancer. *J Thorac Oncol* 2009;4:947-950. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19590457>.

839. Rintoul RC, Tournoy KG, El Daly H, et al. EBUS-TBNA for the clarification of PET positive intra-thoracic lymph nodes-an international multi-centre experience. *J Thorac Oncol* 2009;4:44-48. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19096305>.

840. Defranchi SA, Edell ES, Daniels CE, et al. Mediastinoscopy in patients with lung cancer and negative endobronchial ultrasound guided needle aspiration. *Ann Thorac Surg* 2010;90:1753-1757. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21095301>.

841. Medford AR, Bennett JA, Free CM, Agrawal S. Mediastinal staging procedures in lung cancer: EBUS, TBNA and mediastinoscopy. *Curr Opin Pulm Med* 2009;15:334-342. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19395972>.

842. Mayr NA, Hussey DH, Yuh WT. Cost-effectiveness of high-contrast-dose MR screening of asymptomatic brain metastasis. *AJNR Am J Neuroradiol* 1995;16:215-217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7755752>.

843. Videtic GM, Chang JY, Chetty IJ, et al. ACR appropriateness Criteria(R) early-stage non-small-cell lung cancer. *Am J Clin Oncol* 2014;37:201-207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25180631>.

844. Rusch VW, Kraut MJ, Crowley J, et al. Induction chemoradiotherapy and surgical resection for non-small cell lung carcinomas of the superior sulcus (pancoast tumors): Mature results of Southwest Oncology Group trial 9416 (Intergroup trial 0160) [abstract]. *Proc Am Soc Clin Oncol* 2003

22:Abstract 2548. Available at:

[https://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=23&abstractID=103854](https://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=103854).

845. Barnes JB, Johnson SB, Dahiya RS, et al. Concomitant weekly cisplatin and thoracic radiotherapy for Pancoast tumors of the lung: pilot experience of the San Antonio Cancer Institute. *Am J Clin Oncol* 2002;25:90-92. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11823705>.

846. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: Initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Thorac Cardiovasc Surg* 2001;121:472-483. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11241082>.

847. Pourel N, Santelmo N, Naafa N, et al. Concurrent cisplatin/etoposide plus 3D-conformal radiotherapy followed by surgery for stage IIB (superior sulcus T3N0)/III non-small cell lung cancer yields a high rate of pathological complete response. *Eur J Cardiothorac Surg* 2008;33:829-836. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18367406>.

848. Kunitoh H, Kato H, Tsuboi M, et al. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical Oncology Group trial 9806. *J Clin Oncol* 2008;26:644-649. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18235125>.

849. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003;21:2004-2010. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12743155>.

850. Nakagawa T, Okumura N, Miyoshi K, et al. Prognostic factors in patients with ipsilateral pulmonary metastasis from non-small cell lung cancer. *Eur J Cardiothorac Surg* 2005;28:635-639. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16126398>.

851. Lee JG, Lee CY, Kim DJ, et al. Non-small cell lung cancer with ipsilateral pulmonary metastases: prognosis analysis and staging assessment. *Eur J Cardiothorac Surg* 2008;33:480-484. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18249000>.

852. Bhaskarla A, Tang PC, Mashtare T, et al. Analysis of second primary lung cancers in the SEER database. *J Surg Res* 2010;162:1-6. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20400118>.

853. Aziz TM, Saad RA, Glasser J, et al. The management of second primary lung cancers. A single centre experience in 15 years. *Eur J Cardiothorac Surg* 2002;21:527-533. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11888775>.

854. Adebonojo SA, Moritz DM, Danby CA. The results of modern surgical therapy for multiple primary lung cancers. *Chest* 1997;112:693-701.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9315801>.

855. Nakata M, Sawada S, Yamashita M, et al. Surgical treatments for multiple primary adenocarcinoma of the lung. *Ann Thorac Surg* 2004;78:1194-1199. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15464469>.

856. Ginsberg MS, Griff SK, Go BD, et al. Pulmonary nodules resected at video-assisted thoracoscopic surgery: etiology in 426 patients. *Radiology* 1999;213:277-282. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10540672>.

857. Allen MS. Multiple benign lung tumors. *Semin Thorac Cardiovasc Surg* 2003;15:310-314. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12973710>.

858. Asamura H. Multiple primary cancers or multiple metastases, that is the question. *J Thorac Oncol* 2010;5:930-931. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20581574>.

859. Girard N, Deshpande C, Azzoli CG, et al. Use of epidermal growth factor receptor/Kirsten rat sarcoma 2 viral oncogene homolog mutation testing to define clonal relationships among multiple lung

adenocarcinomas: comparison with clinical guidelines. Chest 2010;137:46-52. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19376842>.

860. Han HS, Eom DW, Kim JH, et al. EGFR mutation status in primary lung adenocarcinomas and corresponding metastatic lesions: discordance in pleural metastases. Clin Lung Cancer 2011;12:380-386. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21729655>.

861. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-612. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/170482>.

862. Chang YL, Wu CT, Lee YC. Surgical treatment of synchronous multiple primary lung cancers: experience of 92 patients. J Thorac Cardiovasc Surg 2007;134:630-637. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17723810>.

863. Tanvetyanon T, Robinson L, Sommers KE, et al. Relationship between tumor size and survival among patients with resection of multiple synchronous lung cancers. J Thorac Oncol 2010;5:1018-1024. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20453687>.

864. Rea F, Zuin A, Callegaro D, et al. Surgical results for multiple primary lung cancers. Eur J Cardiothorac Surg 2001;20:489-495. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11509268>.

865. Gibbs IC, Loo BW, Jr. CyberKnife stereotactic ablative radiotherapy for lung tumors. Technol Cancer Res Treat 2010;9:589-596. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21070081>.

866. Godoy MC, Naidich DP. Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: recommended interim guidelines for assessment and management. Radiology 2009;253:606-622. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19952025>.

867. Pearson FG, DeLarue NC, Ilves R, et al. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with

resectable cancer of the lung. J Thorac Cardiovasc Surg 1982;83:1-11. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7054602>.

868. Rice TW. Thoracoscopy in the staging of thoracic malignancies. In: Kaiser LR, Daniel TM, eds, eds. Thoracoscopic Surgery. Philadelphia: Lippincott Williams & Wilkins; 1993:153-162.

869. Gandara DR, Chansky K, Albain KS, et al. Long-term survival with concurrent chemoradiation therapy followed by consolidation docetaxel in stage IIIB non-small-cell lung cancer: a phase II Southwest Oncology Group Study (S9504). Clin Lung Cancer 2006;8:116-121. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17026812>.

870. Mina LA, Neubauer MA, Ansari RH, et al. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023--Updated results [abstract]. J Clin Oncol 2008;26 (Suppl 15):Abstract 7519. Available at:

[https://meeting.ascopubs.org/cgi/content/abstract/26/15\\_suppl/7519](https://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/7519).

871. Hanna NH, Neubauer M, Ansari R, et al. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023 [abstract]. J Clin Oncol 2007;25 (Suppl 18):Abstract 7512. Available at:

[https://meeting.ascopubs.org/cgi/content/abstract/25/18\\_suppl/7512](https://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7512).

872. Decker DA, Dines DE, Payne WS, et al. The significance of a cytologically negative pleural effusion in bronchogenic carcinoma. Chest 1978;74:640-642. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/216532>.

873. Demmy TL, Gu L, Burkhalter JE, et al. Optimal management of malignant pleural effusions (results of CALGB 30102). J Natl Compr Canc Netw 2012;10:975-982. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22878823>.

874. de Vin T, Engels B, Gevaert T, et al. Stereotactic radiotherapy for oligometastatic cancer: a prognostic model for survival. *Ann Oncol* 2014;25:467-471. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24355488>.

875. Simone CB, 2nd, Burri SH, Heinzerling JH. Novel radiotherapy approaches for lung cancer: combining radiation therapy with targeted and immunotherapies. *Transl Lung Cancer Res* 2015;4:545-552. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26629423>.

876. Campo M, Al-Halabi H, Khandekar M, et al. Integration of Stereotactic Body Radiation Therapy With Tyrosine Kinase Inhibitors in Stage IV Oncogene-Driven Lung Cancer. *Oncologist* 2016;21:964-973. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27354669>.

877. Park SY, Lee JG, Kim J, et al. Efficacy of platinum-based adjuvant chemotherapy in T2aN0 stage IB non-small cell lung cancer. *J Cardiothorac Surg* 2013;8:151. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23759129>.

878. Group NM-aC, Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet* 2010;375:1267-1277. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20338627>.

879. Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. *J Clin Oncol* 2008;26:468-473. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18202422>.

880. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994;330:153-158. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8043059>.

881. Pisters K, Vallieres E, Bunn P, et al. S9900: A phase III trial of surgery alone or surgery plus preoperative (preop) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Preliminary results [abstract]. *J Clin Oncol* 2005;23 (Suppl 16):Abstract LBA7012. Available at:

[https://meeting.ascopubs.org/cgi/content/abstract/23/16\\_suppl/LBA7012](https://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/LBA7012).

882. Pisters K, Vallieres E, Bunn PA, Jr., et al. S9900: Surgery alone or surgery plus induction (ind) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Follow-up on a phase III trial [abstract]. *J Clin Oncol* 2007;25 (Suppl 18):Abstract 7520. Available at:

[https://meeting.ascopubs.org/cgi/content/abstract/25/18\\_suppl/7520](https://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7520).

883. Burkes RL, Ginsberg RJ, Shepherd FA, et al. Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage III unresectable non-small-cell lung cancer: results of the Toronto Phase II Trial. *J Clin Oncol* 1992;10:580-586. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/1312587>.

884. Bonomi P, Faber L. Neoadjuvant chemoradiation therapy in non-small cell lung cancer: The Rush University experience. *Lung Cancer* 1993;9:383-390. Available at:

885. Rusch VW, Albain KS, Crowley JJ, et al. Surgical resection of stage IIIA and stage IIIB non-small-cell lung cancer after concurrent induction chemoradiotherapy. A Southwest Oncology Group trial. *J Thorac Cardiovasc Surg* 1993;105:97-104; discussion 104-106. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8380477>.

886. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet* 1998;352:257-263. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/9690404>.

887. Robinson CG, Patel AP, Bradley JD, et al. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the National Cancer Data Base. *J Clin*

Oncol 2015;33:870-876. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25667283>.

888. Patel SH, Ma Y, Wernicke AG, et al. Evidence supporting contemporary post-operative radiation therapy (PORT) using linear accelerators in N2 lung cancer. Lung Cancer 2014;84:156-160. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24674156>.

889. Decker RH, Langer CJ, Rosenzweig KE, et al. ACR Appropriateness Criteria(R) postoperative adjuvant therapy in non-small cell lung cancer. Am J Clin Oncol 2011;34:537-544. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21946673>.

890. Weisenburger TH, Graham MV, Sause WT, et al. Postoperative radiotherapy in non-small cell lung cancer. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000;215 Suppl:1295-1318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11037548>.

891. Choy H, Schwartzberg LS, Dakhil SR, et al. Phase 2 study of pemetrexed plus carboplatin, or pemetrexed plus cisplatin with concurrent radiation therapy followed by pemetrexed consolidation in patients with favorable-prognosis inoperable stage IIIA/B non-small-cell lung cancer. J Thorac Oncol 2013;8:1308-1316. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23981966>.

892. Garrido P, Engel-Riedel W, Serke M, et al. Final results from a Phase II study of pemetrexed and cisplatin with concurrent thoracic radiation after Pem-Cis induction in patients with unresectable locally advanced non-squamous non-small cell lung cancer (NSCLC). Lung Cancer 2015;88:160-166. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25758556>.

893. Crabtree TD, Puri V, Chen SB, et al. Does the method of radiologic surveillance affect survival after resection of stage I non-small cell lung cancer? J Thorac Cardiovasc Surg 2015;149:45-52, 53 e41-43. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25218540>.

894. Erb CT, Su KW, Soulos PR, et al. Surveillance Practice Patterns after Curative Intent Therapy for Stage I Non-Small-Cell Lung Cancer in the

Medicare Population. Lung Cancer 2016;99:200-207. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27565940>.

895. Colt HG, Murgu SD, Korst RJ, et al. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e437S-e454S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649451>.

896. Lou F, Huang J, Sima CS, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg 2013;145:75-81; discussion 81-72. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23127371>.

897. Srikantharajah D, Ghuman A, Nagendran M, Maruthappu M. Is computed tomography follow-up of patients after lobectomy for non-small cell lung cancer of benefit in terms of survival? Interact Cardiovasc Thorac Surg 2012;15:893-898. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22859511>.

898. Hanna WC, Paul NS, Darling GE, et al. Minimal-dose computed tomography is superior to chest x-ray for the follow-up and treatment of patients with resected lung cancer. J Thorac Cardiovasc Surg 2014;147:30-33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24139896>.

899. Calman L, Beaver K, Hind D, et al. Survival benefits from follow-up of patients with lung cancer: a systematic review and meta-analysis. J Thorac Oncol 2011;6:1993-2004. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21892108>.

900. Dane B, Grechushkin V, Plank A, et al. PET/CT vs. non-contrast CT alone for surveillance 1-year post lobectomy for stage I non-small-cell lung cancer. Am J Nucl Med Mol Imaging 2013;3:408-416. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24116349>.



901. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999;354:99-105. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10408484>.

902. Ulaner GA, Lyall A. Identifying and distinguishing treatment effects and complications from malignancy at FDG PET/CT. *Radiographics* 2013;33:1817-1834. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24108564>.

903. Shi Q, Smith TG, Michonski JD, et al. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. *Cancer* 2011;117:2779-2790. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21495026>.

904. Gelb AF, Tashkin DP, Epstein JD, et al. Physiologic characteristics of malignant unilateral main-stem bronchial obstruction. Diagnosis and Nd-YAG laser treatment. *Am Rev Respir Dis* 1988;138:1382-1385. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/2462389>.

905. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-247. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19097774>.

906. Therasse P, Arbutk SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205-216. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/10655437>.

907. Nishino M, Hatabu H, Johnson BE, McCloud TC. State of the art: Response assessment in lung cancer in the era of genomic medicine. *Radiology* 2014;271:6-27. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24661292>.

908. Howell DD, James JL, Hartsell WF, et al. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone

metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14. *Cancer* 2013;119:888-896. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23165743>.

909. Griffioen GH, Toguri D, Dahele M, et al. Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. *Lung Cancer* 2013;82:95-102. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23973202>.

910. Ashworth A, Rodrigues G, Boldt G, Palma D. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. *Lung Cancer* 2013;82:197-203. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24051084>.

911. Collen C, Christian N, Schallier D, et al. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. *Ann Oncol* 2014;25:1954-1959. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25114022>.

912. Tree AC, Khoo VS, Eeles RA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013;14:e28-37. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23276369>.

913. Kelly P, Balter PA, Rebuena N, et al. Stereotactic body radiation therapy for patients with lung cancer previously treated with thoracic radiation. *Int J Radiat Oncol Biol Phys* 2010;78:1387-1393. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20381271>.

914. Meijneke TR, Petit SF, Wentzler D, et al. Reirradiation and stereotactic radiotherapy for tumors in the lung: dose summation and toxicity. *Radiother Oncol* 2013;107:423-427. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23647748>.

915. Peulen H, Karlsson K, Lindberg K, et al. Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy. *Radiother Oncol* 2011;101:260-266. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22056534>.

916. Reingold M, Wu AJ, McLane A, et al. Toxicity and outcomes of thoracic re-irradiation using stereotactic body radiation therapy (SBRT). *Radiat Oncol* 2013;8:99. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23617949>.

917. Henry D, Vadhan-Raj S, Hirsh V, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. *Support Care Cancer* 2014;22:679-687. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24162260>.

918. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* 2011;29:1125-1132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21343556>.

919. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. *Cancer* 2004;100:2613-2621. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15197804>.

920. Henry DH, von Moos R, Hungria V, et al. Delaying skeletal-related events in a randomized phase III study of denosumab versus zoledronic acid in patients with advanced cancer [abstract]. *J Clin Oncol* 2010;28 (Suppl 15):Abstract 9133. Available at: [https://meeting.ascopubs.org/cgi/content/abstract/28/15\\_suppl/9133](https://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/9133).

921. Scagliotti GV, Hirsh V, Siena S, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. *J Thorac Oncol* 2012;7:1823-1829. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23154554>.

922. Casas A, Llombart A, Martin M. Denosumab for the treatment of bone metastases in advanced breast cancer. *Breast* 2013;22:585-592. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23759273>.

923. Ibrahim A, Scher N, Williams G, et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. *Clin Cancer Res* 2003;9:2394-2399. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12855610>.

924. Sakuma Y, Matsukuma S, Yoshihara M, et al. Distinctive evaluation of nonmucinous and mucinous subtypes of bronchioloalveolar carcinomas in EGFR and K-ras gene-mutation analyses for Japanese lung adenocarcinomas: confirmation of the correlations with histologic subtypes and gene mutations. *Am J Clin Pathol* 2007;128:100-108. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17580276>.

925. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol* 2011;12:1004-1012. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21933749>.

926. Drilon A, Rekhman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol* 2016;17:1653-1660. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27825636>.

927. Lee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. *Ann Oncol* 2017;28:292-297. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27803005>.

928. Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: Results from a phase II basket trial. *J Clin Oncol* 2017;35:Abstract 8510. Available at: [https://abstracts.asco.org/199/AbstView\\_199\\_193079.html](https://abstracts.asco.org/199/AbstView_199_193079.html).

929. Platt A, Morten J, Ji Q, et al. A retrospective analysis of RET translocation, gene copy number gain and expression in NSCLC patients treated with vandetanib in four randomized Phase III studies. *BMC Cancer* 2015;15:171. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25881079>.

930. Lee S-H, Lee J-K, Ahn M-J, et al. A phase II study of vandetanib in patients with non-small cell lung cancer harboring RET rearrangement [abstract]. J Clin Oncol 2016;34:Abstract 9013. Available at: <https://meetinglibrary.asco.org/content/166941-176>.

931. Falchook GS, Ordonez NG, Bastida CC, et al. Effect of the RET Inhibitor Vandetanib in a Patient With RET Fusion-Positive Metastatic Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:e141-144. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25366691>.

932. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med 2015;373:726-736. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26287849>.

933. Drilon AE, Sima CS, Somwar R, et al. Phase II study of cabozantinib for patients with advanced RET-rearranged lung cancers [abstract]. J Clin Oncol 2015;33:Abstract 8007. Available at: <https://meetinglibrary.asco.org/content/147349-156>.

934. Robinson SD, O'Shaughnessy JA, Cowey CL, Konduri K. BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib. Lung Cancer 2014;85:326-330. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24888229>.

935. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-538. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22452896>.

936. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-1500. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15118125>.

937. Peters S, Michielin O, Zimmermann S. Dramatic response induced by vemurafenib in a BRAF V600E-mutated lung adenocarcinoma. J Clin

Oncol 2013;31:e341-344. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23733758>.

938. Planchard D, Mazieres J, Riely GJ, et al. Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation-positive non-small cell lung cancer (NSCLC) patients [abstract]. J Clin Oncol 2013;31(Suppl 15):Abstract 8009. Available at: [https://meeting.ascopubs.org/cqi/content/abstract/31/15\\_suppl/8009](https://meeting.ascopubs.org/cqi/content/abstract/31/15_suppl/8009).

939. Wang SX, Zhang B, Wakelee HA, et al. Case Series of MET Exon 14 Skipping Mutation-positive Non-Small Cell Lung Cancers and Response to Crizotinib. International Journal of Radiation Oncology\*Biophysics 2017;98:239. Available at: <https://dx.doi.org/10.1016/j.ijrobp.2017.01.170>.

940. Heist RS, Shim HS, Gingipally S, et al. MET Exon 14 Skipping in Non-Small Cell Lung Cancer. Oncologist 2016;21:481-486. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27022036>.

941. Li BT, Shen R, Buonocore D, et al. Ado-Trastuzumab Emtansine for Patients With HER2-Mutant Lung Cancers: Results From a Phase II Basket Trial. J Clin Oncol 2018;36:2532-2537. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29989854>.

942. Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. N Engl J Med 2006;354:2619-2621. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16775247>.

943. Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013;31:1997-2003. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23610105>.

944. Lee SY, Kim MJ, Jin G, et al. Somatic mutations in epidermal growth factor receptor signaling pathway genes in non-small cell lung cancers. J Thorac Oncol 2010;5:1734-1740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20881644>.

945. Rekhtman N, Paik PK, Arcila ME, et al. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. *Clin Cancer Res* 2012;18:1167-1176. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22228640>.

946. Pilkington G, Boland A, Brown T, et al. A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer. *Thorax* 2015;70:359-367. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25661113>.

947. Sandler A, Yi J, Dahlberg S, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol* 2010;5:1416-1423. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20686429>.

948. Socinski MA, Langer CJ, Huang JE, et al. Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. *J Clin Oncol* 2009;27:5255-5261. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19738122>.

949. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. *Lancet* 2011;378:1079-1088. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21831418>.

950. Santos FN, de Castria TB, Cruz MR, Riera R. Chemotherapy for advanced non-small cell lung cancer in the elderly population. *Cochrane Database Syst Rev* 2015;10:CD010463. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26482542>.

951. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366:2455-2465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22658128>.

952. Heist RS, Sequist LV, Engelman JA. Genetic changes in squamous cell lung cancer: a review. *J Thorac Oncol* 2012;7:924-933. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22722794>.

953. Smit E, Moro-Sibilot D, Carpeno Jde C, et al. Cisplatin and carboplatin-based chemotherapy in the first-line treatment of non-small cell lung cancer: Analysis from the European FRAME study. *Lung Cancer* 2016;92:35-40. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26775594>.

954. Kubota K, Kawahara M, Ogawara M, et al. Vinorelbine plus gemcitabine followed by docetaxel versus carboplatin plus paclitaxel in patients with advanced non-small-cell lung cancer: a randomised, open-label, phase III study. *Lancet Oncol* 2008;9:1135-1142. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19013107>.

955. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184-2191. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15169807>.

956. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. *J Clin Oncol* 2009;27:1227-1234. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19188680>.

957. Mezger J, von Pawel J, Reck M. Bevacizumab (Bv) single-agent maintenance following Bv-based chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): Results from an exploratory analysis of the AVAIL study [abstract]. *J Clin Oncol* 2009;27 (Suppl 15):Abstract e19001. Available at: <https://meeting.ascopubs.org/cgi/content/abstract/27/15S/e19001>.

958. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. *J*

Thorac Oncol 2011;6:64-70. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21119545>.

959. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004;22:330-353. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/14691125>.

960. Soon YY, Stockler MR, Askie LM, Boyer MJ. Duration of chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized trials. J Clin Oncol 2009;27:3277-3283. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19470938>.

961. Coate LE, Shepherd FA. Maintenance therapy in advanced non-small cell lung cancer: evolution, tolerability and outcomes. Ther Adv Med Oncol 2011;3:139-157. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21904577>.

962. Riely GJ, Kris MG, Zhao B, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. Clin Cancer Res 2007;13:5150-5155. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17785570>.

963. Kuriyama Y, Kim YH, Nagai H, et al. Disease flare after discontinuation of crizotinib in anaplastic lymphoma kinase-positive lung cancer. Case Rep Oncol 2013;6:430-433. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24019783>.

964. Park K, Yu CJ, Kim SW, et al. First-Line Erlotinib Therapy Until and Beyond Response Evaluation Criteria in Solid Tumors Progression in Asian Patients With Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer: The ASPIRATION Study. JAMA Oncol 2016;2:305-312. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/26720423>.

965. Becker K, Xu Y. Management of tyrosine kinase inhibitor resistance in lung cancer with EGFR mutation. World J Clin Oncol 2014;5:560-567. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25302160>.

966. Ou SH. Second-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs): a better mousetrap? A review of the clinical evidence. Crit Rev Oncol Hematol 2012;83:407-421. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/22257651>.

967. Nguyen KS, Kobayashi S, Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer 2009;10:281-289. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19632948>.

968. Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene 2009;28 Suppl 1:S24-31. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/19680293>.

969. Chaft JE, Oxnard GR, Sima CS, et al. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. Clin Cancer Res 2011;17:6298-6303. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21856766>.

970. Conforti F, Catania C, Toffalorio F, et al. EGFR tyrosine kinase inhibitors beyond focal progression obtain a prolonged disease control in patients with advanced adenocarcinoma of the lung. Lung Cancer 2013;81:440-444. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23810573>.

971. Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol 2013;31:3335-3341. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23816963>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

972. Hirsh V, Cadranel J, Cong XJ, et al. Symptom and quality of life benefit of afatinib in advanced non-small-cell lung cancer patients previously treated with erlotinib or gefitinib: results of a randomized phase IIb/III trial (LUX-Lung 1). *J Thorac Oncol* 2013;8:229-237. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23328549>.

973. Meoni G, Cecere FL, Lucherini E, Di Costanzo F. Medical treatment of advanced non-small cell lung cancer in elderly patients: a review of the role of chemotherapy and targeted agents. *J Geriatr Oncol* 2013;4:282-290. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24070465>.

974. Weiss JM, Stinchcombe TE. Second-Line Therapy for Advanced NSCLC. *Oncologist* 2013;18:947-953. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23918070>.

975. van Putten JW, Baas P, Codrington H, et al. Activity of single-agent gemcitabine as second-line treatment after previous chemotherapy or radiotherapy in advanced non-small-cell lung cancer. *Lung Cancer* 2001;33:289-298. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11551424>.

976. Crino L, Mosconi AM, Scagliotti G, et al. Gemcitabine as second-line treatment for advanced non-small-cell lung cancer: A phase II trial. *J Clin Oncol* 1999;17:2081-2085. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10561261>.

977. Anderson H, Hopwood P, Stephens RJ, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer--a randomized trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. *Non-Small Cell Lung Cancer. Br J Cancer* 2000;83:447-453. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10945489>.

978. Sculier JP, Lafitte JJ, Berghmans T, et al. A phase II trial testing gemcitabine as second-line chemotherapy for non small cell lung cancer. The European Lung Cancer Working Party. 101473.1044@compuserve.com. *Lung Cancer* 2000;29:67-73. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10880849>.

979. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354-2362. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10856094>.

980. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095-2103. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10811675>.

981. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589-1597. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15117980>.

982. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123-132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16014882>.

983. Ades F, Yamaguchi N. WHO, RECIST, and immune-related response criteria: is it time to revisit pembrolizumab results? *Ecancermedicallscience* 2015;9:604. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26715941>.

984. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009;15:7412-7420. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19934295>.

985. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov* 2014;4:1036-1045. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25074459>.



# NCCN Guidelines Version 7.2019

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

986. Sacher AG, Janne PA, Oxnard GR. Management of acquired resistance to epidermal growth factor receptor kinase inhibitors in patients with advanced non-small cell lung cancer. *Cancer* 2014;120:2289-2298. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24752335>.

987. Sabari JK, Montecalvo J, Chen R, et al. PD-L1 expression and response to immunotherapy in patients with MET exon 14-altered non-small cell lung cancers (NSCLC) [abstract]. *J Clin Oncol* 2017;35:Abstract 8512. Available at:

988. Demarinis F, Paul S, Hanna N, et al. Survival update for the phase III study of pemetrexed vs docetaxel in non-small cell lung cancer (NSCLC) [abstract]. *J Clin Oncol* 2006;24 (Suppl 18):Abstract 7133. Available at: [https://meeting.ascopubs.org/cgi/content/abstract/24/18\\_suppl/7133](https://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7133).

989. Garassino MC, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol* 2013;14:981-988. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23883922>.

990. Kawaguchi T, Ando M, Asami K, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol* 2014;32:1902-1908. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24841974>.

991. Eccles BK, Geldart TR, Laurence VM, et al. Experience of first- and subsequent-line systemic therapy in the treatment of non-small cell lung cancer. *Ther Adv Med Oncol* 2011;3:163-170. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21904578>.

992. Mok TSK, Kim SW, Wu YL, et al. Gefitinib Plus Chemotherapy Versus Chemotherapy in Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer Resistant to First-Line Gefitinib (IMPRESS): Overall Survival and Biomarker Analyses. *J Clin Oncol* 2017;35:4027-4034. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28968167>.

993. Pop O, Pirvu A, Toffart AC, Moro-Sibilot D. Disease flare after treatment discontinuation in a patient with EML4-ALK lung cancer and acquired resistance to crizotinib. *J Thorac Oncol* 2012;7:e1-2. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22797152>.

994. Langer CJ, Mok T, Postmus PE. Targeted agents in the third-/fourth-line treatment of patients with advanced (stage III/IV) non-small cell lung cancer (NSCLC). *Cancer Treat Rev* 2013;39:252-260. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22703830>.

995. Noble J, Ellis PM, Mackay JA, et al. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a systematic review and practice guideline. *J Thorac Oncol* 2006;1:1042-1058. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17409993>.