NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 1.2022 — December 7, 2021

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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

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

Malcolm DeCamp, MD ¶
University of Wisconsin Carbone Cancer Center

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

Jonathan Dowell, MD †
UT Southwestern Simmons Comprehensive Cancer Center

Scott Gettinger, MD † Þ
Yale Cancer Center/Smilow Cancer Hospital

Travis E. Grotz, MD ¶
Mayo Clinic Cancer Center

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

Aparna Hegde, MD †
O'Neal Comprehensive Cancer Center at UAB

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

Michael Lanuti, MD ¶
Massachusetts General Hospital Cancer Center

Jules Lin, MD ¶
University of Michigan Rogel Cancer Center

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

Christine M. Lovly, MD, PhD †
Vanderbilt-Ingram Cancer Center

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

Erminia Massarelli, MD, PhD, MS †
City of Hope National Medical Center

Daniel Morgensztern, MD †
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Thomas Ng, MD ¶
The University of Tennessee Health Science Center

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

Jose M. Pacheco, MD †
University of Colorado Cancer Center

Continue

NCCN Guidelines Panel Disclosures

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

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

Jonathan Riess, MD ‡
UC Davis Comprehensive Cancer Center

Steven E. Schild, MD §
Mayo Clinic Cancer Center

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

Aditi P. Singh, MD †
Abramson Cancer Center at the University of Pennsylvania

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

Alda Tam, MD ф
The University of Texas MD Anderson Cancer Center

Tawee Tanvetyanon, MD, MPH †
Moffitt Cancer Center

Jane Yanagawa, MD ¶
UCLA Jonsson Comprehensive Cancer Center

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

Edwin Yau, MD, PhD †
Roswell Park Comprehensive Cancer Center

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

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

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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 1.2022 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2021 include:

DIAG-A 2 of 3
- Bullet 1, sub-bullet 2: Diagnostic tools that provide important additional strategies for biopsy include
  - Diamond 4 added: Robotic bronchoscopy

DIAG-A 3 of 3
- Sub-bullet 1: The least invasive biopsy with the highest yield is preferred as the first diagnostic study
  - Diamond 5 added: Rapid on-site evaluation (ROSE), when available, helps to increase diagnostic and molecular yield

NSCL-4
- Adjuvant Treatment
  - The following clarification added to osimertinib: *EGFR exon 19* deletion or *L858R*
- Stage IIIA (T1–2, N2; T3, N1); Stage IIIB (T3, N2)
  - Margins negative: Sequential chemotherapy
    - ◊ RT (N2 only) removed and replaced with *consider RT*

NSCL-4A
- Footnote w modified: For patients with *EGFR* ~~mutation-positive~~ *exon 19 deletion or L858R* who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy. (also applies to NSCL-6, NSCL-7)

NSCL-5
- Pretreatment Evaluation
  - Bullet 5 modified: MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine, subclavian vessels, *or brachial plexus*

NSCL-6
- Surgical reevaluation including chest CT with or without contrast ± PET/CT
  - Footnote z added: MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine, subclavian vessels, or brachial plexus.

NSCL-7
- Concurrent chemoradiation or chemotherapy, followed by surgery
  - Treatment modified for margins positive: Reresection *and/or RT boost*
  - Footnote removed: Consider RT boost if chemoradiation is given as initial treatment.

NSCL-9
- T1–2, T3 (other than invasive), N2 nodes positive, M0
  - Induction chemotherapy ± RT
    - ◊ No apparent progression
      - – Treatment modified: Surgery ~~± RT (if not given)~~ *Consider RT*
    - ◊ Progression
      - – Treatment modified: RT (if ~~not given~~*feasible*) ± chemotherapy

NSCL-10
- Footnote bb modified: Multiple studies suggest that next-generation sequencing (NGS) testing with broad gene coverage may allow for unambiguous determination of clonal relatedness among separate lung nodules.

NSCL-13
- Pretreatment Evaluation
  - Molecular testing changed to Biomarker testing (also applies to NSCL-14)

Continued

Updates in Version 1.2022 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2021 include:

NSCL-18
- **Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy *or plasma testing* if appropriate)**
- **Footnote nn modified: 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 defined as molecular testing that identifies all biomarkers identified in NSCL-19 in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable.***

NSCL-19
- **Testing Results**
  - **Category added for *EGFR S768I, L861Q, and/or G719X mutation positive***
  - **Language for PD-L1 categories changed from molecular markers to molecular biomarkers**

NSCL-20
- **Footnote tt modified: If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when ~~combining checkpoint inhibitors with~~ *using* osimertinib *in combination with or following checkpoint inhibitors*.**

NSCL-21
- **Footnote ww modified: Consider a biopsy at time of progression to rule out SCLC transformation *and evaluate mechanisms of resistance*. (also applies to NSCL-22)**
- **Footnote yy modified: 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 *exon 19 deletion or L858R*, ALK+ NSCLC. (also applies to NSCL-22, NSCL-27, NSCL-28)**

NSCL-22
- ***T790M* testing: category 1 added**
- **Subsequent therapy specifically noted for *T790M-***
- **Footnote zz modified: Plasma *or tissue*-based testing *via broad molecular profiling* should be considered at progression, ~~on EGFR TKIs~~ for the T790M mutation *and other genomic resistance mechanisms*. 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.**

NSCL-23
- **New page added with treatment recommendations for *EGFR S768I, L861Q,* and/or *G719X***

NSCL-24
- **Footnotes ccc and eee modified: high-risk added (also applies to NSCL-25, NSCL-37, NSCL-J)**

NSCL-27
- **Lorlatinib added for *ALK* G1202R**
- **Limited metastases: Therapy for multiple lesions added as an option (also applies to NSCL-28, NSCL-30)**
- **Footnote zz added: Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. 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. (also applies to NSCL-28, NSCL-30)**

NSCL-28
- **Subsequent Therapy: Lorlatinib added as a treatment option**

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Discussion

Updates in Version 1.2022 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2021 include:

NSCL-30
- New page added for more detailed treatment options after progression on entrectinib, crizotinib, or ceritinib

NSCL-31
- First-line Therapy; Useful in Certain Circumstances
  - Dabrafenib added as a treatment option
  - Footnote hhh modified: Single-agent vemurafenib *or dabrafenib are* ~~is a~~ treatment options if the combination of dabrafenib + trametinib is not tolerated.
- Subsequent Therapy
  - A link added to additional subsequent therapy options (NSCL-K 4 of 5) (also applies to NSCL-32, NSCL-33, NSCL-34)

NSCL-34
- First-line Therapy; Useful in Certain Circumstances
  - Vandetanib removed as a treatment option.

NSCL-35
- Footnote jjj added: For patients who require an urgent start to therapy but molecular testing is pending, consider holding immunotherapy for one cycle, unless confirmed that no driver mutations are present. (also applies to NSCL-36)

NSCL-A 4 of 4
- Immunohistochemistry
  - Bullet 1; sub-bullet 1 modified: NCAM (CD56), chromogranin, ~~and~~ synaptophysin, *and INSM1* are used to identify neuroendocrine tumors in cases in which morphologic suspicion of neuroendocrine differentiation exists.

NSCL-B 2 of 4
- Margins and Nodal Assessment
  - Bullet 5 modified: Patients with pathologic stage II or greater, *or high-risk factors,* should be referred to medical oncology for evaluation.

NSCL-B 3 of 4
- The Role of Surgery in Patients with Stage IIIA NSCLC
  - Bullet 5 modified: Neoadjuvant chemoradiotherapy is used in ~~50%~~*one-third* of the NCCN Member Institutions, while neoadjuvant chemotherapy is used in the other ~~50%~~*two-thirds*.
- Data from the updated questionnaire (2021) included regarding the approach to patients with N2 disease at the NCCN Member Institutions
  - All NCCN institutions treat select N2 patients with multimodality therapy that includes surgery.
  - The majority of NCCN institutions prefer EBUS for initial mediastinal staging, reserving mediastinoscopy for possible restaging.
  - The majority of institutions do not pathologically restage mediastinal lymph nodes after induction therapy and prior to surgery.
  - All NCCN institutions consider surgery for single-station non-bulky N2 disease.
  - Approximately half of the institutions consider surgery for single-station bulky disease, 39% for multi-station non-bulky disease, and 21% for multi-station bulky disease.
  - Two-thirds of institutions prefer induction chemotherapy; one-third prefer chemoradiation.
  - The majority require at least stable disease after induction, but do not require radiologic or pathologic response prior to surgery.
  - Roughly a half would consider pneumonectomy after induction chemotherapy, but less than a quarter would consider pneumonectomy after chemoradiation.
  - Approximately three-fourths would give adjuvant RT for positive residual N2 disease, but only approximately one-fourth would give RT for N2 pathologic complete response.

Continued

Updates in Version 1.2022 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2021 include:

NSCL-C 1 of 11
- General Principles
  - Bullet 2 and Bullet 4: definitive changed to definitive/consolidative

NSCL-C 3 of 11
- Early-Stage NSCLC
  - Bullet 1:
    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, and higher than conventionally fractionated radiotherapy, although not proven equivalent to lobectomy.
    replaced with
    SABR (also known as SBRT) has achieved good primary tumor control rates and overall survival, higher than conventionally fractionated radiotherapy. Although SABR is not proven equivalent to lobectomy, some prospective series have demonstrated similar overall and cancer-specific survival.
  - Bullet 5 added: Close follow-up and salvage therapy for isolated local and/or locoregional recurrence after SABR have been shown to improve overall survival in a large retrospective study.

NSCL-C 4 of 11
- Conventionally Fractionated RT for Locally Advanced NSCLC
  - Bullet 2; sub-bullet 1; last sentence modified: A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens, ~~and individualized accelerated RT dose intensification is now being analyzed in a randomized trial (RTOG 1106)~~ *and RTOG 1106 found that PET-based individualized accelerated RT dose intensification potentially improved local control but not overall survival*.

NSCL-C 5 of 11
- Advanced/Metastatic NSCLC (Stage IV)
  - Bullet 2: definitive changed to definitive/consolidative
  - Bullet 6 added: A pooled analysis of two randomized trials indicated that adding radiotherapy to a certain immune checkpoint inhibitor (anti-PD-1) significantly increased responses and clinical outcomes in patients with metastatic non-small cell lung cancer. Larger phase III randomized studies are ongoing.

NSCL-C 7 of 11
- Table 2. Commonly Used Doses for SABR
  - Example Indications
    - ◊ Definition of small tumors (<2 cm) removed
    - ◊ Distance from chest wall removed

NSCL-C 8 of 11
- Table 4; footnote ** added: This regimen includes one dose per week, as the phase 3 study included day 1 & 8 treatments.
- Table 5; reference removed: Al-Halabi H, et al. A contralateral esophagus-sparing technique to limit severe esophagitis associated with concurrent high-dose radiation and chemotherapy in patients with thoracic malignancies. Int J Radiat Oncol Biol Phys 2015;92:803-810.
- Table 5; reference added: Kamran SC, et al. JAMA Oncol 2021;7:910-914.

Continued

Updates in Version 1.2022 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2021 include:

NSCL-C 9 of 11 through NSCL-C 11 of 11
- Reference 3: Sejpal S, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for non-small cell lung cancer. Cancer 2011;117:3004-3013.
  replaced with
  Gjyshi O, et al. Toxicity and survival after intensity-modulated proton therapy versus passive scattering proton therapy for NSCLC. J Thorac Oncol 2021;16:269-277.
- Reference 30 added: Chang JY, et al. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. Lancet Oncol 2021;22:1448-1457.
- Reference 34 added: Brooks ED, et al. Association of long-term outcomes and survival with multidisciplinary salvage treatment for local and regional recurrence after stereotactic ablative radiotherapy for early-stage lung cancer. JAMA Netw Open 2018;1:e181390.
- Reference 86: Schild SE, et al. Toxicity related to radiotherapy dose and targeting strategy: a pooled analysis of cooperative group trials of combined modality therapy for locally advanced non-small cell lung cancer. J Thorac Oncol 2019;14:298-303.
  replaced with
  Schild SE, et al. Exploring radiotherapy targeting strategy and dose: a pooled analysis of cooperative group trials of combined modality therapy for stage III NSCLC. J Thorac Oncol 2018;13:1171-1182.
- Reference 88 added: Kong F-M S, et al. NRG-RTOG 1106/ACRIN 6697: A phase IIR trial of standard versus adaptive (mid-treatment PET-based) chemoradiotherapy for stage III NSCLC—Results and comparison to NRG-RTOG 0617 (non-personalized RT dose escalation). J Clin Oncol 2021;39:8548-8548.
- Reference 103 added: Theelen WSME, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a polled analysis of two randomised trials. The Lancet 2021;9:467-475.

NSCL-D
- Evaluation
  - Bullet 3 modified: If an interventional radiologist or center is uncertain about the feasibility or safety of IGTA *or the use of IGTA for radiation failure,* consider obtaining an additional interventional radiology opinion from a high-volume specialized center.
- Ablation for NSCLC
  - Bullet 3 added: Like surgery, pneumothorax may occur after IGTA, particularly if multiple lesions are treated in a single session. Pneumothorax has been reported in 18.7%–45.7% of IGTA cases. Self-limited pneumothorax, not requiring chest tube placement, is an expected event and not considered a complication unless escalation of care is required. In 20.7% of IGTA cases, chest tube insertion may be required.
  - Reference 10 added: Genshaft SJ, Suh RD, Abtin F, et al. Society of Interventional Radiology Quality Improvement Standards on Percutaneous Ablation of Non-Small Cell Lung Cancer and Metastatic Disease to the Lungs. J Vasc Interv Radiol 2021;32:1242.e1-1242.e10.

NSCL-E 1 of 2
- Previous Adjuvant Chemotherapy or Ineligible for Platinum-Based Chemotherapy
  - Osimertinib for patients with completely resected ~~stage IIB-IIIA or high risk~~ stage IB-IIIA EGFR ~~mutation-positive~~ *(exon 19 deletion, L858R)* NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.

NSCL-F 1 of 2
- Consolidation Immunotherapy for Patients with Unresectable Stage II/III NSCLC, PS 0–1, and No Disease Progression After ~~2 or More Cycles of~~ Definitive Concurrent Chemoradiation
- Footnote § modified: If using durvalumab, an additional 2 cycles of chemotherapy is not recommended~~, if patients have not received full-dose chemotherapy concurrently with RT~~.

Continued

Updates in Version 1.2022 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2021 include:

NSCL-F 2 of 2
- Reference 6: 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.
  replaced with
  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.
- Reference removed: Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342-2550.
- Reference 8 added: Faivre-Finn C, Vicente D, Kurata T, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. J Thorac Oncol 2021;16:860-867.

NSCL-H 1 of 7
- Bullet 3: *Tissue* Specimen Acquisition and Management
  - Sub-bullet 2 modified: A major limitation in obtaining *tissue* molecular testing results for NSCLC occurs when minimally invasive techniques are used to obtain samples.
  - Sub-bullet 3 modified: 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. *Peripheral blood (plasma circulating tumor DNA) can be a surrogate sample* (NSCL-H 7 of 7).

NSCL-H 2 of 7
- Testing Methodologies
  - New entry under diamond 2: Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-19 in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable.
  - Diamond 5 added: Any method that interrogates sequences other than a subset of highly specific alterations (eg, NGS, Sanger) has the potential to identify variants of uncertain significance (VUS). Any variant classified as a VUS, even if in a gene in which other variants are clinically actionable, should not be considered as a basis for targeted therapy selection.
  - Diamond removed: IHC is specifically utilized for some specific analytes, and can be a useful surrogate or screening assay for others.

NSCL-H 3 of 7
- Bullet 1: Molecular Targets for Analysis
  - Sub-bullet 2: *EGFR* Gene Mutations
    - ◊ Diamond 2 updated: Molecular testing for EGFR mutations ~~to~~ *should* be performed *when adjuvant TKI therapy is a consideration for NSCLC stage IB-IIIA. While the testing process may be technically easier on a resected specimen, initial diagnostic biopsy specimens are also acceptable for testing for this indication.* ~~on diagnostic biopsy or surgical resection sample to ensure the EGFR mutation results are available for adjuvant treatment decisions for patients with stage IIB-IIIA or high risk stage IB-IIA NSCLC~~.
    - ◊ Diamond 3 modified: Many of the less commonly observed alterations in EGFR, which cumulatively account for ~10% of EGFR-mutation positive NSCLC (ie, exon 19 insertions, p.L861Q, p.G719X, p.S768I) are also associated with responsiveness to *certain* EGFR TKIs ~~therapy,~~ *such as osimertinib and afatinib, and should be considered on a mutation-specific basis, when possible* ~~although the number of studied patients is lower~~.

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Updates in Version 1.2022 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2021 include:

NSCL-H 3 of 7

- Bullet 1: Molecular Targets for Analysis
  - ▸ Sub-bullet 2: *EGFR* Gene Mutations
    - ◊ Diamond 4; entry modified: If *EGFR p.T790M* is ~~observed~~ *identified* in the absence of prior EGFR TKI therapy, genetic counseling and possible germline genetic testing are warranted. *Identification of germline EGFR p.T790M confers a high risk for lung cancer regardless of smoking status.*
    - ◊ Diamond 5 modified: *EGFR exon 20 (EGFRex20)* mutations *(other than EGFR p.T790M)* are a heterogeneous group, some of which are responsive to targeted therapy and that require detailed knowledge of the specific alteration.
      - – Sub-bullet 1 modified: These are generally associated with lack of response to *first-, second-, and third-generation* EGFR TKI therapy, with select exceptions: *p.A763_Y764insFQEA* is associated with sensitivity to TKI therapy *and p.A763_Y764insLQEA* may be associated with sensitivity *to first- and third-generation* TKI therapy.
      - – Sub-bullet 2 added: *EGFRex20* insertions/duplications are associated with responsiveness to specific targeted subsequent therapy agents. The most commonly represented *EGFRex20* insertions/duplications in the clinical studies have been insASV, insSVD, and insNPH, although a wide spectrum of other alterations were included. There is currently no evidence that the specific alteration type impacts the probability of responsiveness to this class of kinase inhibitor.
      - – Sub-bullet 3 modified: *Because some EGFRex20 mutations are or may be sensitive to first- and third-generation inhibitors,* ~~For this reason~~, the specific sequence of *EGFRex20* insertion mutations ~~is~~*remains* important.~~, and~~ Some assays will identify the presence of an *EGFRex20* insertion without specifying the sequence. ~~In this scenario~~, and additional testing to further clarify the *EGFRex20* insertion ~~is~~*may be* indicated *for therapy selection*.
      - – Sub-bullet 4 added: Targeted PCR-based approaches for detection of EGFR variants may under-detect *EGFRex20* insertion events; therefore, NGS-based strategies are preferred.
    - ◊ Diamond removed, as content added to NSCL-H 2 of 7: 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.

NSCL-H 5 of 7

- Bullet 1: Molecular Targets for Analysis
  - ▸ Sub-bullet 1: *KRAS* point mutations
    - ◊ Diamond 5 added: The presence of *KRAS* p.G12C is associated with responsiveness to an oral KRAS G12C inhibitor used for subsequent therapy, which was designed specifically for this mutation. Responsiveness to this class of inhibitor has not been prospectively evaluated with mutations other than *KRAS* p.G12C.
    - ◊ Diamond 6 added: Testing methodologies: NGS, real-time PCR, and Sanger sequencing (ideally paired with tumor enrichment) are the most commonly deployed methodologies for examining *KRAS* mutation status.
  - ▸ Sub-bullet 2: *MET exon 14* skipping variants
    - ◊ Diamond 3 modified: Testing Methodologies: NGS-based testing is the primary method for detection of *METex14* skipping events; RNA-based NGS *may have improved* ~~demonstrating improvement in~~ detection.

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Updates in Version 1.2022 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2021 include:

NSCL-H 6 of 7

- Bullet 1: Molecular Targets for Analysis
  - ▸ Sub-bullet 1: *NTRK1/2/3* gene fusions
    - ◊ Diamond 1 added: The presence of *NTRK1/2/3* gene fusions is associated with responsiveness to oral TRK inhibitors.
- Bullet 3: Testing in the Setting of Progression on Targeted Therapy
  - ▸ Diamond 3 added: Broad genomic profiling may be the most informative approach to examining potential mechanisms of resistance, which may require more than one instance of such profiling over the course of an individual patient's therapy.
- Bullet 4 added: Testing in the setting of a limited number of pulmonary nodules can aid in distinguishing separate primary lung carcinoma versus intrapulmonary metastatic disease.
  - ▸ Sub-bullet 1 added: Studies to explore tumor relatedness by testing tissue from separately sampled lesions using a broad gene coverage NGS approach suggest it may be superior to histopathologic assessment.
  - ▸ Sub-bullet 2 added: Tumor pairs exhibiting entirely non-overlapping, unique mutations are considered clonally unrelated separate primary lung cancers, even if histologically similar. Tumors that share multiple (≥2) mutations are more likely to be clonally related; however, this may depend on the extent to which any individual mutation is extremely common in NSCLC and whether identified alterations are driver or passenger alterations. Results in which no mutations or only one mutation are identified are not informative for this evaluation.

NSCL-H 7 of 7

- PD-L1
  - ▸ Diamond one modified: Various antibody clones have been developed for IHC analysis of PD-L1 expression, and while several ~~show relative equivalence,~~ *are comparable regarding intensity and proportion of cells stained*, some ~~do~~*are* not.
  - ▸ Diamond one; entry removed: The FDA-approved companion diagnostic for PD-L1 guides utilization of pembrolizumab in patients with NSCLC and is based on the tumor proportion score (TPS). TPS is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity.
  - ▸ Diamond one; entry one modified: The definition of positive and negative testing is dependent on the individual antibody, *clone,* and platform deployed, which may be unique to each checkpoint inhibitor therapy. The ~~potential for~~ *approval of* multiple different assays for PD-L1 has raised concern among both pathologists and oncologists.
  - ▸ Diamond one; entry two added: While some clones for PD-L1 IHC are FDA-approved for specific indications, use of multiple IHC tests is not necessary, provided any individual IHC test has been internally validated for comparability for categorical results against the FDA-approved clone.
- Plasma Cell-Free/Circulating Tumor DNA Testing
  - ▸ Sub-bullet 3 modified: Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to a 30% false-negative rate; *however, data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection*.
  - ▸ Sub-bullet 4 modified: *Published guidelines elaborating* 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.
  - ▸ Sub-bullet 6; Diamond 3 added: In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available, consider repeat biopsy and/or cell-free/circulating tumor DNA testing.

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Updates in Version 1.2022 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2021 include:

NSCL-I
- High-level *MET* amplification: Tepotinib added as an available targeted agent
- Footnote * added: The definition of high-level *MET* amplification is evolving and may differ according to the assay used for testing. For NGS-based results, a copy number greater than 10 is consistent with high-level *MET* amplification.
- Footnote ** added: For oncogenic or likely oncogenic *HER2* mutations, refer to definitions at oncokb.org.
- Reference 4 added: Le X, Paz-Ares LG, Van Meerbeeck, J, et al. Tepotinib in patients with advanced non-small cell lung cancer (NSCLC) with *MET* amplification (*MET*amp). J Clin Oncol 2021;39(suppl_15):Abstract 9021.
- Reference 6 updated: Li BT, Smit EF, Goto Y, et al; DESTINY-Lung01 Trial Investigators. Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer. N Engl J Med. 2021 Sep 18. Epub ahead of print.

NSCL-J 1 of 2
- Section added for *EGFR S768I, L861Q,* and/or *G719X*
- *BRAF* V600E Mutation Positive
  - Dabrafenib added
  - Vemurafenib added
- *RET* Rearrangement Positive
  - Vandetanib removed
- Footnotes a and b modified: Monitoring During Subsequent *or Maintenance Therapy;* and addition of *high-risk* to disease sites

NSCL-K 1 of 5
- Footnote c added: If first-line systemic therapy completed before treatment for an actionable mutation, and disease has progressed, see Subsequent Therapy NSCL-K 4 of 5. (also applies to NSCL-K 2 of 5)
- Footnote d modified: 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 (~~eg,~~*ie, EGFR exon 19 deletion or L858R, ALK* rearrangements~~, RET rearrangements~~), which would predict lack of benefit. (also applies to NSCL-K 2 of 5)

NSCL-K 3 of 5
- Squamous Cell Carcinoma
  - Switch maintenance with docetaxel removed

NSCL-K 4 of 5
- Subsequent Systemic Therapy Options
  - Other Recommended: Albumin-bound paclitaxel added
- Progression
  - PS 0-2: Albumin-bound paclitaxel added as a category 2B.
- Footnote removed: 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* exon 19 deletion or *L858R*, *ALK*+ NSCLC.

ST-3
- Footnote ** added: The staging of tumor size in the AJCC Cancer Staging Manual, 7th Edition is based on the total tumor size (invasive and lepidic/noninvasive); whereas, in the AJCC Cancer Staging Manual, 8th Edition, staging is based on invasive size only for non-mucinous adenocarcinoma. However, in mucinous adenocarcinoma, the total tumor size is used.

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) 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.
- **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

Incidental finding of nodule suspicious for lung cancer →

- **Multidisciplinary evaluation[a]**
- **Smoking cessation counseling**

→

RISK ASSESSMENT[b]

Patient factors
- **Age**
- **Smoking history**
- **Previous cancer history**
- **Family history**
- **Occupational exposures**
- **Other lung disease (chronic obstructive pulmonary disease [COPD], pulmonary fibrosis)**
- **Exposure to infectious agents (eg, endemic areas of fungal infections, tuberculosis) or risk factors or history suggestive of infection (eg, immune suppression, aspiration, infectious respiratory symptoms)**

Radiologic factors[c,d]
- **Size, shape, and density of the pulmonary nodule**
- **Associated parenchymal abnormalities (eg, scarring or suspicion of inflammatory changes)**
- **Fluorodeoxyglucose (FDG) avidity on PET/CT imaging**

→ **Solid nodules**
See Follow-up (DIAG-2)

→ **Subsolid nodules**
See Follow-up (DIAG-3)

Lung nodules in asymptomatic, high-risk patients detected during lung cancer screening with LDCT → **NCCN Guidelines for Lung Cancer Screening**

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[a] 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.

[b] 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.

[c] Principles of Diagnostic Evaluation (DIAG-A 1 of 3).

[d] The most important radiologic factor is change or stability compared with a previous imaging study.

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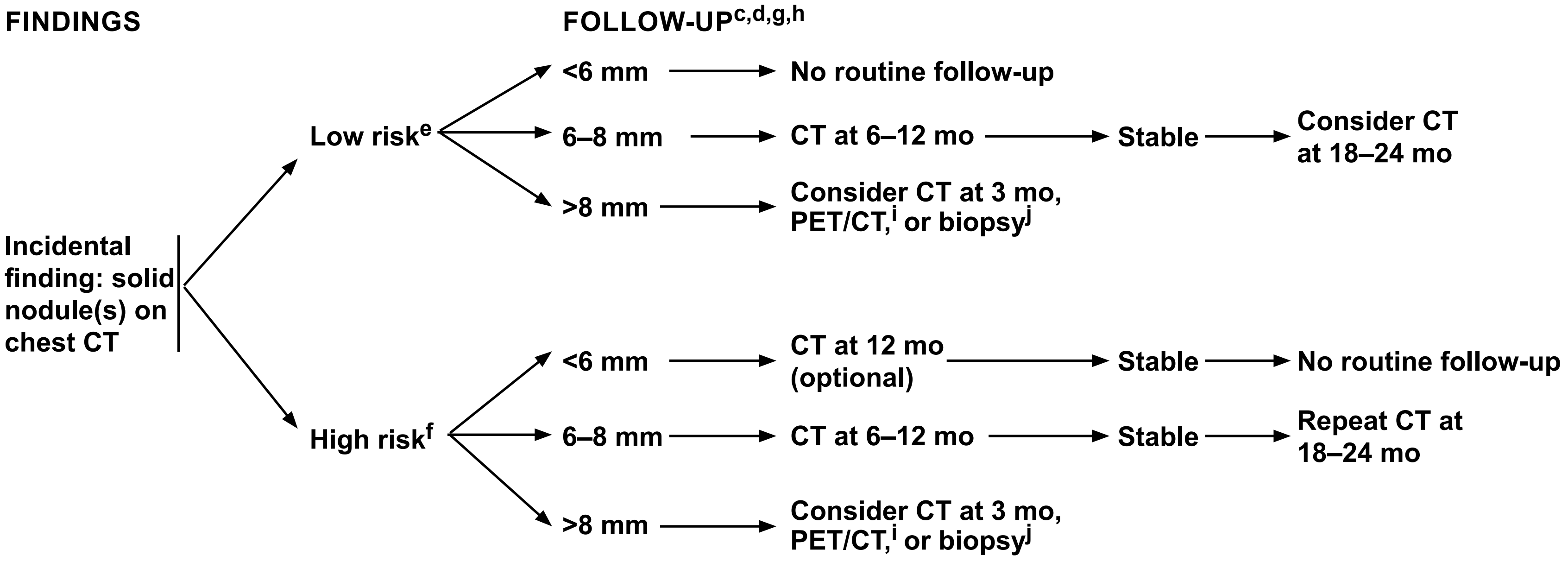

FINDINGS | **FOLLOW-UP**[c,d,g,h]

- **Incidental finding: solid nodule(s) on chest CT**
  - **Low risk**[e]
    - **<6 mm** → **No routine follow-up**
    - **6–8 mm** → **CT at 6–12 mo** → **Stable** → **Consider CT at 18–24 mo**
    - **>8 mm** → **Consider CT at 3 mo, PET/CT,**[i] **or biopsy**[j]
  - **High risk**[f]
    - **<6 mm** → **CT at 12 mo (optional)** → **Stable** → **No routine follow-up**
    - **6–8 mm** → **CT at 6–12 mo** → **Stable** → **Repeat CT at 18–24 mo**
    - **>8 mm** → **Consider CT at 3 mo, PET/CT,**[i] **or biopsy**[j]

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[c] Principles of Diagnostic Evaluation (DIAG-A 1 of 3).

[d] The most important radiologic factor is change or stability compared with a previous imaging study.

[e] Low risk = minimal or absent history of smoking or other known risk factors.

[f] 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.

[g] Non-solid (ground-glass) nodules may require longer follow-up to exclude indolent adenocarcinoma.

[h] 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.

[i] 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).

[j] If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)

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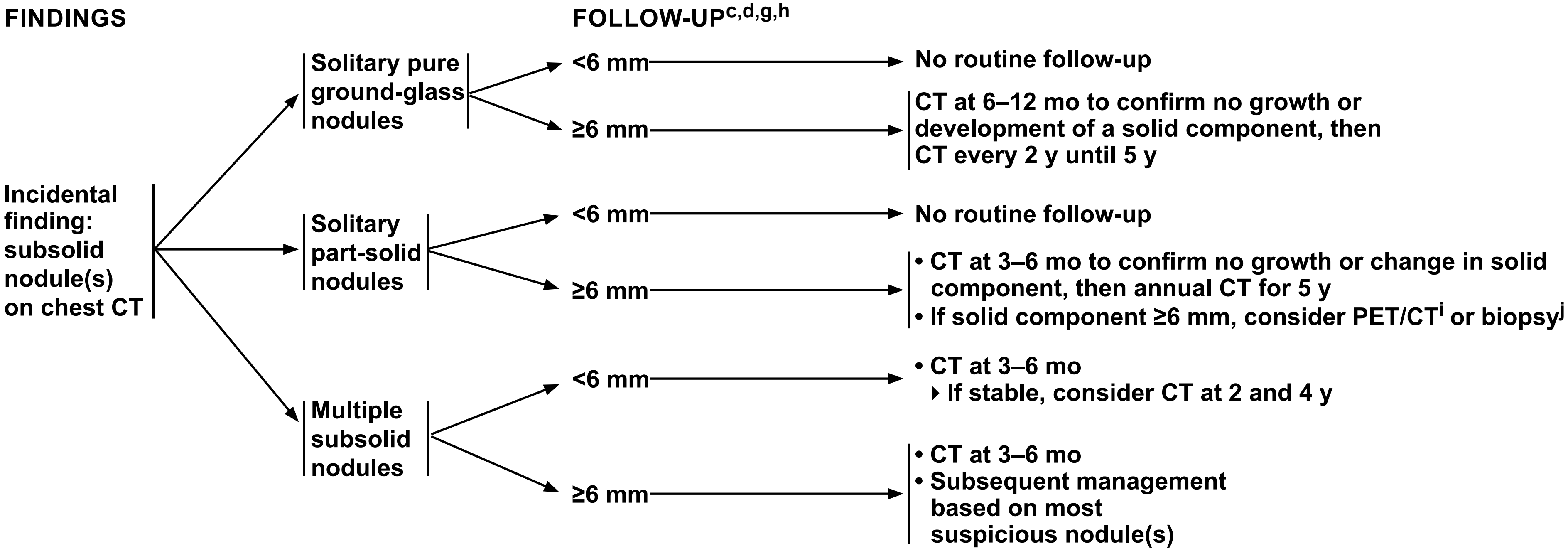

FINDINGS | **FOLLOW-UP**[c,d,g,h]

Incidental finding: subsolid nodule(s) on chest CT

- **Solitary pure ground-glass nodules**
  - **<6 mm** → **No routine follow-up**
  - **≥6 mm** → **CT at 6–12 mo to confirm no growth or development of a solid component, then CT every 2 y until 5 y**
- **Solitary part-solid nodules**
  - **<6 mm** → **No routine follow-up**
  - **≥6 mm** →
    - **CT at 3–6 mo to confirm no growth or change in solid component, then annual CT for 5 y**
    - **If solid component ≥6 mm, consider PET/CT[i] or biopsy[j]**
- **Multiple subsolid nodules**
  - **<6 mm** →
    - **CT at 3–6 mo**
      - **If stable, consider CT at 2 and 4 y**
  - **≥6 mm** →
    - **CT at 3–6 mo**
    - **Subsequent management based on most suspicious nodule(s)**

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[c] Principles of Diagnostic Evaluation (DIAG-A 1 of 3).

[d] The most important radiologic factor is change or stability compared with a previous imaging study.

[g] Non-solid (ground-glass) nodules may require longer follow-up to exclude indolent adenocarcinoma.

[h] 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.

[i] PET/CT performed skull base to knees or whole body. A positive PET result is defined as a 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 GGO), or low tumor avidity for FDG (eg, adenocarcinoma in situ [previously known as bronchoalveolar carcinoma], carcinoid tumor).

[j] If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)

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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.[1]**
  - **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.[1]**
- **Bronchoscopy should preferably be performed during the planned surgical resection, rather than as a separate procedure.**
  - **Bronchoscopy is required before surgical resection (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 (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.**

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[1] Patients require tissue confirmation of non-small cell lung cancer (NSCLC) before a lobectomy, bilobectomy, or pneumonectomy. If a preoperative or intraoperative tissue diagnosis appears risky or unreliable, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is recommended to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with anatomic resection without tissue confirmation.

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PRINCIPLES OF DIAGNOSTIC EVALUATION

- **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**
    - ◊ **Robotic bronchoscopy**
- **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/CT 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/CT imaging**
  - **Decisions about the optimal diagnostic steps for suspected stage I to III lung cancer should be made by thoracic radiologists, interventional radiologists, and 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.**

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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.**
  - ◊ **Rapid on-site evaluation (ROSE), when available, helps to increase diagnostic and molecular yield.**
  - ◊ **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 thoracoscopic 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.**

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PATHOLOGIC DIAGNOSIS OF NSCLC

NSCLC →

INITIAL EVALUATION

- Pathology review[a]
- H&P (include performance status + weight loss)[b]
- 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[c] NCCN Guidelines for Palliative Care
- For tools to aid in the optimal assessment and management of older adults, see the NCCN Guidelines for Older Adult Oncology

CLINICAL STAGE

Stage IA, peripheral[d] (T1abc, N0) → Pretreatment Evaluation (NSCL-2)

Stage IB, peripheral[d] (T2a, N0);
Stage I, central[d] (T1abc–T2a, N0);
Stage II (T1abc–T2ab, N1; T2b, N0);
Stage IIB (T3, N0)[e]; Stage IIIA (T3, N1) → Pretreatment Evaluation (NSCL-3)

Stage IIB[f] (T3 invasion, N0);
Stage IIIA[f] (T4 extension, N0–1; T3, N1; T4, N0–1) → Pretreatment Evaluation (NSCL-5)

Stage IIIA[f] (T1–2, N2); Stage IIIB (T3, N2) → Pretreatment Evaluation (NSCL-8)

Separate pulmonary nodule(s) (Stage IIB, IIIA, IV) → Pretreatment Evaluation (NSCL-8)

Multiple lung cancers → Treatment (NSCL-10)

Stage IIIB[f] (T1–2, N3); Stage IIIC (T3, N3) → Pretreatment Evaluation (NSCL-12)

Stage IIIB[f] (T4, N2); Stage IIIC (T4, N3) → Pretreatment Evaluation (NSCL-13)

Stage IVA (M1a)[c] (pleural or pericardial effusion) → Pretreatment Evaluation (NSCL-13)

Stage IVA (M1b)[c] → Pretreatment Evaluation (NSCL-14)

Stage IVB (M1c)[c] disseminated metastases → Systemic Therapy (NSCL-18)

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[a] Principles of Pathologic Review (NSCL-A).

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

[c] Temel JS, et al. N Engl J Med 2010;363:733-742.

[d] Based on the CT of the chest: Peripheral = outer third of lung; Central = inner two thirds of lung.

[e] T3, N0 related to size or satellite nodules.

[f] 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.

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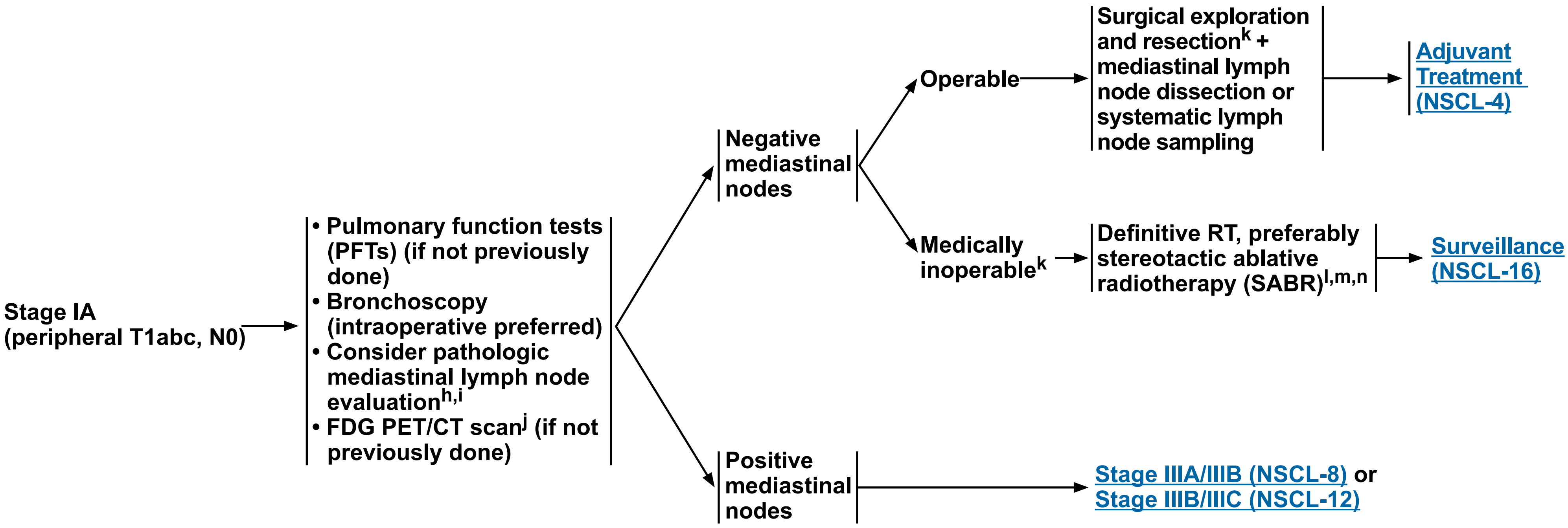

CLINICAL ASSESSMENT

Stage IA (peripheral T1abc, N0)

PRETREATMENT EVALUATION[g]

- **Pulmonary function tests (PFTs) (if not previously done)**
- **Bronchoscopy (intraoperative preferred)**
- **Consider pathologic mediastinal lymph node evaluation[h,i]**
- **FDG PET/CT scan[j] (if not previously done)**

Negative mediastinal nodes

- **Operable** → **Surgical exploration and resection[k] + mediastinal lymph node dissection or systematic lymph node sampling** → **Adjuvant Treatment (NSCL-4)**
- **Medically inoperable[k]** → **Definitive RT, preferably stereotactic ablative radiotherapy (SABR)[l,m,n]** → **Surveillance (NSCL-16)**

Positive mediastinal nodes → **Stage IIIA/IIIB (NSCL-8) or Stage IIIB/IIIC (NSCL-12)**

INITIAL TREATMENT

---

[g] Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.

[h] 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.

[i] 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.

[j] 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.

[k] Principles of Surgical Therapy (NSCL-B).

[l] Principles of Radiation Therapy (NSCL-C).

[m] Image-guided thermal ablation (IGTA) therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[n] If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)

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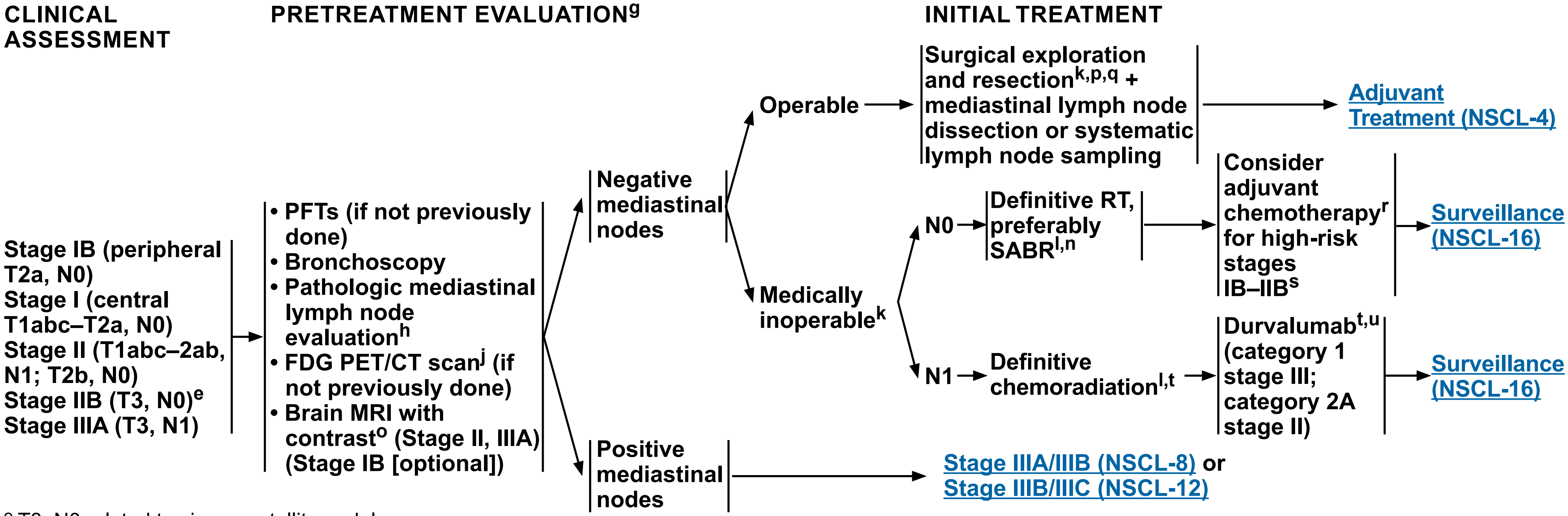

CLINICAL ASSESSMENT

Stage IB (peripheral T2a, N0)
Stage I (central T1abc–T2a, N0)
Stage II (T1abc–2ab, N1; T2b, N0)
Stage IIB (T3, N0)[e]
Stage IIIA (T3, N1)

PRETREATMENT EVALUATION[g]

- **PFTs (if not previously done)**
- **Bronchoscopy**
- **Pathologic mediastinal lymph node evaluation[h]**
- **FDG PET/CT scan[j] (if not previously done)**
- **Brain MRI with contrast[o] (Stage II, IIIA) (Stage IB [optional])**

Negative mediastinal nodes

Operable → **Surgical exploration and resection[k,p,q] + mediastinal lymph node dissection or systematic lymph node sampling** → **Adjuvant Treatment (NSCL-4)**

Medically inoperable[k]

N0 → **Definitive RT, preferably SABR[l,n]** → **Consider adjuvant chemotherapy[r] for high-risk stages IB–IIB[s]** → **Surveillance (NSCL-16)**

N1 → **Definitive chemoradiation[l,t]** → **Durvalumab[t,u] (category 1 stage III; category 2A stage II)** → **Surveillance (NSCL-16)**

Positive mediastinal nodes → **Stage IIIA/IIIB (NSCL-8) or Stage IIIB/IIIC (NSCL-12)**

INITIAL TREATMENT

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[e] T3, N0 related to size or satellite nodules.

[g] Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.

[h] 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.

[j] 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.

[k] Principles of Surgical Therapy (NSCL-B).

[l] Principles of Radiation Therapy (NSCL-C).

[n] If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)

[o] If MRI is not possible, CT of head with contrast.

[p] After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

[q] Test for *EGFR* mutation (stages IB–IIIA) and PD-L1 status (stages II–IIIA) on surgical tissue or biopsy. Principles of Molecular and Biomarker Analysis (NSCL-H).

[r] Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).

[s] 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.

[t] Concurrent Chemoradiation Regimens (NSCL-F).

[u] Durvalumab is not recommended for patients following definitive surgical resection.

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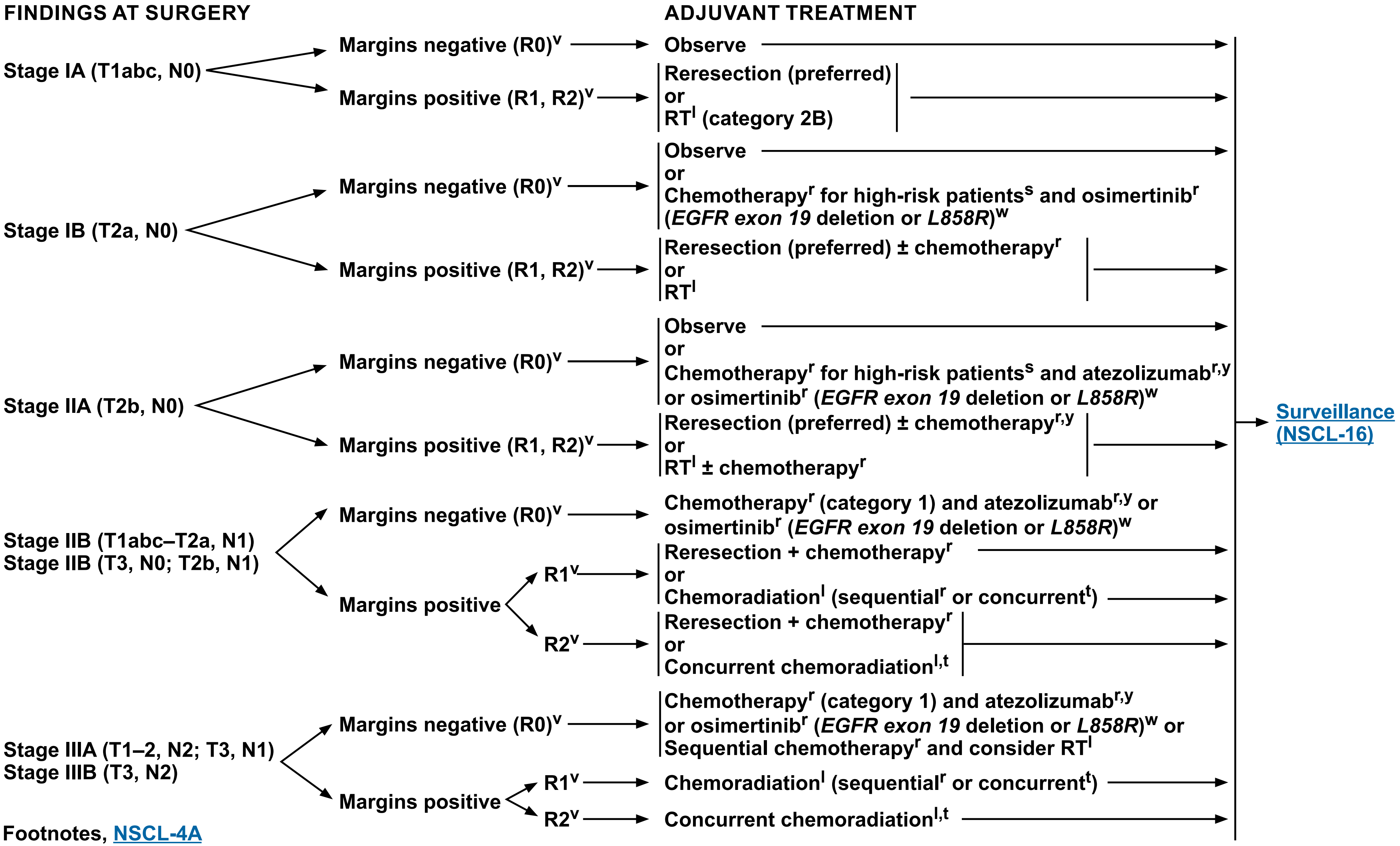

FINDINGS AT SURGERY → **ADJUVANT TREATMENT**

- **Stage IA (T1abc, N0)**
  - Margins negative (R0)[v] → Observe → Surveillance (NSCL-16)
  - Margins positive (R1, R2)[v] → Reresection (preferred) or RT[l] (category 2B) → Surveillance (NSCL-16)
- **Stage IB (T2a, N0)**
  - Margins negative (R0)[v] → Observe or Chemotherapy[r] for high-risk patients[s] and osimertinib[r] (*EGFR exon 19* deletion or *L858R*)[w] → Surveillance (NSCL-16)
  - Margins positive (R1, R2)[v] → Reresection (preferred) ± chemotherapy[r] or RT[l] → Surveillance (NSCL-16)
- **Stage IIA (T2b, N0)**
  - Margins negative (R0)[v] → Observe or Chemotherapy[r] for high-risk patients[s] and atezolizumab[r,y] or osimertinib[r] (*EGFR exon 19* deletion or *L858R*)[w] → Surveillance (NSCL-16)
  - Margins positive (R1, R2)[v] → Reresection (preferred) ± chemotherapy[r,y] or RT[l] ± chemotherapy[r] → Surveillance (NSCL-16)
- **Stage IIB (T1abc–T2a, N1)**
  Stage IIB (T3, N0; T2b, N1)
  - Margins negative (R0)[v] → Chemotherapy[r] (category 1) and atezolizumab[r,y] or osimertinib[r] (*EGFR exon 19* deletion or *L858R*)[w] → Surveillance (NSCL-16)
  - Margins positive
    - R1[v] → Reresection + chemotherapy[r] or Chemoradiation[l] (sequential[r] or concurrent[t]) → Surveillance (NSCL-16)
    - R2[v] → Reresection + chemotherapy[r] or Concurrent chemoradiation[l,t] → Surveillance (NSCL-16)
- **Stage IIIA (T1–2, N2; T3, N1)**
  Stage IIIB (T3, N2)
  - Margins negative (R0)[v] → Chemotherapy[r] (category 1) and atezolizumab[r,y] or osimertinib[r] (*EGFR exon 19* deletion or *L858R*)[w] or Sequential chemotherapy[r] and consider RT[l] → Surveillance (NSCL-16)
  - Margins positive
    - R1[v] → Chemoradiation[l] (sequential[r] or concurrent[t]) → Surveillance (NSCL-16)
    - R2[v] → Concurrent chemoradiation[l,t] → Surveillance (NSCL-16)

Footnotes, NSCL-4A

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.

FOOTNOTES

[l] Principles of Radiation Therapy (NSCL-C).
[r] Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).
[s] 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.
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[v] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[w] For patients with *EGFR exon 19* deletion or *L858R* who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
[x] Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.
[y] For patients with PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

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CLINICAL ASSESSMENT

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

PRETREATMENT EVALUATION

- **PFTs (if not previously done)**
- **Bronchoscopy**
- **Pathologic mediastinal lymph node evaluation**[h]
- **Brain MRI with contrast**[o]
- **MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine, subclavian vessels, or brachial plexus**
- **FDG PET/CT scan**[j] **(if not previously done)**

CLINICAL EVALUATION

- **Superior sulcus tumor** → Treatment (NSCL-6)
- **Chest wall** → Treatment (NSCL-7)
- **Proximal airway or mediastinum** → Treatment (NSCL-7)
- **Stage IIIA (T4, N0–1)** → Treatment (NSCL-7)
- **Unresectable disease** → Treatment (NSCL-7)
- **Positive mediastinal nodes** → Stage IIIA/IIIB (NSCL-8)
- **Metastatic disease** → Treatment for Metastasis limited sites (NSCL-14) or distant disease (NSCL-17)

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[h] 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.

[j] 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.

[o] If MRI is not possible, CT of head with contrast.

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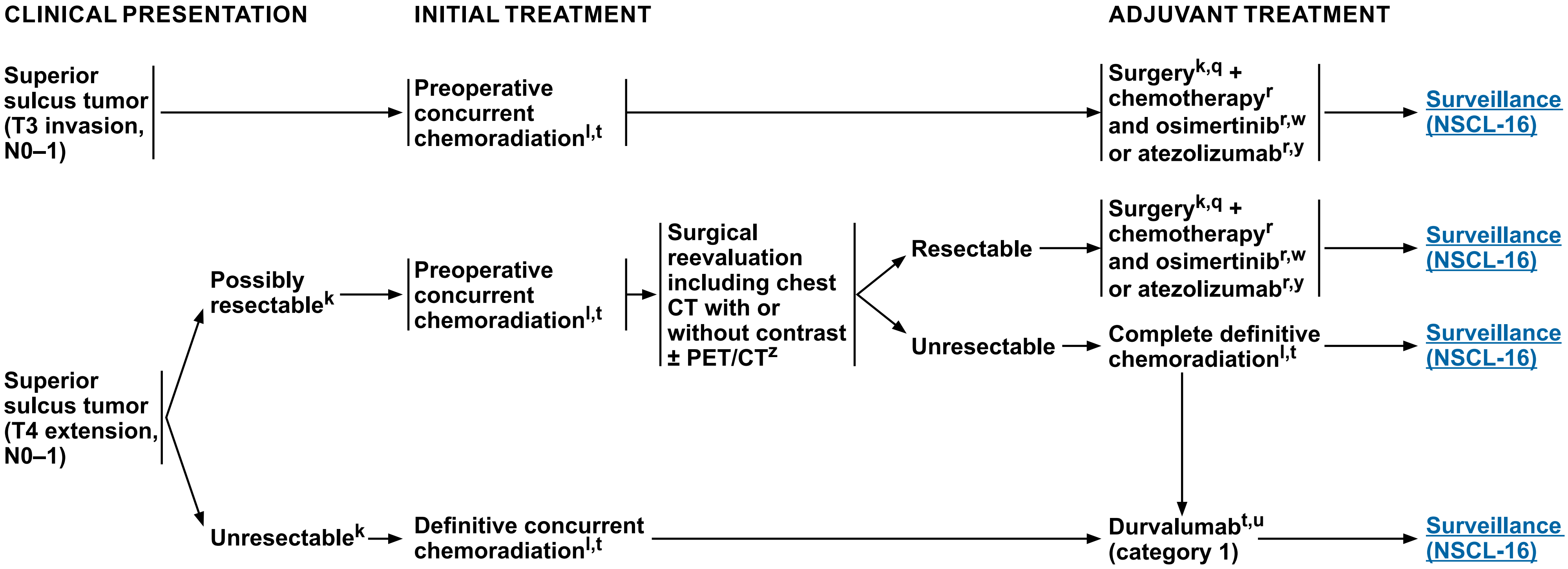

CLINICAL PRESENTATION | **INITIAL TREATMENT** | **ADJUVANT TREATMENT**

Superior sulcus tumor (T3 invasion, N0–1) → **Preoperative concurrent chemoradiation[l,t]** → **Surgery[k,q] + chemotherapy[r] and osimertinib[r,w] or atezolizumab[r,y]** → **Surveillance (NSCL-16)**

Superior sulcus tumor (T4 extension, N0–1)

- **Possibly resectable[k]** → **Preoperative concurrent chemoradiation[l,t]** → **Surgical reevaluation including chest CT with or without contrast ± PET/CT[z]**
  - **Resectable** → **Surgery[k,q] + chemotherapy[r] and osimertinib[r,w] or atezolizumab[r,y]** → **Surveillance (NSCL-16)**
  - **Unresectable** → **Complete definitive chemoradiation[l,t]** → **Surveillance (NSCL-16)**
    - → **Durvalumab[t,u] (category 1)** → **Surveillance (NSCL-16)**
- **Unresectable[k]** → **Definitive concurrent chemoradiation[l,t]** → **Durvalumab[t,u] (category 1)** → **Surveillance (NSCL-16)**

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[k] Principles of Surgical Therapy (NSCL-B).
[l] Principles of Radiation Therapy (NSCL-C).
[q] Test for *EGFR* mutation on surgical tissue or biopsy in stages IB–IIIA. Principles of Molecular and Biomarker Analysis (NSCL-H).
[r] Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[u] Durvalumab is not recommended for patients following definitive surgical resection.
[w] For patients with *EGFR exon 19* deletion or *L858R* who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
[y] For patients with PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.
[z] MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine, subclavian vessels, or brachial plexus.

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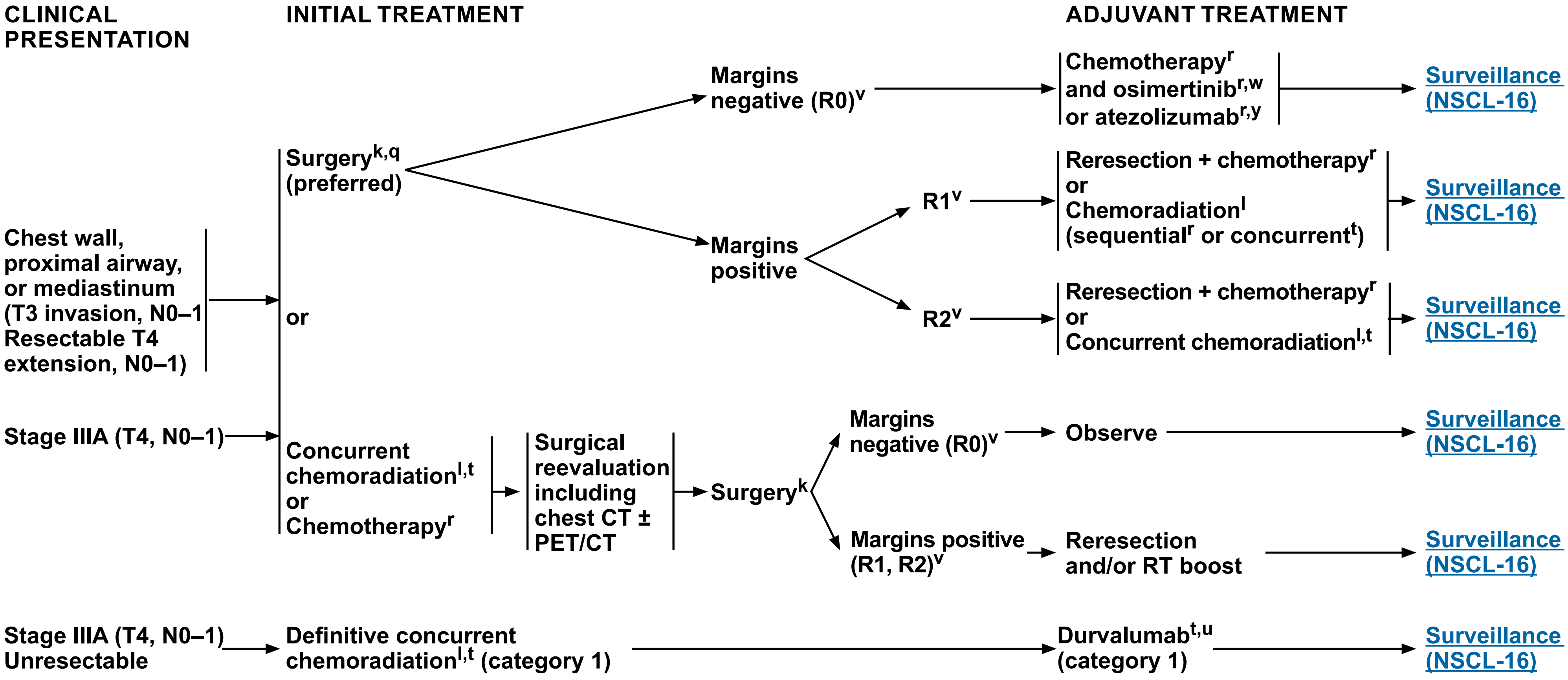

CLINICAL PRESENTATION | **INITIAL TREATMENT** | **ADJUVANT TREATMENT**

Chest wall, proximal airway, or mediastinum (T3 invasion, N0–1) Resectable T4 extension, N0–1) → **Surgery[k,q] (preferred)**
- → **Margins negative (R0)[v]** → **Chemotherapy[r] and osimertinib[r,w] or atezolizumab[r,y]** → **Surveillance (NSCL-16)**
- → **Margins positive**
  - → **R1[v]** → **Reresection + chemotherapy[r] or Chemoradiation[l] (sequential[r] or concurrent[t])** → **Surveillance (NSCL-16)**
  - → **R2[v]** → **Reresection + chemotherapy[r] or Concurrent chemoradiation[l,t]** → **Surveillance (NSCL-16)**

or

Stage IIIA (T4, N0–1) → **Concurrent chemoradiation[l,t] or Chemotherapy[r]** → **Surgical reevaluation including chest CT ± PET/CT** → **Surgery[k]**
- → **Margins negative (R0)[v]** → **Observe** → **Surveillance (NSCL-16)**
- → **Margins positive (R1, R2)[v]** → **Reresection and/or RT boost** → **Surveillance (NSCL-16)**

Stage IIIA (T4, N0–1) Unresectable → **Definitive concurrent chemoradiation[l,t] (category 1)** → **Durvalumab[t,u] (category 1)** → **Surveillance (NSCL-16)**

[k] Principles of Surgical Therapy (NSCL-B).
[l] Principles of Radiation Therapy (NSCL-C).
[q] Test for *EGFR* mutation on surgical tissue or biopsy in stages IB–IIIA. Principles of Molecular and Biomarker Analysis (NSCL-H).
[r] Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[u] Durvalumab is not recommended for patients following definitive surgical resection.
[v] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[w] For patients with *EGFR exon 19* deletion or *L858R* who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
[y] For patients with PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

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CLINICAL ASSESSMENT | **PRETREATMENT EVALUATION** | **MEDIASTINAL BIOPSY FINDINGS AND RESECTABILITY**

Stage IIIA (T1–2, N2)
Stage IIIB (T3, N2)
→
- **PFTs (if not previously done)**
- **Bronchoscopy**
- **Pathologic mediastinal lymph node evaluation[h]**
- **FDG PET/CT scan[j] (if not previously done)**
- **Brain MRI with contrast[o]**

→
- **N2, N3 nodes negative** → Treatment T1–3, N0–1 (NSCL-9)
- **N2 nodes positive, M0** → Treatment (NSCL-9)
- **N3 nodes positive, M0** → Stage IIIB (NSCL-12)
- **Metastatic disease** → Treatment for Metastasis limited sites (NSCL-14) **or distant disease** (NSCL-17)

Separate pulmonary nodule(s) (Stage IIB, IIIA, IV)
→
- **PFTs (if not previously done)**
- **Bronchoscopy**
- **Pathologic mediastinal lymph node evaluation[h]**
- **Brain MRI with contrast[o]**
- **FDG PET/CT scan[j] (if not previously done)**

→
- **Separate pulmonary nodule(s), same lobe (T3, N0–1) or ipsilateral non-primary lobe (T4, N0–1)** → Treatment (NSCL-10)
- **Stage IVA (N0, M1a): Contralateral lung (solitary nodule)** → Treatment (NSCL-10)
- **Extrathoracic metastatic disease** → Treatment for Metastasis limited sites (NSCL-14) **or** distant disease (NSCL-17)

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[h] 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.

[j] 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.

[o] If MRI is not possible, CT of head with contrast.

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MEDIASTINAL BIOPSY FINDINGS → **INITIAL TREATMENT** → **ADJUVANT TREATMENT**

T1–3, N0–1 (including T3 with multiple nodules in same lobe)
- Resectable[k,p] → Surgical resection[k] + mediastinal lymph node dissection or systematic lymph node sampling → Adjuvant Treatment (NSCL-4)
- Medically inoperable → Treatment according to clinical stage (NSCL-3)

T1–2, T3 (other than invasive), N2 nodes positive, M0 →
- Definitive concurrent chemoradiation[l,t] (category 1) → Durvalumab[t,u] (category 1) → Surveillance (NSCL-16)
- or
- Induction chemotherapy[r,aa] ± RT[l]
  - No apparent progression → • Surgery[k] • Consider RT[l] → Surveillance (NSCL-16)
  - Progression
    - Local → RT[l] (if feasible) ± chemotherapy[r]
    - Systemic → Treatment for Metastasis limited sites (NSCL-14) or distant disease (NSCL-17)

T3 (invasion), N2 nodes positive, M0 → Definitive concurrent chemoradiation[l,t] → Durvalumab[t,u] (category 1) → Surveillance (NSCL-16)

[k] Principles of Surgical Therapy (NSCL-B).
[l] Principles of Radiation Therapy (NSCL-C).
[p] After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.
[r] Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[u] Durvalumab is not recommended for patients following definitive surgical resection.
[aa] Chest CT with contrast and/or PET/CT to evaluate progression.

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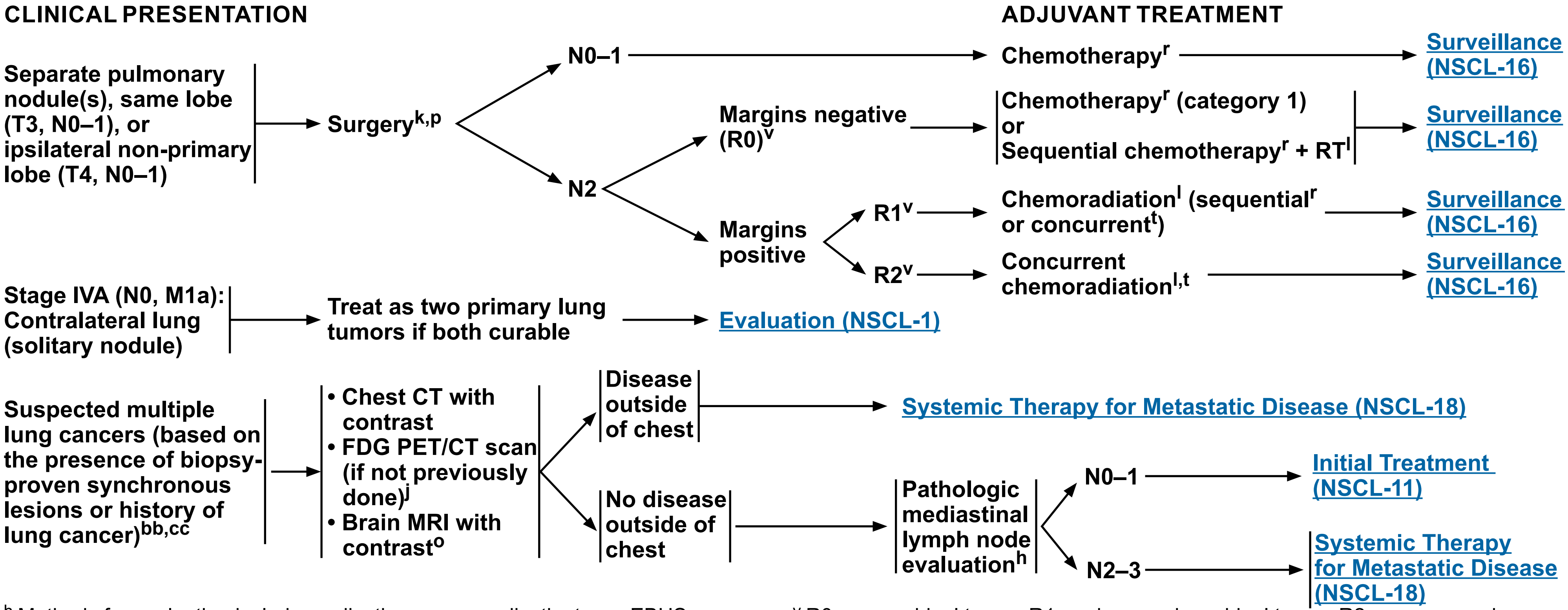

CLINICAL PRESENTATION

ADJUVANT TREATMENT

Separate pulmonary nodule(s), same lobe (T3, N0–1), or ipsilateral non-primary lobe (T4, N0–1) → **Surgery[k,p]**
- **N0–1** → **Chemotherapy[r]** → **Surveillance (NSCL-16)**
- **N2**
  - **Margins negative (R0)[v]** → **Chemotherapy[r] (category 1) or Sequential chemotherapy[r] + RT[l]** → **Surveillance (NSCL-16)**
  - **Margins positive**
    - **R1[v]** → **Chemoradiation[l] (sequential[r] or concurrent[t])** → **Surveillance (NSCL-16)**
    - **R2[v]** → **Concurrent chemoradiation[l,t]** → **Surveillance (NSCL-16)**

Stage IVA (N0, M1a): Contralateral lung (solitary nodule) → **Treat as two primary lung tumors if both curable** → **Evaluation (NSCL-1)**

Suspected multiple lung cancers (based on the presence of biopsy-proven synchronous lesions or history of lung cancer)[bb,cc] →
- **Chest CT with contrast**
- **FDG PET/CT scan (if not previously done)[j]**
- **Brain MRI with contrast[o]**

- **Disease outside of chest** → **Systemic Therapy for Metastatic Disease (NSCL-18)**
- **No disease outside of chest** → **Pathologic mediastinal lymph node evaluation[h]**
  - **N0–1** → **Initial Treatment (NSCL-11)**
  - **N2–3** → **Systemic Therapy for Metastatic Disease (NSCL-18)**

---

[h] 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.

[j] 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.

[k] Principles of Surgical Therapy (NSCL-B).

[l] Principles of Radiation Therapy (NSCL-C).

[o] If MRI is not possible, CT of head with contrast.

[p] After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

[r] Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).

[t] Concurrent Chemoradiation Regimens (NSCL-F).

[v] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

[bb] Lesions with different cell types (eg, squamous cell carcinoma, adenocarcinoma) are usually different primary tumors. This analysis may be limited by small biopsy samples. However, lesions of the same cell type are not necessarily metastases. Single contralateral lung nodules with clinical, radiologic, or pathologic features suggestive of a synchronous primary lung cancer (eg, long disease-free survival, ground glass components, different histologic characteristics) that are amenable to local therapy should be considered as probable separate primary cancers and eligible for local therapy (NSCL-11). Multiple studies suggest that next-generation sequencing (NGS) testing with broad gene coverage may allow for unambiguous determination of clonal relatedness among separate lung nodules.

[cc] 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).

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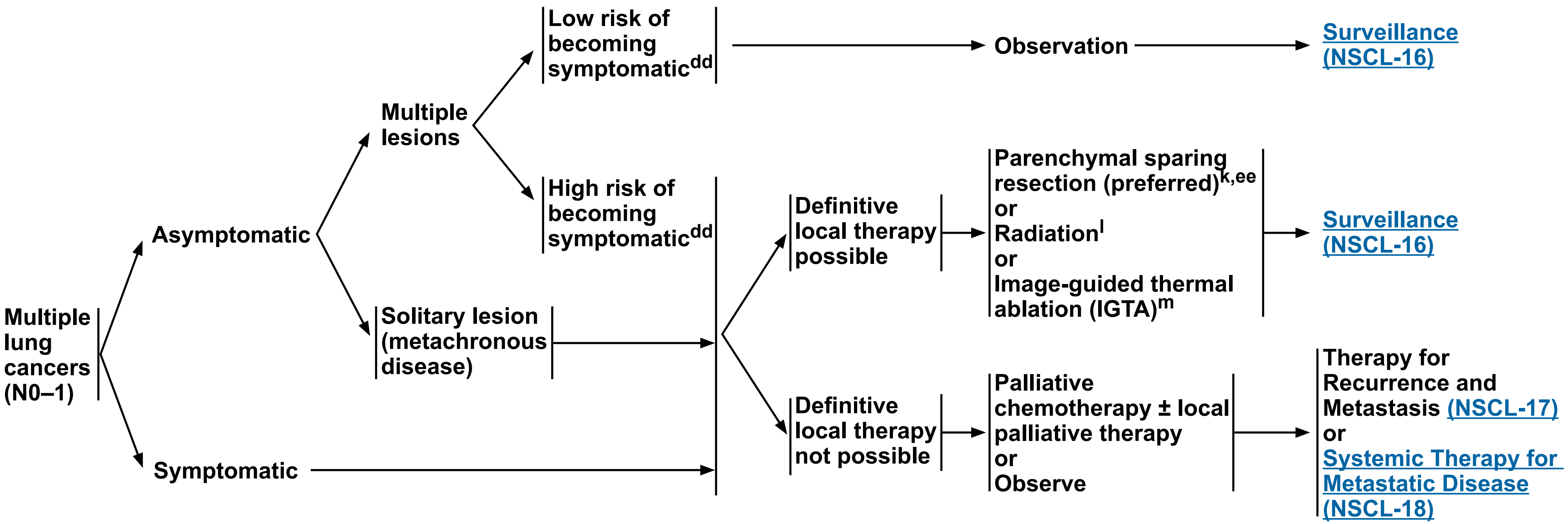
CLINICAL PRESENTATION

INITIAL TREATMENT



Multiple lung cancers (N0–1)

- **Asymptomatic**
  - **Multiple lesions**
    - **Low risk of becoming symptomatic**[dd] → **Observation** → **Surveillance (NSCL-16)**
    - **High risk of becoming symptomatic**[dd]
  - **Solitary lesion (metachronous disease)**
- **Symptomatic**

High risk of becoming symptomatic, Solitary lesion, or Symptomatic:

- **Definitive local therapy possible** → **Parenchymal sparing resection (preferred)**[k,ee] **or Radiation**[l] **or Image-guided thermal ablation (IGTA)**[m] → **Surveillance (NSCL-16)**
- **Definitive local therapy not possible** → **Palliative chemotherapy ± local palliative therapy or Observe** → **Therapy for Recurrence and Metastasis (NSCL-17) or Systemic Therapy for Metastatic Disease (NSCL-18)**

---

[k] Principles of Surgical Therapy (NSCL-B).

[l] Principles of Radiation Therapy (NSCL-C).

[m] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[dd] 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.

[ee] 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, interventional oncology).

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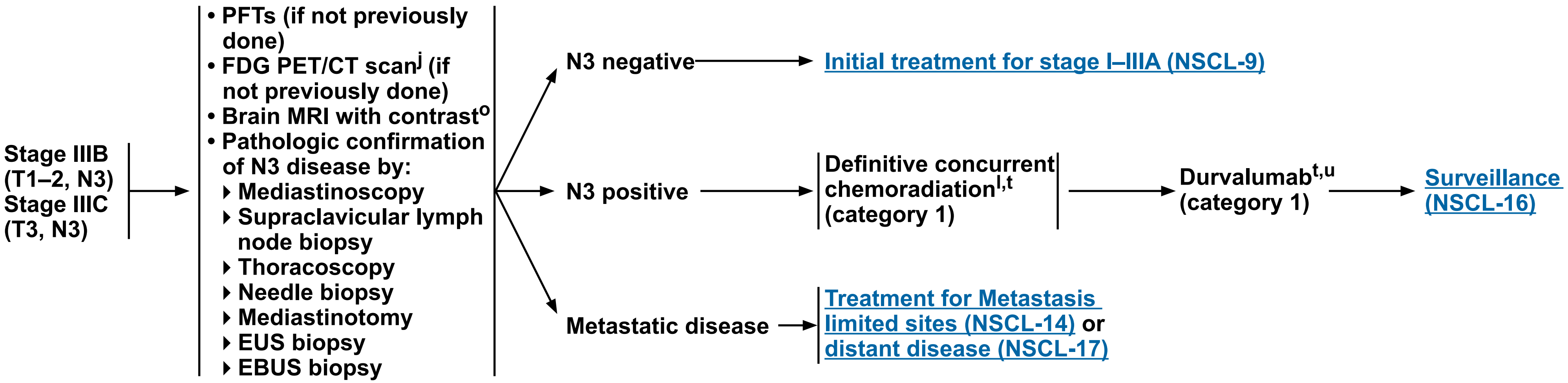
CLINICAL ASSESSMENT | **PRETREATMENT EVALUATION** | **INITIAL TREATMENT**



Stage IIIB (T1–2, N3)
Stage IIIC (T3, N3)
→
- **PFTs (if not previously done)**
- **FDG PET/CT scan[j] (if not previously done)**
- **Brain MRI with contrast[o]**
- **Pathologic confirmation of N3 disease by:**
  - **Mediastinoscopy**
  - **Supraclavicular lymph node biopsy**
  - **Thoracoscopy**
  - **Needle biopsy**
  - **Mediastinotomy**
  - **EUS biopsy**
  - **EBUS biopsy**

N3 negative → Initial treatment for stage I–IIIA (NSCL-9)

N3 positive → **Definitive concurrent chemoradiation[l,t] (category 1)** → **Durvalumab[t,u] (category 1)** → Surveillance (NSCL-16)

Metastatic disease → Treatment for Metastasis limited sites (NSCL-14) or distant disease (NSCL-17)

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[j] 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.

[l] Principles of Radiation Therapy (NSCL-C).

[o] If MRI is not possible, CT of head with contrast.

[t] Concurrent Chemoradiation Regimens (NSCL-F).

[u] Durvalumab is not recommended for patients following definitive surgical resection.

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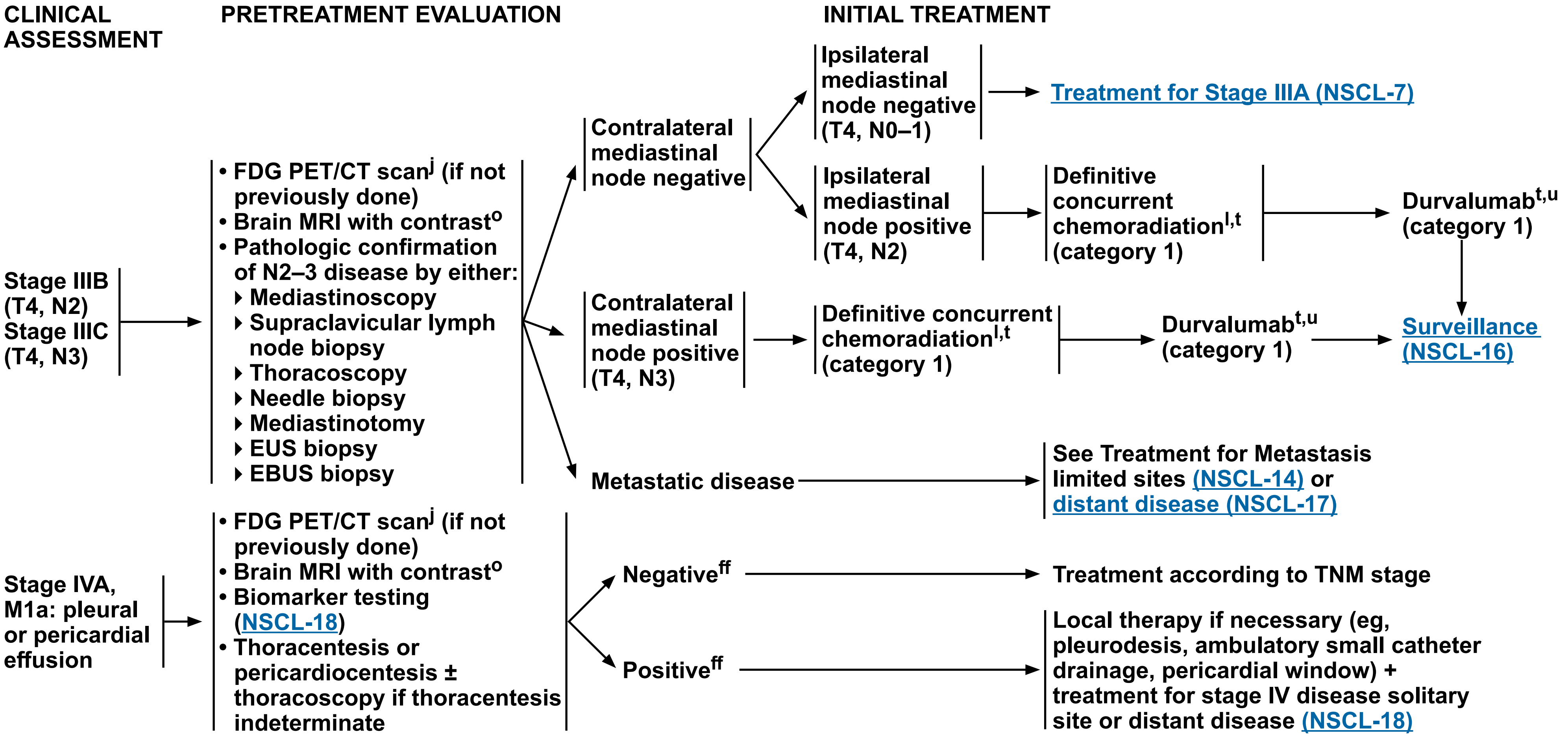

CLINICAL ASSESSMENT | **PRETREATMENT EVALUATION** | **INITIAL TREATMENT**

- **Stage IIIB (T4, N2) Stage IIIC (T4, N3)** →
  - FDG PET/CT scan[j] (if not previously done)
  - Brain MRI with contrast[o]
  - Pathologic confirmation of N2–3 disease by either:
    - Mediastinoscopy
    - Supraclavicular lymph node biopsy
    - Thoracoscopy
    - Needle biopsy
    - Mediastinotomy
    - EUS biopsy
    - EBUS biopsy
  - → **Contralateral mediastinal node negative**
    - → **Ipsilateral mediastinal node negative (T4, N0–1)** → Treatment for Stage IIIA (NSCL-7)
    - → **Ipsilateral mediastinal node positive (T4, N2)** → Definitive concurrent chemoradiation[l,t] (category 1) → Durvalumab[t,u] (category 1) → Surveillance (NSCL-16)
  - → **Contralateral mediastinal node positive (T4, N3)** → Definitive concurrent chemoradiation[l,t] (category 1) → Durvalumab[t,u] (category 1) → Surveillance (NSCL-16)
  - → **Metastatic disease** → See Treatment for Metastasis limited sites (NSCL-14) or distant disease (NSCL-17)

- **Stage IVA, M1a: pleural or pericardial effusion** →
  - FDG PET/CT scan[j] (if not previously done)
  - Brain MRI with contrast[o]
  - Biomarker testing (NSCL-18)
  - Thoracentesis or pericardiocentesis ± thoracoscopy if thoracentesis indeterminate
  - → **Negative[ff]** → Treatment according to TNM stage
  - → **Positive[ff]** → Local therapy if necessary (eg, pleurodesis, ambulatory small catheter drainage, pericardial window) + treatment for stage IV disease solitary site or distant disease (NSCL-18)

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[j] 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.

[l] Principles of Radiation Therapy (NSCL-C).

[o] If MRI is not possible, CT of head with contrast.

[t] Concurrent Chemoradiation Regimens (NSCL-F).

[u] Durvalumab is not recommended for patients following definitive surgical resection.

[ff] 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.

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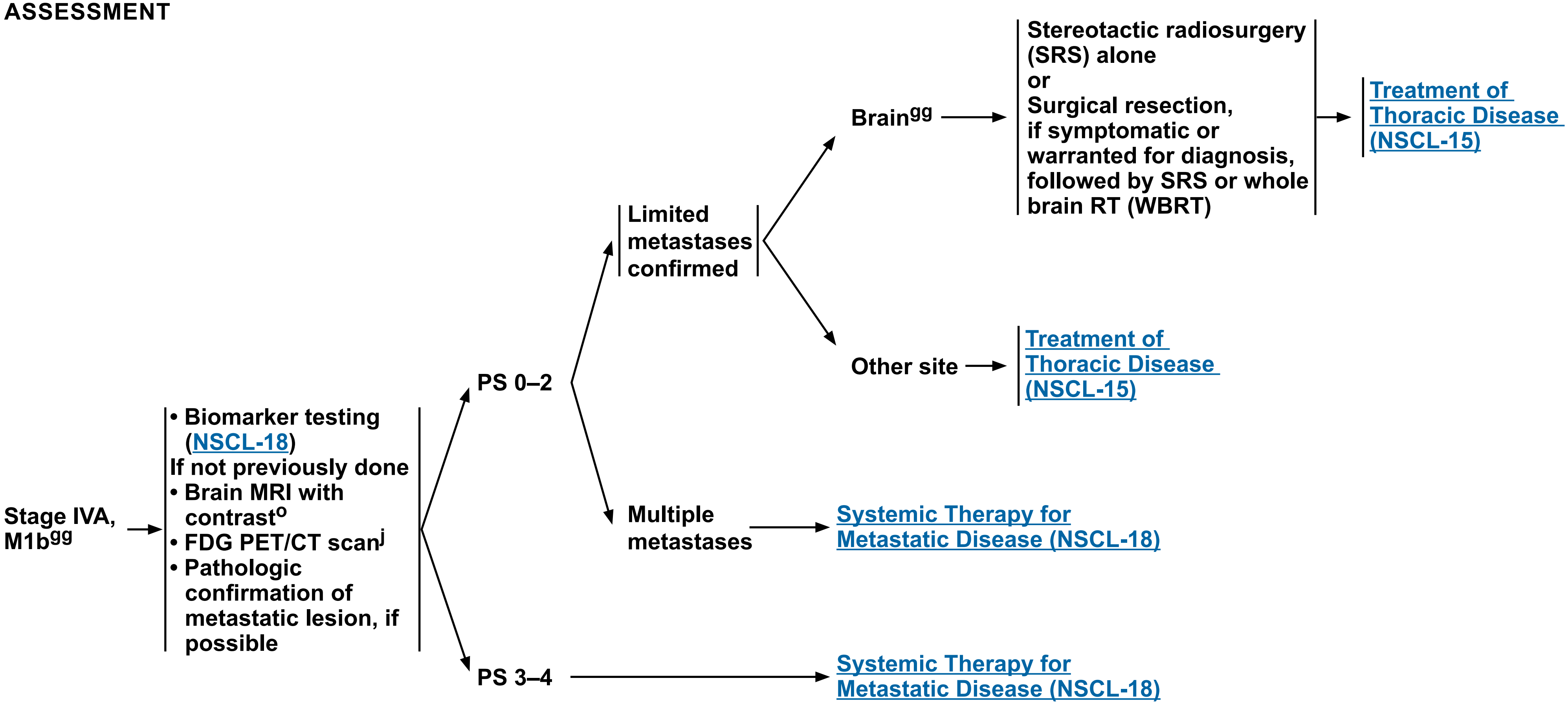
CLINICAL ASSESSMENT | **PRETREATMENT EVALUATION** | **INITIAL TREATMENT**[hh]



Stage IVA, M1b[gg] →

- **Biomarker testing (NSCL-18)**

If not previously done

- **Brain MRI with contrast**[o]
- **FDG PET/CT scan**[j]
- **Pathologic confirmation of metastatic lesion, if possible**

→ **PS 0–2** → **Limited metastases confirmed** → **Brain**[gg] → **Stereotactic radiosurgery (SRS) alone or Surgical resection, if symptomatic or warranted for diagnosis, followed by SRS or whole brain RT (WBRT)** → **Treatment of Thoracic Disease (NSCL-15)**

→ **PS 0–2** → **Limited metastases confirmed** → **Other site** → **Treatment of Thoracic Disease (NSCL-15)**

→ **PS 0–2** → **Multiple metastases** → **Systemic Therapy for Metastatic Disease (NSCL-18)**

→ **PS 3–4** → **Systemic Therapy for Metastatic Disease (NSCL-18)**

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[j] 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.

[o] If MRI is not possible, CT of head with contrast.

[gg] 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 3 to 5 metastases.

[hh] NCCN Guidelines for Central Nervous System Cancers.

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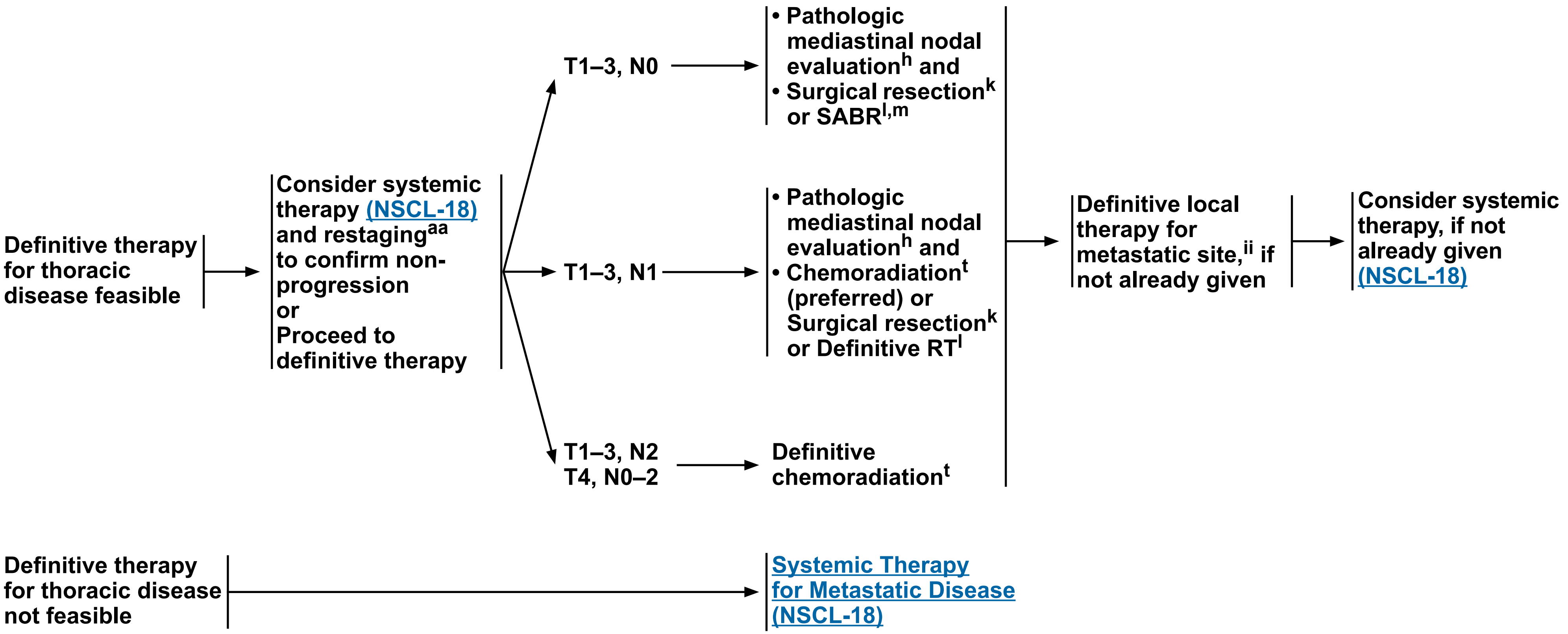
TREATMENT OF THORACIC DISEASE



Definitive therapy for thoracic disease feasible → **Consider systemic therapy (NSCL-18) and restaging[aa] to confirm non-progression or Proceed to definitive therapy**

- **T1–3, N0** → **• Pathologic mediastinal nodal evaluation[h] and • Surgical resection[k] or SABR[l,m]**
- **T1–3, N1** → **• Pathologic mediastinal nodal evaluation[h] and • Chemoradiation[t] (preferred) or Surgical resection[k] or Definitive RT[l]**
- **T1–3, N2 T4, N0–2** → **Definitive chemoradiation[t]**

→ **Definitive local therapy for metastatic site,[ii] if not already given** → **Consider systemic therapy, if not already given (NSCL-18)**

Definitive therapy for thoracic disease not feasible → **Systemic Therapy for Metastatic Disease (NSCL-18)**

---

[h] 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.

[k] Principles of Surgical Therapy (NSCL-B).

[l] Principles of Radiation Therapy (NSCL-C).

[m] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[t] Concurrent Chemoradiation Regimens (NSCL-F).

[aa] Chest CT with contrast and/or PET/CT to evaluate progression.

[ii] Typically, RT (including SABR) or surgical resection. IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving RT or surgery.

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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[jj] ± 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[kk] or brain MRI is not routinely indicated**
- **Cancer Survivorship Care (NSCL-G)**

→ **Recurrence** →

- **PET/CT**
- **Brain MRI with contrast[o]**

Locoregional recurrence → **Therapy for Recurrence and Metastasis (NSCL-17)**

Distant metastases → **Therapy for Recurrence and Metastasis (NSCL-17)**

---

[o] If MRI is not possible, CT of head with contrast.

[jj] Timing of CT scans within Guidelines parameters is a clinical decision.

[kk] 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.

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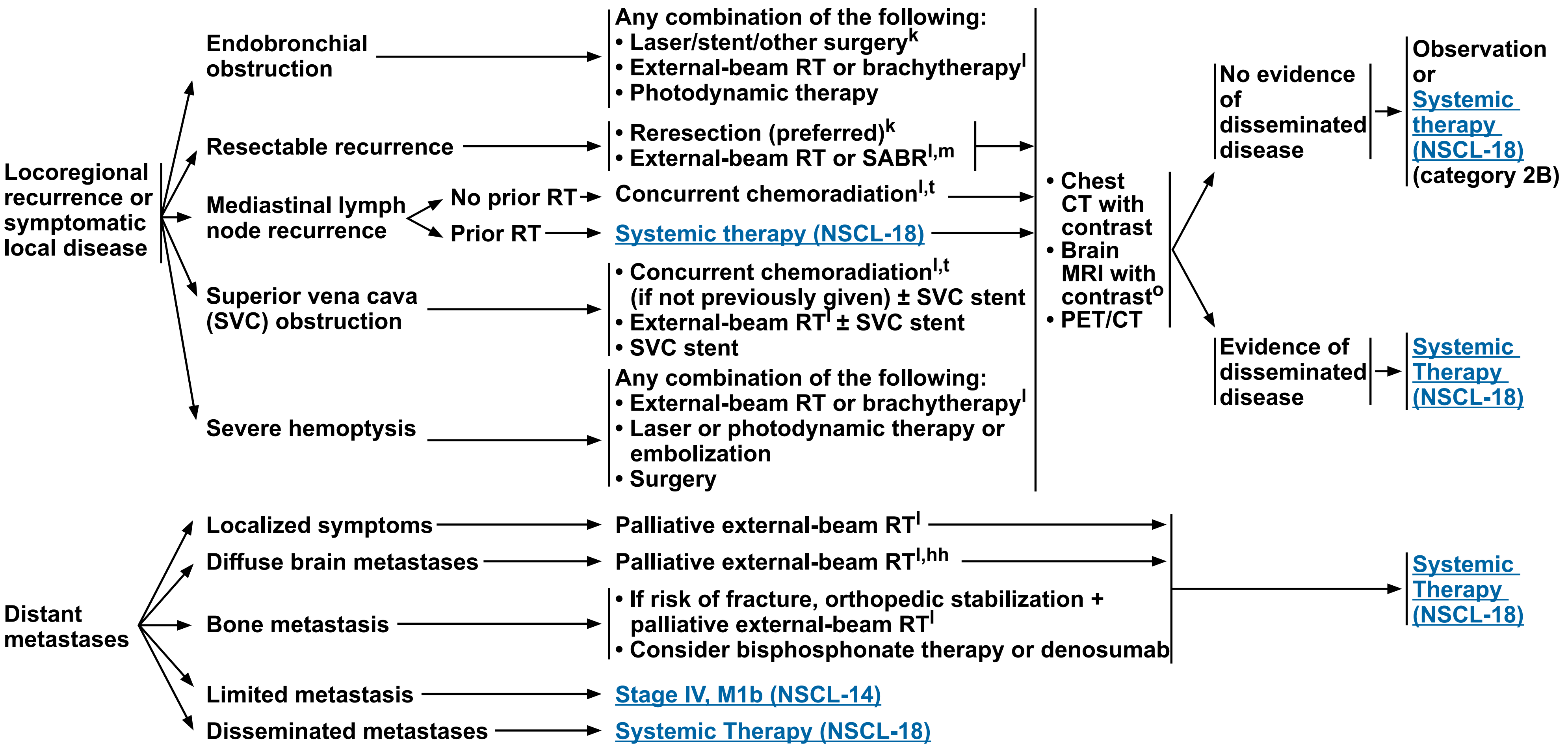
THERAPY FOR RECURRENCE AND METASTASIS



Locoregional recurrence or symptomatic local disease

- **Endobronchial obstruction** → Any combination of the following:
  - Laser/stent/other surgery[k]
  - External-beam RT or brachytherapy[l]
  - Photodynamic therapy
- **Resectable recurrence** →
  - Reresection (preferred)[k]
  - External-beam RT or SABR[l,m]
- **Mediastinal lymph node recurrence**
  - No prior RT → Concurrent chemoradiation[l,t]
  - Prior RT → Systemic therapy (NSCL-18)
- **Superior vena cava (SVC) obstruction** →
  - Concurrent chemoradiation[l,t] (if not previously given) ± SVC stent
  - External-beam RT[l] ± SVC stent
  - SVC stent
- **Severe hemoptysis** → Any combination of the following:
  - External-beam RT or brachytherapy[l]
  - Laser or photodynamic therapy or embolization
  - Surgery

→
- Chest CT with contrast
- Brain MRI with contrast[o]
- PET/CT

→ No evidence of disseminated disease → Observation or Systemic therapy (NSCL-18) (category 2B)

→ Evidence of disseminated disease → Systemic Therapy (NSCL-18)

Distant metastases

- **Localized symptoms** → Palliative external-beam RT[l]
- **Diffuse brain metastases** → Palliative external-beam RT[l,hh]
- **Bone metastasis** →
  - If risk of fracture, orthopedic stabilization + palliative external-beam RT[l]
  - Consider bisphosphonate therapy or denosumab

→ Systemic Therapy (NSCL-18)

- **Limited metastasis** → Stage IV, M1b (NSCL-14)
- **Disseminated metastases** → Systemic Therapy (NSCL-18)

---

[k] Principles of Surgical Therapy (NSCL-B).

[l] Principles of Radiation Therapy (NSCL-C).

[m] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[o] If MRI is not possible, CT of head with contrast.

[t] Concurrent Chemoradiation Regimens (NSCL-F).

[hh] NCCN Guidelines for Central Nervous System Cancers.

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NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL PRESENTATION

Advanced or metastatic disease →

- **Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[ll] or plasma testing if appropriate)**
- **Smoking cessation counseling**
- **Integrate palliative care[c] (NCCN Guidelines for Palliative Care)**

HISTOLOGIC SUBTYPE[a]

BIOMARKER TESTING[mm]

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

→

- **Molecular testing, including:**
  - ***EGFR* mutation (category 1), *ALK* (category 1), *KRAS, ROS1, BRAF, NTRK1/2/3, METex14* skipping, *RET***
  - **Testing should be conducted as part of broad molecular profiling[nn]**
- **PD-L1 testing (category 1)**

→ **Testing Results (NSCL-19)**

Squamous cell carcinoma →

- **Consider molecular testing, including:[oo]**
  - ***EGFR* mutation, *ALK, KRAS, ROS1, BRAF, NTRK1/2/3, METex14* skipping, *RET***
  - **Testing should be conducted as part of broad molecular profiling[nn]**
- **PD-L1 testing (category 1)**

→ **Testing Results (NSCL-19)**

---

[a] Principles of Pathologic Review (NSCL-A).

[c] Temel JS, et al. N Engl J Med 2010;363:733-742.

[ll] If there is insufficient tissue to allow testing for all of *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3, MET, and RET,* repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[nn] 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 defined as molecular testing that identifies all biomarkers identified in NSCL-19 in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. Emerging Biomarkers to Identify Patients for Therapies (NSCL-I).

[oo] Lam VK, et al. Clin Lung Cancer 2019;20:30-36.e3; Sands JM, et al. Lung Cancer 2020;140:35-41.

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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.

TESTING RESULTS[ll,mm]

EGFR exon 19 **deletion or** ***L858R*** **mutation positive**	NSCL-20
EGFR S768I, L861Q, **and/or** ***G719X*** **mutation positive**	NSCL-23
EGFR exon 20 **insertion mutation positive**	NSCL-24
KRAS G12C **mutation positive**	NSCL-25
ALK **rearrangement positive**	NSCL-26
ROS1 **rearrangement positive**	NSCL-29
BRAF **V600E mutation positive**	NSCL-31
NTRK1/2/3 **gene fusion positive**	NSCL-32
METex14 **skipping mutation positive**	NSCL-33
RET **rearrangement positive**	NSCL-34
PD-L1 ≥50% and negative for actionable molecular biomarkers above	NSCL-35
PD-L1 ≥1%–49% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

[ll] If there is insufficient tissue to allow testing for all of *EGFR*, *KRAS, ALK*, *ROS1*, *BRAF*, *NTRK1/2/3, MET, and RET,* repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

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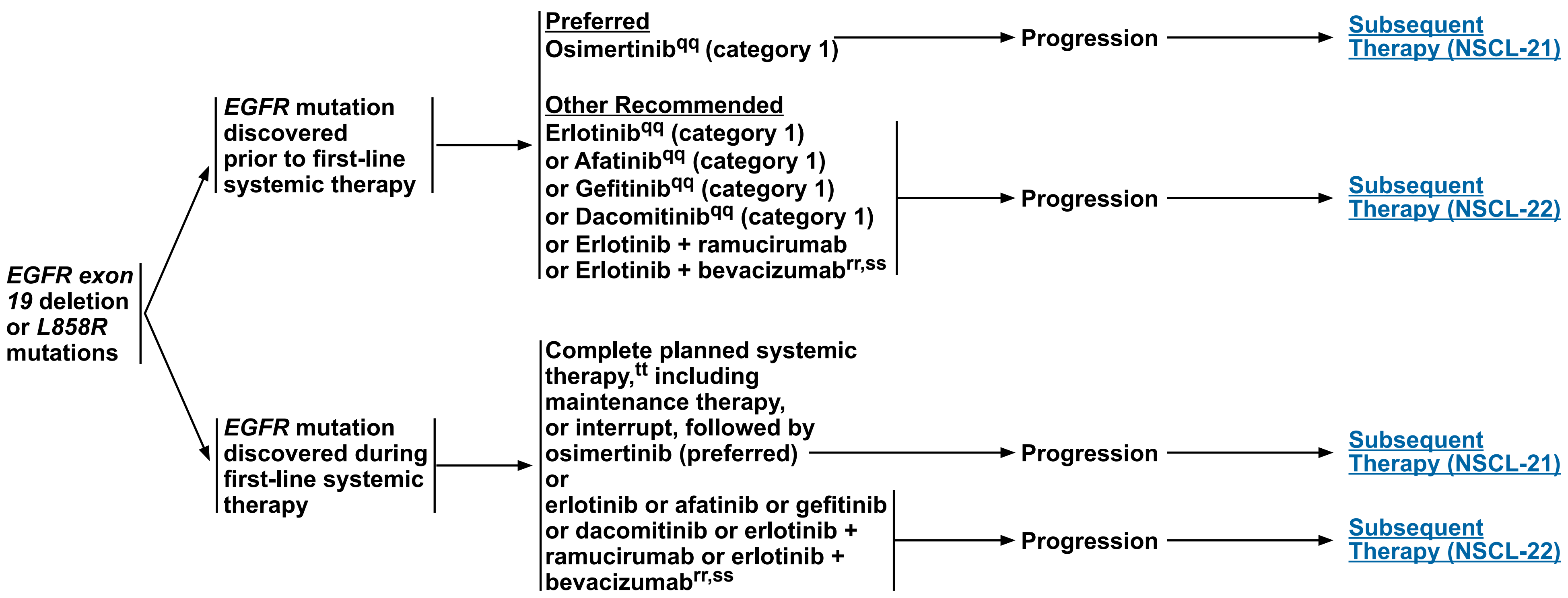
EGFR EXON 19 DELETION OR *L858R* MUTATIONS[mm]

FIRST-LINE THERAPY[pp]



***EGFR* exon 19 deletion or *L858R* mutations**

- ***EGFR* mutation discovered prior to first-line systemic therapy** →
  - **Preferred**
    - **Osimertinib[qq] (category 1)** → **Progression** → **Subsequent Therapy (NSCL-21)**
  - **Other Recommended**
    - **Erlotinib[qq] (category 1)**
    - **or Afatinib[qq] (category 1)**
    - **or Gefitinib[qq] (category 1)**
    - **or Dacomitinib[qq] (category 1)**
    - **or Erlotinib + ramucirumab**
    - **or Erlotinib + bevacizumab[rr,ss]**
    - → **Progression** → **Subsequent Therapy (NSCL-22)**
- ***EGFR* mutation discovered during first-line systemic therapy** →
  - **Complete planned systemic therapy,[tt] including maintenance therapy, or interrupt, followed by osimertinib (preferred)** → **Progression** → **Subsequent Therapy (NSCL-21)**
  - **or**
  - **erlotinib or afatinib or gefitinib or dacomitinib or erlotinib + ramucirumab or erlotinib + bevacizumab[rr,ss]** → **Progression** → **Subsequent Therapy (NSCL-22)**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[qq] For performance status 0–4.

[rr] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis.

[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

[tt] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516.

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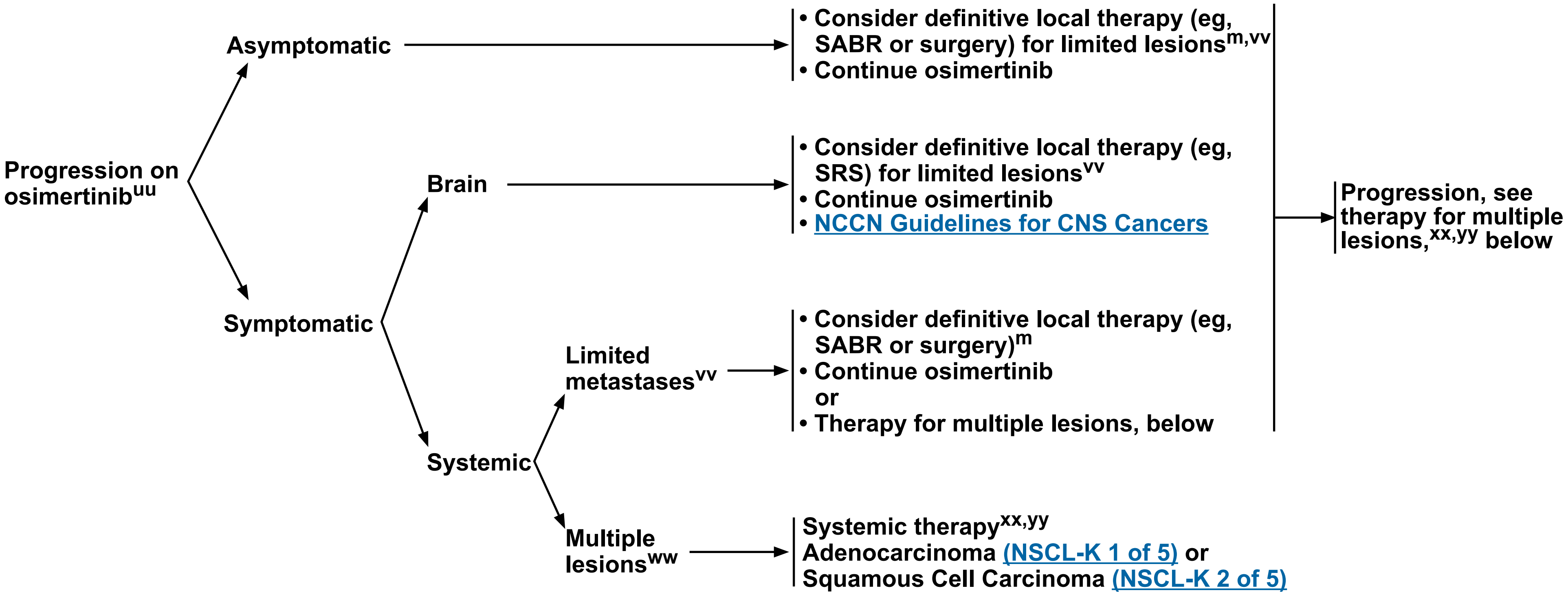
EGFR EXON 19 DELETION OR *L858R* MUTATIONS[mm]

SUBSEQUENT THERAPY[pp]



Progression on osimertinib[uu]

Asymptomatic
- **Consider definitive local therapy (eg, SABR or surgery) for limited lesions[m,vv]**
- **Continue osimertinib**

Symptomatic

Brain
- **Consider definitive local therapy (eg, SRS) for limited lesions[vv]**
- **Continue osimertinib**
- **NCCN Guidelines for CNS Cancers**

Systemic

Limited metastases[vv]
- **Consider definitive local therapy (eg, SABR or surgery)[m]**
- **Continue osimertinib**

or
- **Therapy for multiple lesions, below**

Progression, see therapy for multiple lesions,[xx,yy] below

Multiple lesions[ww]

Systemic therapy[xx,yy]
Adenocarcinoma (NSCL-K 1 of 5) or
Squamous Cell Carcinoma (NSCL-K 2 of 5)

[m] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[vv] Limited number is undefined but clinical trials have included 3 to 5 metastases.
[ww] Consider a biopsy at time of progression to rule out SCLC transformation and evaluate mechanisms of resistance. NCCN Guidelines for Small Cell Lung Cancer.
[xx] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
[yy] 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 exon 19* deletion or *L858R, ALK*+ NSCLC.

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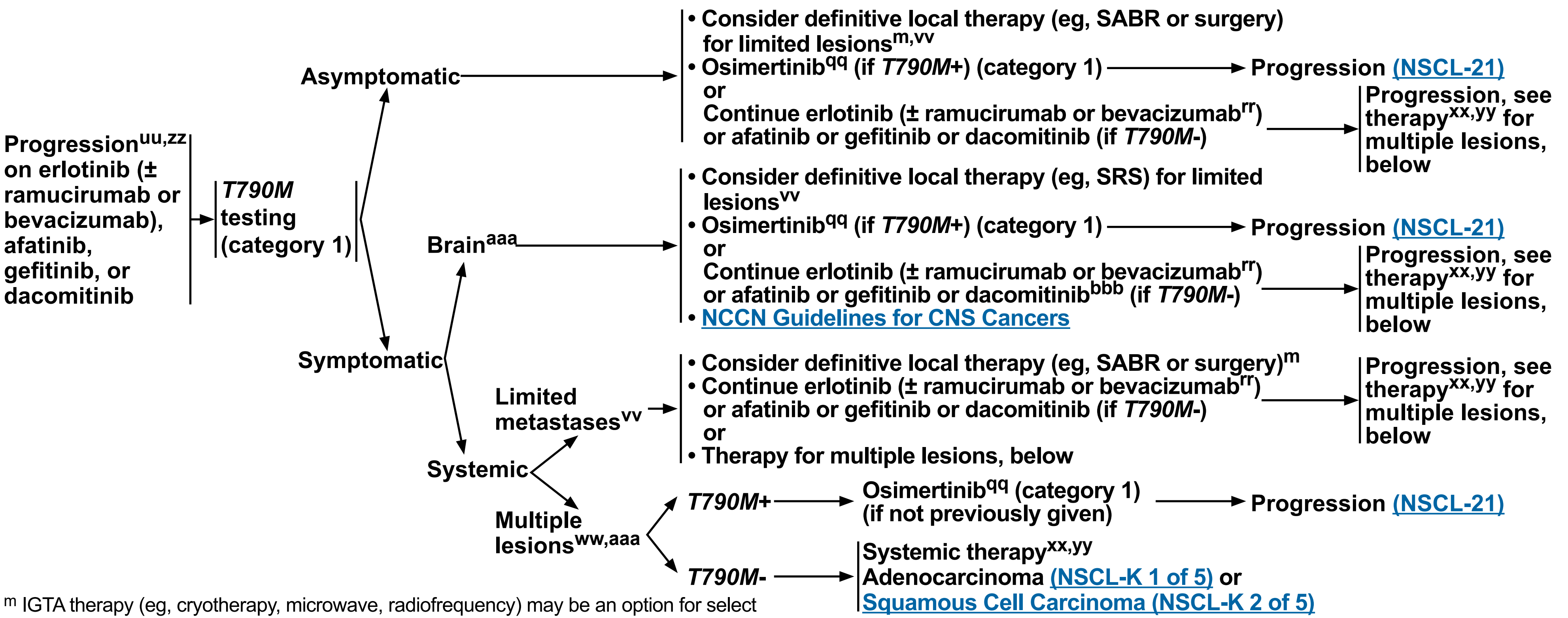
EGFR EXON 19 DELETION OR *L858R* MUTATIONS[mm]

SUBSEQUENT THERAPY[pp]



Progression[uu,zz] on erlotinib (± ramucirumab or bevacizumab), afatinib, gefitinib, or dacomitinib → ***T790M* testing (category 1)**

Asymptomatic →
- **Consider definitive local therapy (eg, SABR or surgery) for limited lesions[m,vv]**
- **Osimertinib[qq] (if *T790M+*) (category 1)** → **Progression (NSCL-21)**

or

Continue erlotinib (± ramucirumab or bevacizumab[rr]) or afatinib or gefitinib or dacomitinib (if *T790M-*) → **Progression, see therapy[xx,yy] for multiple lesions, below**

Symptomatic → **Brain[aaa]** →
- **Consider definitive local therapy (eg, SRS) for limited lesions[vv]**
- **Osimertinib[qq] (if *T790M+*) (category 1)** → **Progression (NSCL-21)**

or

Continue erlotinib (± ramucirumab or bevacizumab[rr]) or afatinib or gefitinib or dacomitinib[bbb] (if *T790M-*) → **Progression, see therapy[xx,yy] for multiple lesions, below**
- **NCCN Guidelines for CNS Cancers**

Symptomatic → **Systemic** → **Limited metastases[vv]** →
- **Consider definitive local therapy (eg, SABR or surgery)[m]**
- **Continue erlotinib (± ramucirumab or bevacizumab[rr]) or afatinib or gefitinib or dacomitinib (if *T790M-*)** → **Progression, see therapy[xx,yy] for multiple lesions, below**

or
- **Therapy for multiple lesions, below**

Systemic → **Multiple lesions[ww,aaa]** →

T790M+ → **Osimertinib[qq] (category 1) (if not previously given)** → **Progression (NSCL-21)**

T790M- → **Systemic therapy[xx,yy]**
Adenocarcinoma (NSCL-K 1 of 5) or
Squamous Cell Carcinoma (NSCL-K 2 of 5)

---

[m] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[qq] For performance status 0–4.

[rr] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis.

[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

[vv] Limited number is undefined but clinical trials have included 3 to 5 metastases.

[ww] Consider a biopsy at time of progression to rule out SCLC transformation and evaluate mechanisms of resistance. NCCN Guidelines for Small Cell Lung Cancer.

[xx] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

[yy] 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 exon 19* deletion or *L858R, ALK+* NSCLC.

[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression, for the *T790M* mutation and other genomic resistance mechanisms. 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.

[aaa] Consider osimertinib (regardless of *T790M* status) for progressive CNS disease or leptomeningeal disease. In the Bloom study, osimertinib was used at 160 mg for patients with leptomeningeal disease.

[bbb] 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.

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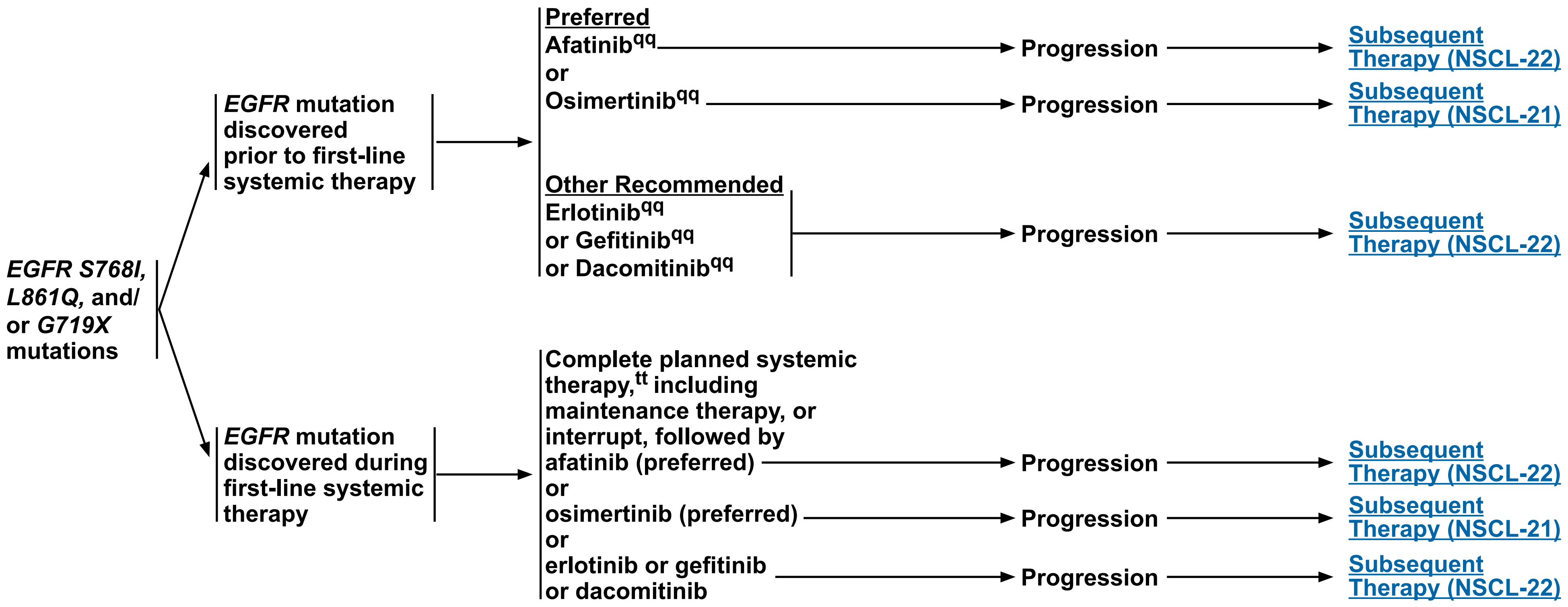
EGFR S768I, L861Q, and/or *G719X* MUTATIONS[mm]

FIRST-LINE THERAPY[pp]



***EGFR S768I, L861Q,* and/or *G719X* mutations**

- ***EGFR* mutation discovered prior to first-line systemic therapy**
  - **Preferred**
    - **Afatinib[qq]** → **Progression** → **Subsequent Therapy (NSCL-22)**
    - **or**
    - **Osimertinib[qq]** → **Progression** → **Subsequent Therapy (NSCL-21)**
  - **Other Recommended**
    - **Erlotinib[qq]**
    - **or Gefitinib[qq]**
    - **or Dacomitinib[qq]** → **Progression** → **Subsequent Therapy (NSCL-22)**
- ***EGFR* mutation discovered during first-line systemic therapy**
  - **Complete planned systemic therapy,[tt] including maintenance therapy, or interrupt, followed by**
    - **afatinib (preferred)** → **Progression** → **Subsequent Therapy (NSCL-22)**
    - **or**
    - **osimertinib (preferred)** → **Progression** → **Subsequent Therapy (NSCL-21)**
    - **or**
    - **erlotinib or gefitinib or dacomitinib** → **Progression** → **Subsequent Therapy (NSCL-22)**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[qq] For performance status 0–4.

[tt] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516.

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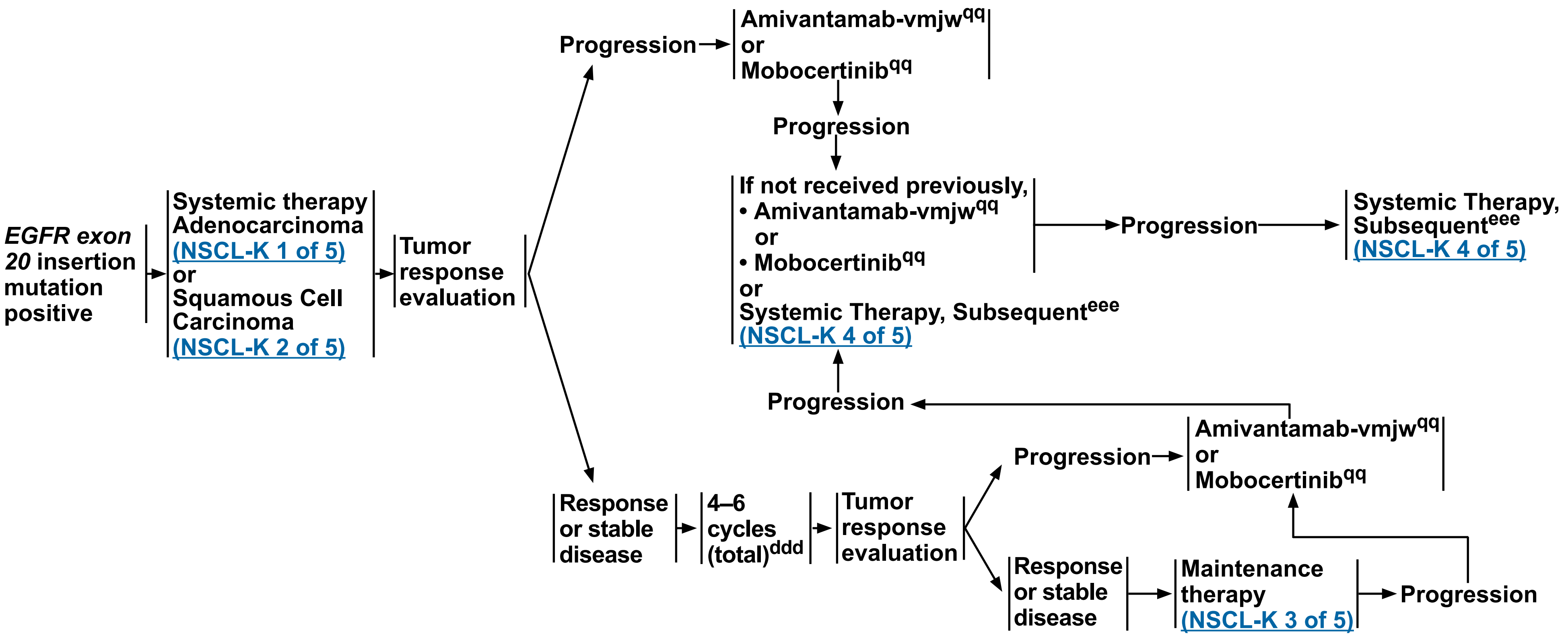
EGFR EXON 20 INSERTION MUTATION POSITIVE[mm]

FIRST-LINE THERAPY[ccc]

SUBSEQUENT THERAPY[pp]



EGFR exon 20 insertion mutation positive → **Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)** → **Tumor response evaluation**

- **Progression** → **Amivantamab-vmjw[qq] or Mobocertinib[qq]** → **Progression** → **If not received previously, • Amivantamab-vmjw[qq] or • Mobocertinib[qq] or Systemic Therapy, Subsequent[eee] (NSCL-K 4 of 5)** → **Progression** → **Systemic Therapy, Subsequent[eee] (NSCL-K 4 of 5)**
- **Response or stable disease** → **4–6 cycles (total)[ddd]** → **Tumor response evaluation**
  - **Progression** → **Amivantamab-vmjw[qq] or Mobocertinib[qq]** → **Progression** → **If not received previously, • Amivantamab-vmjw[qq] or • Mobocertinib[qq] or Systemic Therapy, Subsequent[eee] (NSCL-K 4 of 5)**
  - **Response or stable disease** → **Maintenance therapy (NSCL-K 3 of 5)** → **Progression** → **Amivantamab-vmjw[qq] or Mobocertinib[qq]**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[ccc] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[ddd] In general, 4 cycles of initial systemic therapy (ie, with carboplatin or cisplatin) are administered prior to maintenance therapy. However, if patient is tolerating therapy well, consideration can be given to continue to 6 cycles.
[eee] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

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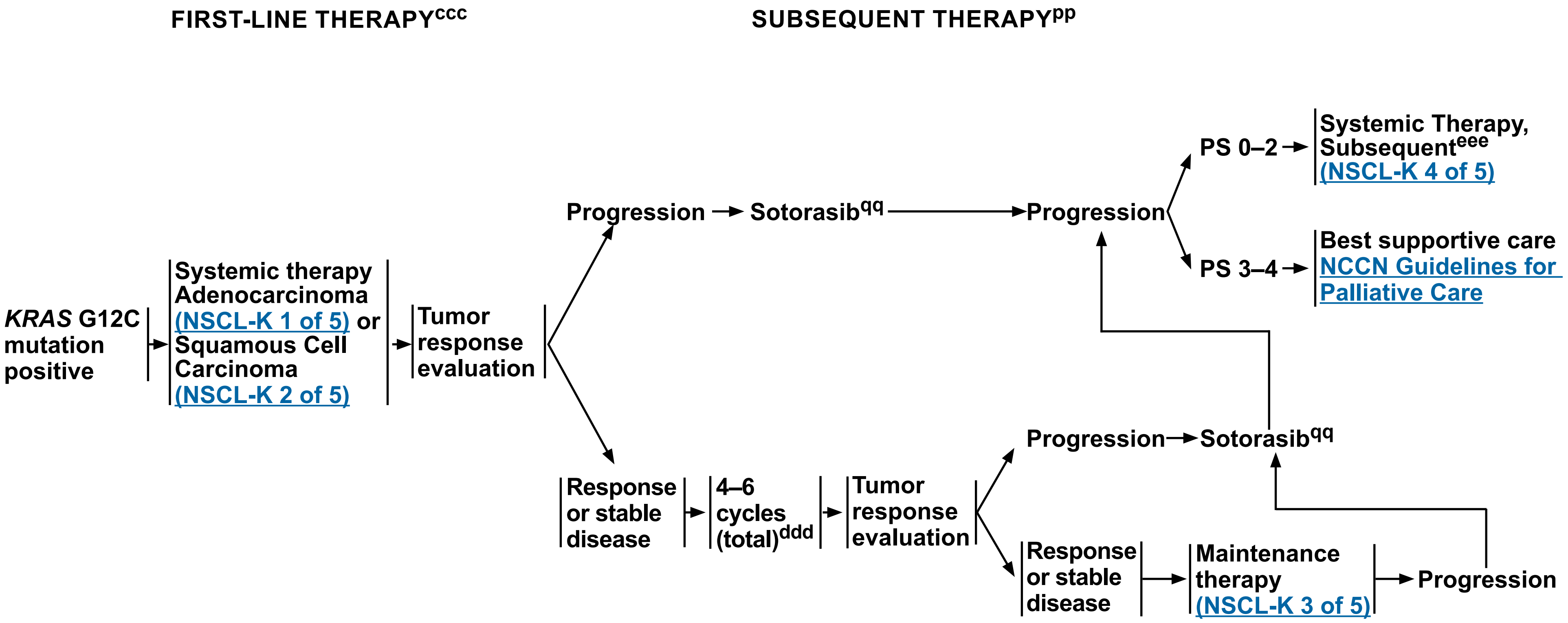
KRAS G12C MUTATION POSITIVE[mm]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[qq] For performance status 0–4.

[ccc] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.

[ddd] In general, 4 cycles of initial systemic therapy (ie, with carboplatin or cisplatin) are administered prior to maintenance therapy. However, if patient is tolerating therapy well, consideration can be given to continue to 6 cycles.

[eee] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

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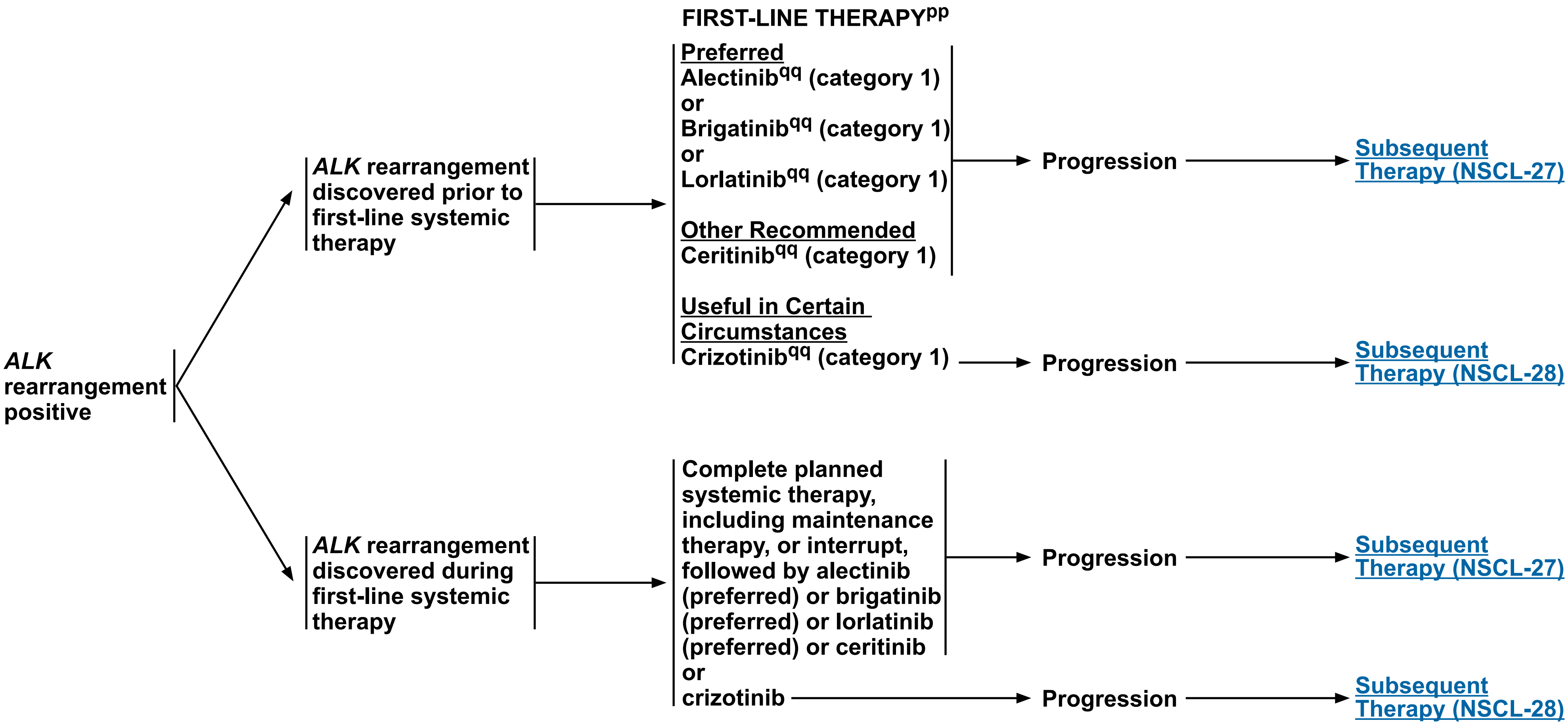
ALK REARRANGEMENT POSITIVE[mm]



ALK rearrangement positive

ALK rearrangement discovered prior to first-line systemic therapy

FIRST-LINE THERAPY[pp]

Preferred
- Alectinib[qq] (category 1)
or
- Brigatinib[qq] (category 1)
or
- Lorlatinib[qq] (category 1)

Progression → Subsequent Therapy (NSCL-27)

Other Recommended
- Ceritinib[qq] (category 1)

Useful in Certain Circumstances
- Crizotinib[qq] (category 1) → Progression → Subsequent Therapy (NSCL-28)

ALK rearrangement discovered during first-line systemic therapy

Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by alectinib (preferred) or brigatinib (preferred) or lorlatinib (preferred) or ceritinib → Progression → Subsequent Therapy (NSCL-27)

or

crizotinib → Progression → Subsequent Therapy (NSCL-28)

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[qq] For performance status 0–4.

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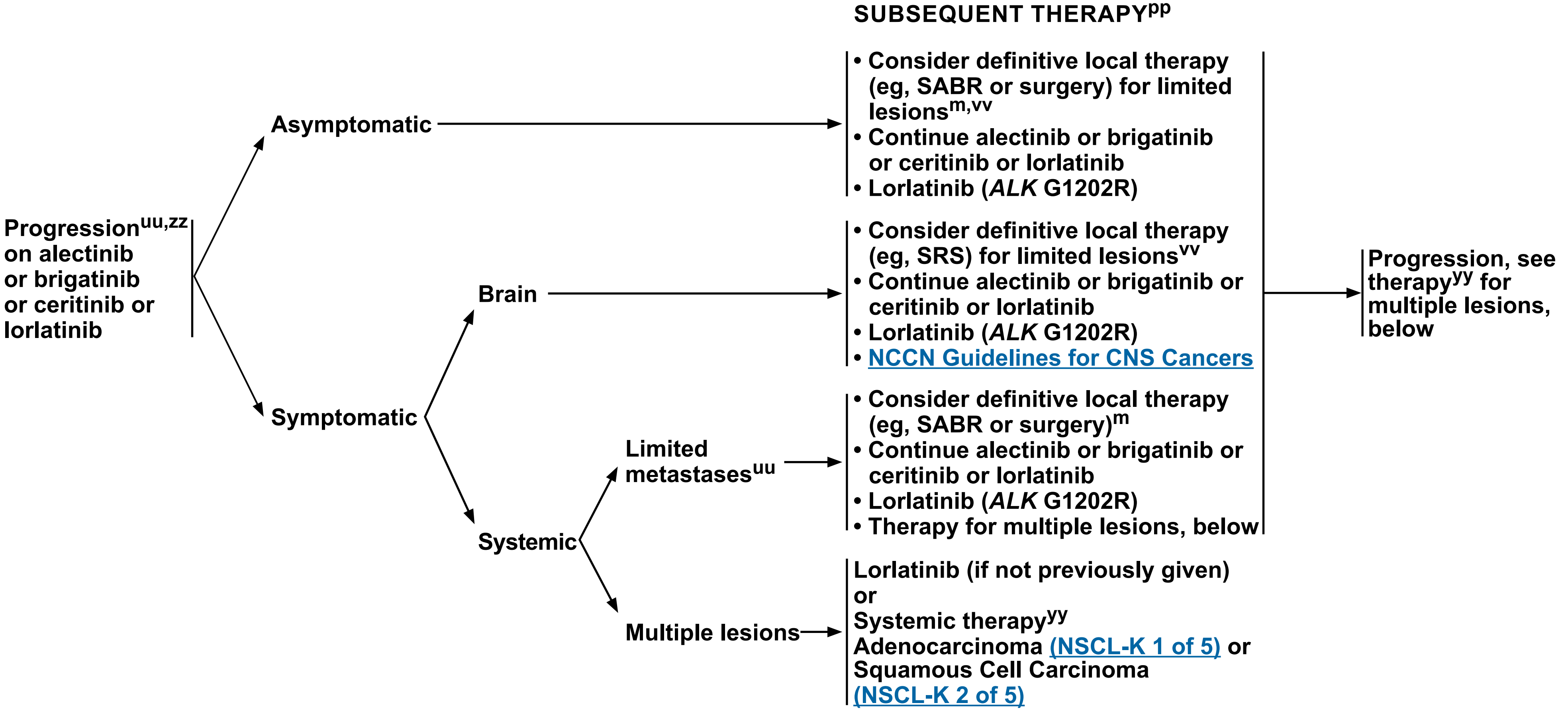
ALK REARRANGEMENT POSITIVE[mm]



SUBSEQUENT THERAPY[pp]

Progression[uu,zz] on alectinib or brigatinib or ceritinib or lorlatinib

- **Asymptomatic** →
  - Consider definitive local therapy (eg, SABR or surgery) for limited lesions[m,vv]
  - Continue alectinib or brigatinib or ceritinib or lorlatinib
  - Lorlatinib (*ALK* G1202R)
- **Symptomatic**
  - **Brain** →
    - Consider definitive local therapy (eg, SRS) for limited lesions[vv]
    - Continue alectinib or brigatinib or ceritinib or lorlatinib
    - Lorlatinib (*ALK* G1202R)
    - NCCN Guidelines for CNS Cancers
  - **Systemic**
    - **Limited metastases[uu]** →
      - Consider definitive local therapy (eg, SABR or surgery)[m]
      - Continue alectinib or brigatinib or ceritinib or lorlatinib
      - Lorlatinib (*ALK* G1202R)
      - Therapy for multiple lesions, below
    - **Multiple lesions** → Lorlatinib (if not previously given) or Systemic therapy[yy] Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)

Asymptomatic, Brain and Limited metastases therapy → **Progression, see therapy[yy] for multiple lesions, below**

---

[m] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

[vv] Limited number is undefined but clinical trials have included 3 to 5 metastases.

[yy] 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 exon 19* deletion *or L858R, ALK*+ NSCLC.

[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. 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.

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[mm]

Progression on crizotinib[uu,zz,fff]

- **Asymptomatic** → **SUBSEQUENT THERAPY[pp]**
  - Consider definitive local therapy (eg, SABR or surgery) for limited lesions[m,vv]
  - Continue crizotinib
    or
    Alectinib[qq] or brigatinib[qq] or ceritinib[qq] or lorlatinib[qq]
- **Symptomatic**
  - **Brain** →
    - Consider definitive local therapy (eg, SRS) for limited lesions[vv]
    - Alectinib[qq] or brigatinib[qq] or ceritinib[qq] or lorlatinib[qq]
    - NCCN Guidelines for CNS Cancers
  - **Systemic**
    - **Limited metastases[vv]** →
      - Consider definitive local therapy (eg, SABR or surgery)[m]
      - Continue crizotinib
      - Therapy for multiple lesions, below
    - **Multiple lesions** →
      - Alectinib[qq] or brigatinib[qq] or ceritinib[qq] or lorlatinib[qq]
        or
      - Systemic therapy[yy] Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)

→ **Progression, lorlatinib (if not previously given)**
or
Systemic therapy[yy]
Adenocarcinoma (NSCL-K 1 of 5)
or
Squamous Cell Carcinoma (NSCL-K 2 of 5)

---

[m] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[qq] For performance status 0–4.

[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

[vv] Limited number is undefined but clinical trials have included 3 to 5 metastases.

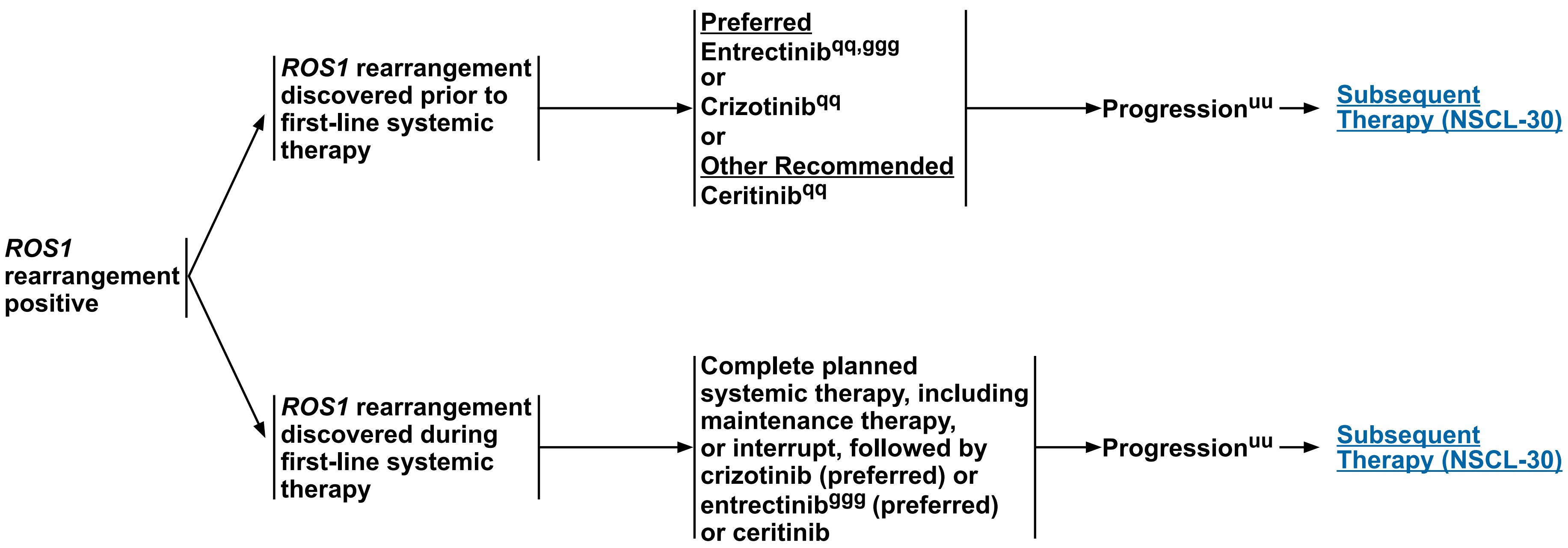
[yy] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR exon 19 deletion or L858R*, *ALK*+ NSCLC.

[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. 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.

[fff] Patients who are intolerant to crizotinib may be switched to ceritinib, alectinib, brigatinib, or lorlatinib.

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[mm]



FIRST-LINE THERAPY[pp]

SUBSEQUENT THERAPY[pp]

***ROS1* rearrangement positive**

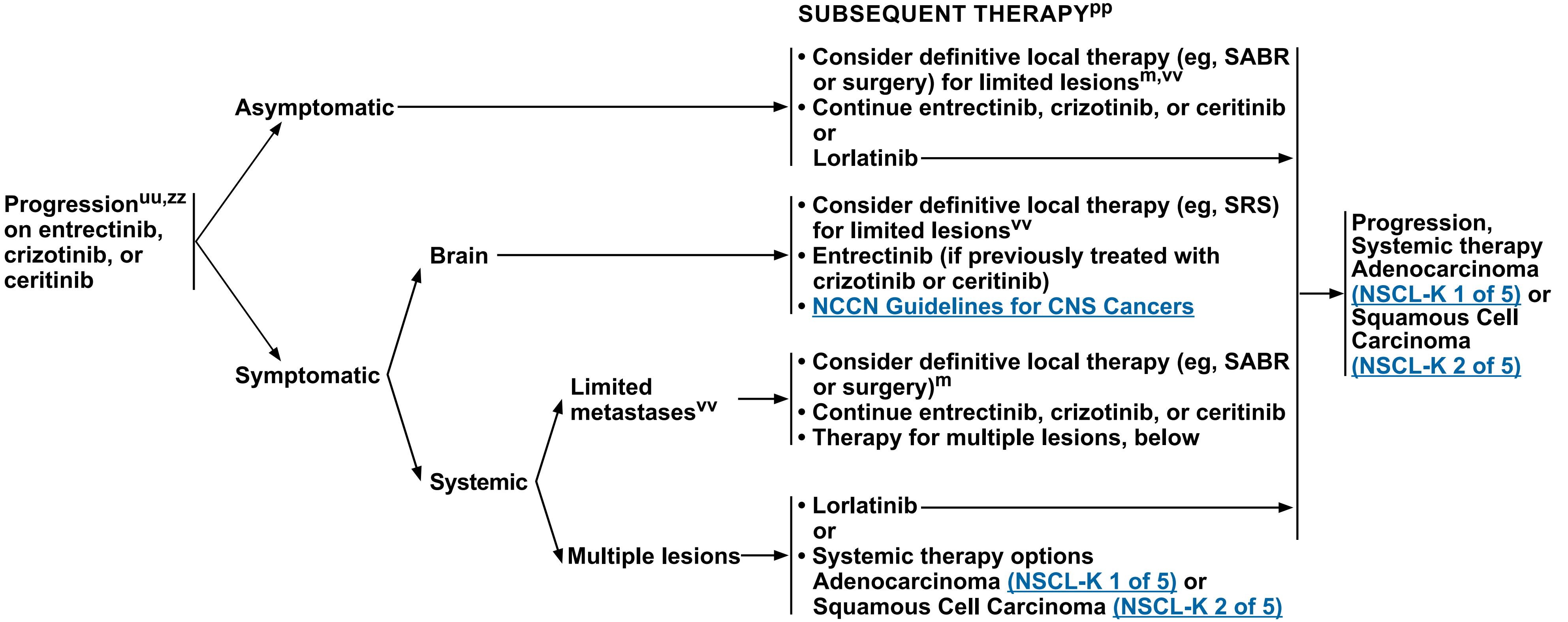
***ROS1* rearrangement discovered prior to first-line systemic therapy** → **Preferred**
Entrectinib[qq,ggg]
or
Crizotinib[qq]
or
Other Recommended
Ceritinib[qq] → **Progression[uu]** → **Subsequent Therapy (NSCL-30)**

***ROS1* rearrangement discovered during first-line systemic therapy** → **Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by crizotinib (preferred) or entrectinib[ggg] (preferred) or ceritinib** → **Progression[uu]** → **Subsequent Therapy (NSCL-30)**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[ggg] Entrectinib may be better for patients with brain metastases.

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[mm]



SUBSEQUENT THERAPY[pp]

Progression[uu,zz] on entrectinib, crizotinib, or ceritinib

Asymptomatic →
- **Consider definitive local therapy (eg, SABR or surgery) for limited lesions[m,vv]**
- **Continue entrectinib, crizotinib, or ceritinib**
  or
  Lorlatinib →

Symptomatic

Brain →
- **Consider definitive local therapy (eg, SRS) for limited lesions[vv]**
- **Entrectinib (if previously treated with crizotinib or ceritinib)**
- **NCCN Guidelines for CNS Cancers**

Systemic

Limited metastases[vv] →
- **Consider definitive local therapy (eg, SABR or surgery)[m]**
- **Continue entrectinib, crizotinib, or ceritinib**
- **Therapy for multiple lesions, below**

Multiple lesions →
- **Lorlatinib** →
  or
- **Systemic therapy options**
  Adenocarcinoma (NSCL-K 1 of 5) or
  Squamous Cell Carcinoma (NSCL-K 2 of 5)

→ **Progression, Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)**

---

[m] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

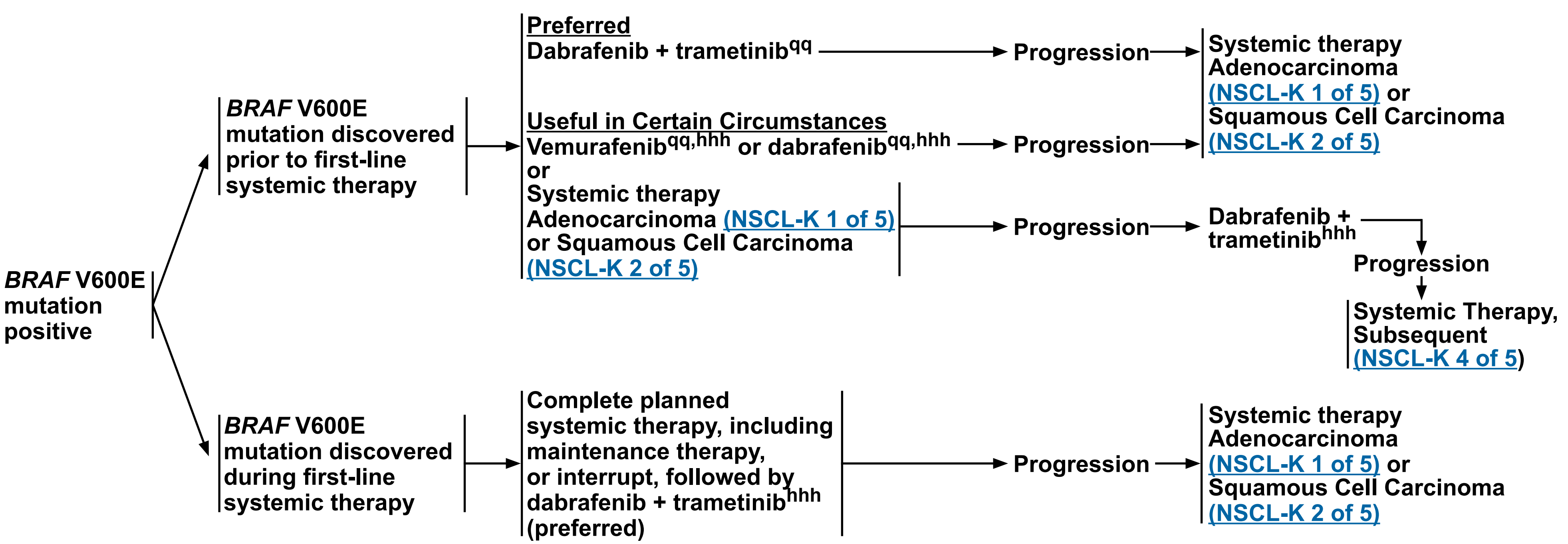
[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

[vv] Limited number is undefined but clinical trials have included 3 to 5 metastases.

[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. 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.

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[mm]



FIRST-LINE THERAPY[pp]

SUBSEQUENT THERAPY[pp]

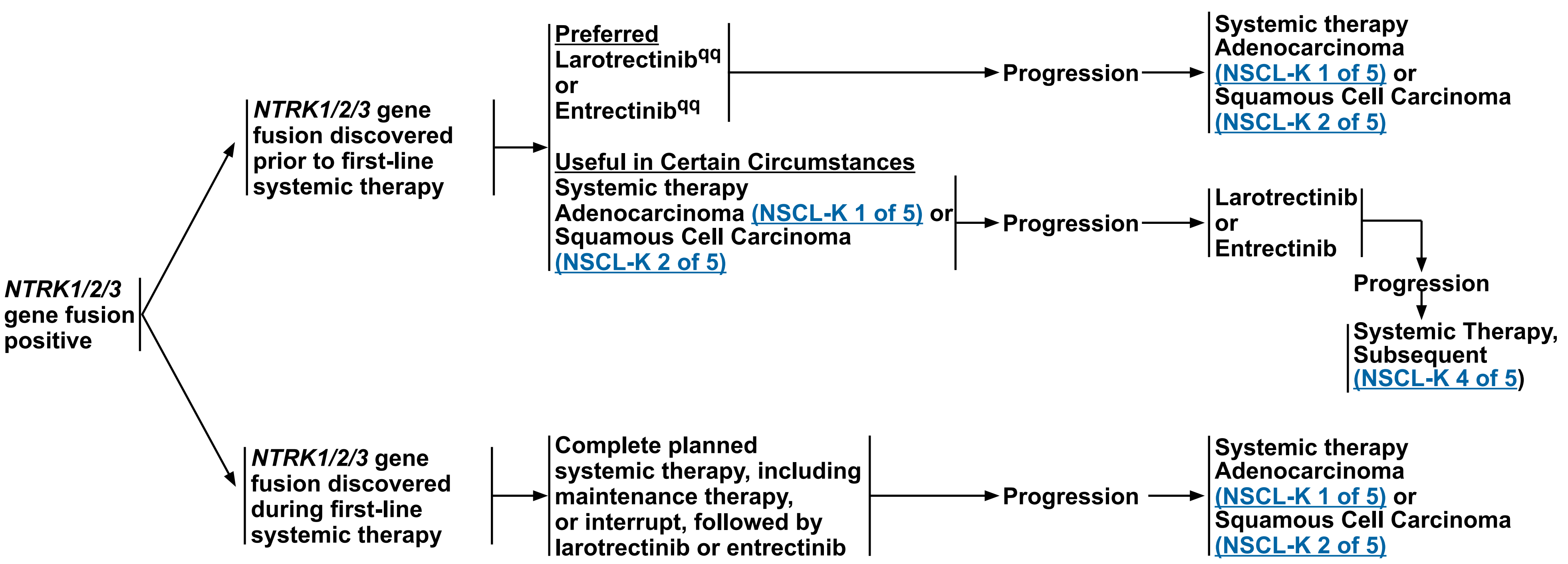
BRAF V600E mutation positive

- **_BRAF_ V600E mutation discovered prior to first-line systemic therapy**
  - **Preferred**
    - **Dabrafenib + trametinib[qq]** → **Progression** → **Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)**
  - **Useful in Certain Circumstances**
    - **Vemurafenib[qq,hhh] or dabrafenib[qq,hhh]** → **Progression** → **Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)**
    - **or**
    - **Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)** → **Progression** → **Dabrafenib + trametinib[hhh]** → **Progression** → **Systemic Therapy, Subsequent (NSCL-K 4 of 5)**
- **_BRAF_ V600E mutation discovered during first-line systemic therapy** → **Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by dabrafenib + trametinib[hhh] (preferred)** → **Progression** → **Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[hhh] 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[mm]



FIRST-LINE THERAPY[pp]

SUBSEQUENT THERAPY[pp]

***NTRK1/2/3* gene fusion positive**

***NTRK1/2/3* gene fusion discovered prior to first-line systemic therapy** → **Preferred**: Larotrectinib[qq] or Entrectinib[qq] → **Progression** → **Systemic therapy**: Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)

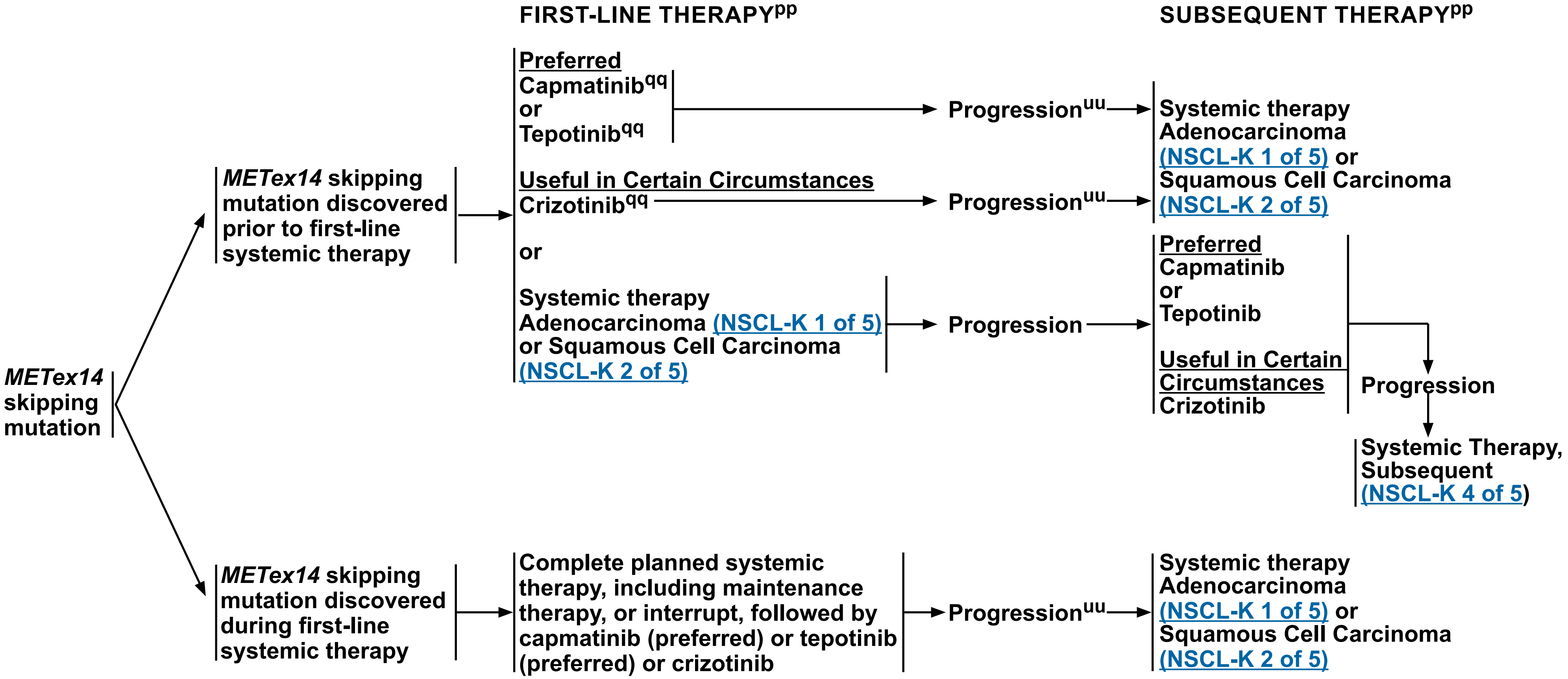
Useful in Certain Circumstances: Systemic therapy: Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5) → **Progression** → **Larotrectinib or Entrectinib** → **Progression** → **Systemic Therapy, Subsequent (NSCL-K 4 of 5)**

***NTRK1/2/3* gene fusion discovered during first-line systemic therapy** → **Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by larotrectinib or entrectinib** → **Progression** → **Systemic therapy**: Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] 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.

METex14 SKIPPING MUTATION[mm]



FIRST-LINE THERAPY[pp]

SUBSEQUENT THERAPY[pp]

***METex14* skipping mutation**

→ *METex14* skipping mutation discovered prior to first-line systemic therapy

- **Preferred**
  Capmatinib[qq] or Tepotinib[qq] → **Progression[uu]** → **Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)**
- **Useful in Certain Circumstances**
  Crizotinib[qq] → **Progression[uu]** → **Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)**

or

- **Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)** → **Progression** → **Preferred**
  Capmatinib or Tepotinib
  Useful in Certain Circumstances
  Crizotinib → **Progression** → **Systemic Therapy, Subsequent (NSCL-K 4 of 5)**

→ *METex14* skipping mutation discovered during first-line systemic therapy → **Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by capmatinib (preferred) or tepotinib (preferred) or crizotinib** → **Progression[uu]** → **Systemic therapy Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

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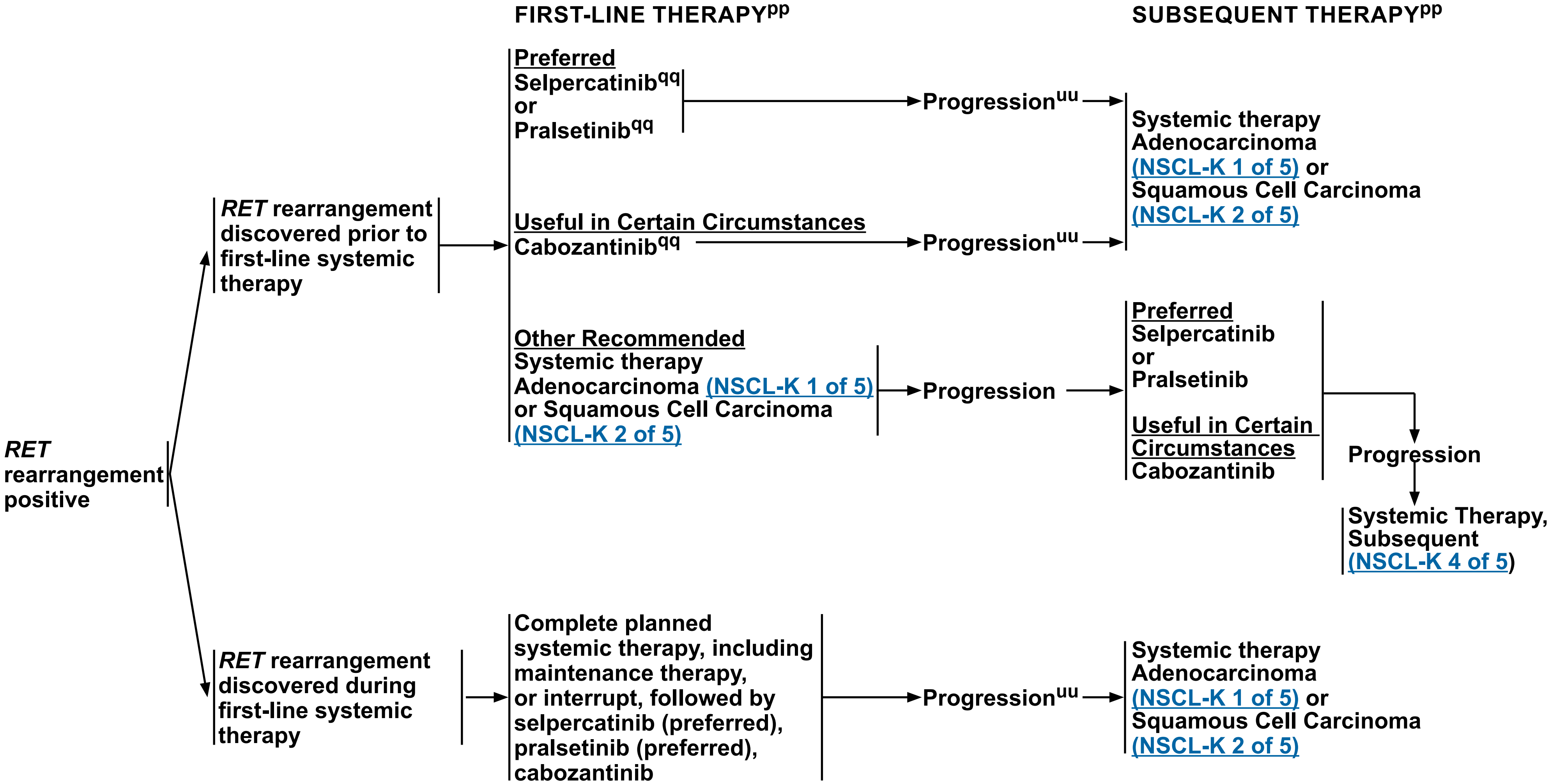
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

RET REARRANGEMENT POSITIVE[mm]



FIRST-LINE THERAPY[pp]

SUBSEQUENT THERAPY[pp]

***RET* rearrangement positive**

***RET* rearrangement discovered prior to first-line systemic therapy**

Preferred
Selpercatinib[qq]
or
Pralsetinib[qq]
→ **Progression[uu]** →

Useful in Certain Circumstances
Cabozantinib[qq]
→ **Progression[uu]** →

Systemic therapy
Adenocarcinoma (NSCL-K 1 of 5) or
Squamous Cell Carcinoma (NSCL-K 2 of 5)

Other Recommended
Systemic therapy
Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)
→ **Progression** →

Preferred
Selpercatinib
or
Pralsetinib

Useful in Certain Circumstances
Cabozantinib

→ **Progression** →

Systemic Therapy, Subsequent (NSCL-K 4 of 5)

***RET* rearrangement discovered during first-line systemic therapy**
→ **Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by selpercatinib (preferred), pralsetinib (preferred), cabozantinib**
→ **Progression[uu]** →

Systemic therapy
Adenocarcinoma (NSCL-K 1 of 5) or
Squamous Cell Carcinoma (NSCL-K 2 of 5)

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

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 Index
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Discussion

PD-L1 POSITIVE (≥50%)[mm] AND NEGATIVE FOR ACTIONABLE MOLECULAR BIOMARKERS[iii]

See PD-L1 expression positive (≥1%–49%) NSCL-36

FIRST-LINE THERAPY[pp,jjj]

PS 0–2

Adenocarcinoma, large cell, NSCLC NOS →

Preferred
- **Pembrolizumab (category 1) or**
- **(Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1) or**
- **Atezolizumab (category 1) or**
- **Cemiplimab-rwlc (category 1)**

Other Recommended
- **Carboplatin + paclitaxel + bevacizumab[rr,ss] + atezolizumab (category 1) or**
- **Carboplatin + albumin-bound paclitaxel + atezolizumab or**
- **Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)**

Useful in Certain Circumstances
- **Nivolumab + ipilimumab (category 1)**

→ **Response or stable disease** →

Continuation maintenance[pp]
- **Pembrolizumab (category 1)[kkk]**
- **Pembrolizumab + pemetrexed (category 1)[lll]**
- **Atezolizumab and bevacizumab (category 1)[mmm]**
- **Atezolizumab[nnn]**
- **Nivolumab + ipilimumab (category 1)[ooo]**
- **Cemiplimab-rwlc (category 1)**

→ **Progression** → **Systemic Therapy[ppp] (NSCL-K 1 of 5) or Systemic Therapy, Subsequent[ppp] (NSCL-K 4 of 5)**

Squamous cell carcinoma →

Preferred
- **Pembrolizumab (category 1) or**
- **Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1) or**
- **Atezolizumab (category 1) or**
- **Cemiplimab-rwlc (category 1)**

Other Recommended
- **Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)**

Useful in Certain Circumstances
- **Nivolumab + ipilimumab (category 1)**

→ **Response or stable disease** →

Continuation maintenance[pp]
- **Pembrolizumab (category 1)[kkk,qqq]**
- **Atezolizumab[nnn]**
- **Nivolumab + ipilimumab (category 1)[ooo]**
- **Cemiplimab-rwlc (category 1)**

→ **Progression** → **Systemic Therapy[ppp] (NSCL-K 1 of 5) or Systemic Therapy, Subsequent[ppp] (NSCL-K 4 of 5)**

PS 3–4 → **Best supportive care NCCN Guidelines for Palliative Care**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[rr] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis.

[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

[iii] 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-K 1 of 5 (adenocarcinoma) or NSCL-K 2 of 5 (squamous cell carcinoma).

[jjj] For patients who require an urgent start to therapy but molecular testing is pending, consider holding immunotherapy for one cycle, unless confirmed that no driver mutations are present.

[kkk] If pembrolizumab monotherapy given.

[lll] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.

[mmm] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.

[nnn] If atezolizumab/carboplatin/albumin-bound paclitaxel or atezolizumab given (category 1 following atezolizumab alone).

[ooo] If nivolumab + ipilimumab ± chemotherapy given.

[ppp] 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."

[qqq] If pembrolizumab/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.

PD-L1 POSITIVE (≥1%–49%)[mm] AND NEGATIVE FOR ACTIONABLE MOLECULAR BIOMARKERS[iii]

PD-L1 expression positive (≥50%) NSCL-35

FIRST-LINE THERAPY[pp,jjj]

PS 0–2

- **Adenocarcinoma, large cell, NSCLC NOS** →
  - Preferred
    - (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
  - Other Recommended
    - Carboplatin + paclitaxel + bevacizumab[rr,ss] + atezolizumab (category 1) or
    - Carboplatin + albumin-bound paclitaxel + atezolizumab or
    - Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)
  - Useful in Certain Circumstances
    - Nivolumab + ipilimumab (category 1) or
    - Pembrolizumab (category 2B)[rrr]
  - **Response or stable disease** → Continuation maintenance[pp]
    - Pembrolizumab (category 1)[kkk]
    - Pembrolizumab + pemetrexed (category 1)[lll]
    - Atezolizumab and bevacizumab (category 1)[mmm]
    - Atezolizumab[nnn]
    - Nivolumab + ipilimumab (category 1)[ooo]
  - **Progression** → Systemic Therapy[ppp] (NSCL-K 1 of 5) or Systemic Therapy, Subsequent[ppp] (NSCL-K 4 of 5)
- **Squamous cell carcinoma** →
  - Preferred
    - Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)
  - Other Recommended
    - Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)
  - Useful in Certain Circumstances
    - Nivolumab + ipilimumab (category 1) or
    - Pembrolizumab (category 2B)[rrr]
  - **Response or stable disease** → Continuation maintenance[pp]
    - Pembrolizumab[kkk,qqq]
    - Nivolumab + ipilimumab (category 1)[ooo]
  - **Progression** → Systemic Therapy[ppp] (NSCL-K 1 of 5) or Systemic Therapy, Subsequent[ppp] (NSCL-K 4 of 5)

PS 3–4 → Best supportive care
NCCN Guidelines for Palliative Care

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[rr] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis.

[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

[iii] 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-K 1 of 5 (adenocarcinoma) or NSCL-K 2 of 5 (squamous cell carcinoma).

[jjj] For patients who require an urgent start to therapy but molecular testing is pending, consider holding immunotherapy for one cycle, unless confirmed that no driver mutations are present.

[kkk] If pembrolizumab monotherapy given.

[lll] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.

[mmm] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.

[nnn] If atezolizumab/carboplatin/albumin-bound paclitaxel given.

[ooo] If nivolumab + ipilimumab ± chemotherapy given.

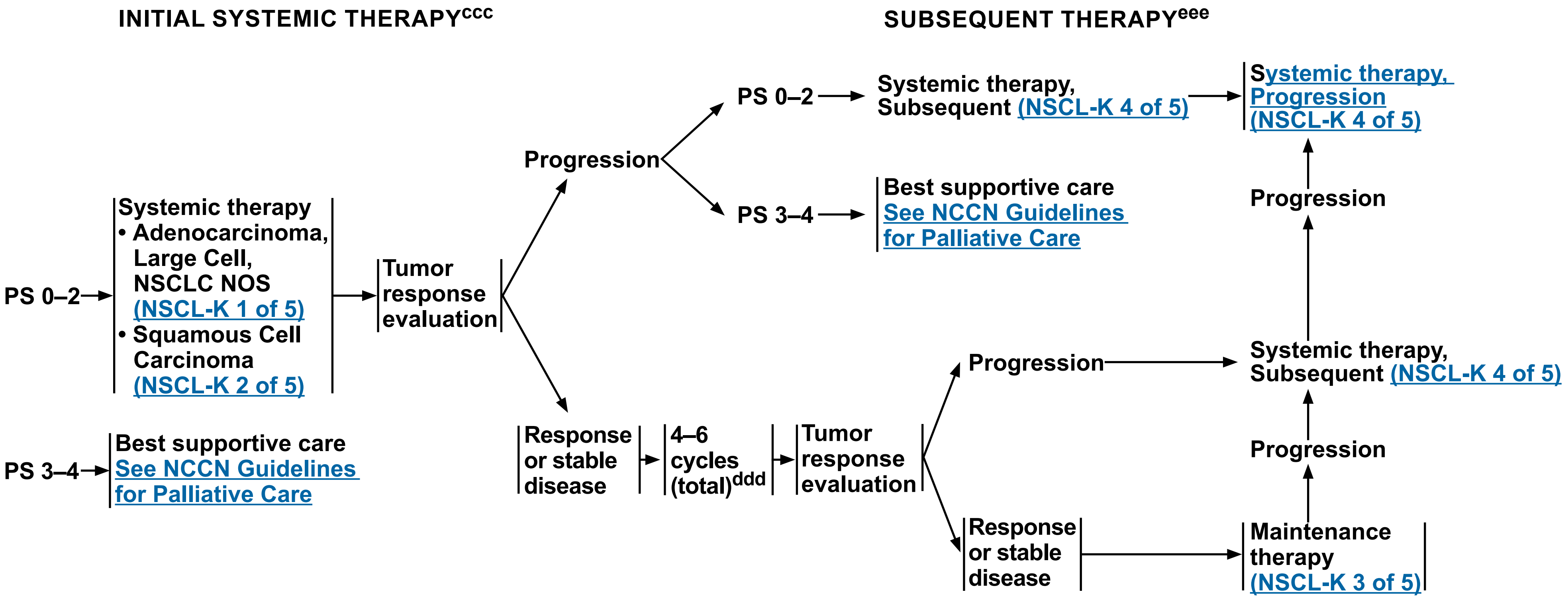
[ppp] If patient has not received platinum-doublet chemotherapy, refer to "systemic therapy." If patient received platinum chemotherapy and anti-PD-1/PD-L1, refer to “subsequent therapy.”

[qqq] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.

[rrr] Pembrolizumab monotherapy can be considered in PD-L1 1%–49%, in patients with poor PS or other contraindications to combination 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.

PD-L1 <1% AND NEGATIVE FOR ACTIONABLE MOLECULAR BIOMARKERS



INITIAL SYSTEMIC THERAPY[ccc]

PS 0–2 → **Systemic therapy**
- **Adenocarcinoma, Large Cell, NSCLC NOS (NSCL-K 1 of 5)**
- **Squamous Cell Carcinoma (NSCL-K 2 of 5)**

→ **Tumor response evaluation**
- **Progression**
  - **PS 0–2** → **Systemic therapy, Subsequent (NSCL-K 4 of 5)** → **Systemic therapy, Progression (NSCL-K 4 of 5)**
  - **PS 3–4** → **Best supportive care See NCCN Guidelines for Palliative Care**
- **Response or stable disease** → **4–6 cycles (total)[ddd]** → **Tumor response evaluation**
  - **Progression** → **Systemic therapy, Subsequent (NSCL-K 4 of 5)** → **Progression** → **Systemic therapy, Progression (NSCL-K 4 of 5)**
  - **Response or stable disease** → **Maintenance therapy (NSCL-K 3 of 5)** → **Progression** → **Systemic therapy, Subsequent (NSCL-K 4 of 5)**

PS 3–4 → **Best supportive care See NCCN Guidelines for Palliative Care**

SUBSEQUENT THERAPY[eee]

[ccc] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.

[ddd] In general, 4 cycles of initial systemic therapy (ie, with carboplatin or cisplatin) are administered prior to maintenance therapy. However, if patient is tolerating therapy well, consideration can be given to continue to 6 cycles.

[eee] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

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)[1]" 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 (IHC) 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.**
    - **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 IHC 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.**

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[1] 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-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.

Continued

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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. 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.
      - Refer to College of American Pathologists Protocols for additional information.
  - 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.

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PRINCIPLES OF PATHOLOGIC REVIEW

Immunohistochemistry

- Judicious use of IHC 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, IHC 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 IHC 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.
- IHC 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.

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PRINCIPLES OF PATHOLOGIC REVIEW

Immunohistochemistry

- IHC 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, synaptophysin, and INSM1 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 and napsin A), breast carcinoma (ERα, PR, GCDFP15, mammaglobin, and GATA-3), 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.

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PRINCIPLES OF SURGICAL THERAPY

Evaluation

- Determination of resectability, surgical staging, and ***pulmonary resection should be performed by 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 therapy for 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 ≥2 cm or ≥ 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[a] ≤2 cm with at least one of the following:
    - ◊ Pure AIS histology
    - ◊ Nodule has ≥50% ground-glass appearance on CT
    - ◊ Radiologic surveillance confirms a long doubling time (≥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)

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

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[a] Peripheral is defined as the outer one third of the lung parenchyma.

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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, or high-risk factors, 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.[1] Two randomized trials evaluated the role of surgery in this population, but neither showed an overall survival benefit with the use of surgery.[2,3] 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 thoracic surgeon who has a major part of his/her practice dedicated to thoracic oncology.[4]
- 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

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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.[5]
- Patients with a single lymph node smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.[1,6,7]
- 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.[7,8]
- Neoadjuvant chemoradiotherapy is used in one-third of the NCCN Member Institutions, while neoadjuvant chemotherapy is used in the other two-thirds. Overall survival appears similar provided RT is given postoperatively, if not given preoperatively.[5,9] Neoadjuvant chemoradiotherapy is associated with higher rates of pathologic complete response and negative mediastinal lymph nodes.[10] 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.[11,12] 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.[2] 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.[13-16] 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.[17]

A questionnaire was submitted to the NCCN Member Institutions in 2021 regarding their approach to patients with N2 disease. Their responses indicate the patterns of practice when approaching this difficult clinical problem.

- All NCCN institutions treat select N2 patients with multimodality therapy that includes surgery.
- The majority of NCCN institutions prefer EBUS for initial mediastinal staging, reserving mediastinoscopy for possible restaging.
- The majority of institutions do not pathologically restage mediastinal lymph nodes after induction therapy and prior to surgery.
- All NCCN institutions consider surgery for single-station non-bulky N2 disease.
- Approximately half of the institutions consider surgery for single-station bulky disease, 39% for multi-station non-bulky disease, and 21% for multi-station bulky disease.
- Two-thirds of institutions prefer induction chemotherapy; one-third prefer chemoradiation.
- The majority require at least stable disease after induction, but do not require radiologic or pathologic response prior to surgery.
- Roughly a half would consider pneumonectomy after induction chemotherapy, but less than a quarter would consider pneumonectomy after chemoradiation.
- Approximately three-fourths would give adjuvant RT for positive residual N2 disease, but only approximately one-fourth would give RT for N2 pathologic complete response.

References

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

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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 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/consolidative or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with stage III NSCLC, with early-stage disease who are medically inoperable, who refuse surgery, or who are high-risk surgical candidates, and with 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.[1]
- 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.[2-4] In a prospective trial of definitive/consolidative 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;[5] 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).
- The interaction of strong VEGF inhibitors with prior or subsequent dose-intensive RT (SABR or definitive dose accelerated fractionation) involving the proximal bronchial tree, hilar vessels, or esophagus can lead to serious toxicity. Careful coordination of medical and radiation oncology on the therapeutic strategy is important, including the choice and sequencing of systemic agents with strong VEGF inhibitors and the dose and fractionation of radiation, especially for patients with metastatic disease.

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,[6] 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.[7] Given the potential for rapid progression of NSCLC,[8,9] 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.

Continued

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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.[10]**
- **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.[11]**
- **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.nrgoncology.org/ciro-lung**
- **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.nrgoncology.org/ciro-lung**
- **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.[12,13] Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.[14-18] 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.**

PRINCIPLES OF RADIATION THERAPY

IV. General Treatment Information

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

- SABR (also known as SBRT)[19] has achieved good primary tumor control rates and overall survival, higher than conventionally fractionated radiotherapy. Although SABR is not proven equivalent to lobectomy, some prospective series have demonstrated similar overall and cancer-specific survival.[20-30]
- 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]).
- More modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are less preferred alternatives and may be considered if referral for SABR is not feasible.[31-33]
- 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).
- Close follow-up and salvage therapy for isolated local and/or locoregional recurrence after SABR have been shown to improve overall survival in a large retrospective study.[34]

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.[35,36] 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.[35,37] 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,[38-41] while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.[42] However, particular attention should be paid to tumors abutting the bronchial tree and esophagus to avoid severe toxicity. RTOG 0813 evaluated the toxicity of 5-fraction regimens and found no high-grade toxicities at 50 Gy in 5 fractions.[43]
- 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.[43,44]
- 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.[10,45,46] All of these must be considered when interpreting or emulating regimens from prior studies.

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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.[47-50]**
- **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.[51,52] Accelerated RT regimens may be beneficial, particularly if concurrent chemotherapy would not be tolerated (ie, in a sequential or RT-only approach).[53,54]**
- **Preoperative concurrent chemotherapy/RT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)[55] NSCLC and is recommended for resectable superior sulcus tumors.[56,57] 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 disease.[58,59] The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and is controversial.[60,61]**
- **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.[62,63] Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy and concurrently with chemotherapy for positive resection margins.[64-67]**
- **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.[68]**

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.[69-73] Three randomized trials found improved survival for IFI versus ENI, possibly because it enabled dose escalation.[74-76] IFI is reasonable in order to optimize definitive dosing to the tumor and/or decrease normal tissue toxicity. [75,76]**
- **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.[77] Dose escalation is associated with better survival in non-randomized comparisons in RT alone,[78] sequential chemo/RT,[79] or concurrent chemo/RT.[80] While optimal RT dose intensification remains a valid question, a high dose of 74 Gy is not currently recommended for routine use.[81-86] A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens,[87] and RTOG 1106 found that PET-based individualized accelerated RT dose intensification potentially improved local control but not overall survival.[88]**

Continued

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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.[89] Definitive RT doses delivered as preoperative chemoRT can safely be administered and achieve promising nodal clearance and survival rates,[90-93] 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.[94] 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.[62,63,95] 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.[96]

Advanced/Metastatic NSCLC (Stage IV)

- RT is recommended for local palliation or prevention of symptoms (such as pain, bleeding, or obstruction).
- Definitive/consolidative 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.[97] Definitive RT to oligometastases (limited number is not universally defined but clinical trials have included 3–5 metastases), particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.[98,99] In two randomized phase II trials, significantly improved progression-free survival and overall survival in one trial[100,101] were found for local consolidative therapy (RT or surgery) to oligometastatic lesions versus maintenance systemic therapy or observation for patients not progressing on systemic therapy.[100-102]
- 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 CRT regimens may be used.
- See the NCCN Guidelines for Central Nervous System Cancers regarding RT for brain metastases.
- A pooled analysis of two randomized trials indicated that adding radiotherapy to a certain immune checkpoint inhibitor (anti-PD-1) significantly increased responses and clinical outcomes in patients with metastatic non-small cell lung cancer. Larger phase III randomized studies are ongoing.[103]

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.[104-107] 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.[108,109] 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.
- Single-fraction stereotactic RT of 12–16 Gy produced better control of pain response and local control of non-spine bone metastases compared to standard 30 Gy in 10 fractions in a randomized phase II trial, and may be promising for patients with longer expected survival.[110]

Continued

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Table 1. Commonly Used Abbreviations in Radiation Therapy

RT	Radiation Therapy or Radiotherapy
2D-RT	2-Dimensional RT
3D-CRT	3-Dimensional Conformal RT
4D-CT	4-Dimensional Computed Tomography
AAPM	American Association of Physicists in Medicine
ABC	Active Breathing Control
ACR	American College of Radiology
ASTRO	American Society for Radiation Oncology
BED	Biologically Effective Dose
CBCT	Cone-Beam CT
CTV*	Clinical Target Volume
ENI	Elective Nodal Irradiation
GTV*	Gross Tumor Volume

ICRU	International Commission on Radiation Units and Measurements
IFI	Involved Field Irradiation
IGRT	Image-Guided RT
IMRT	Intensity-Modulated RT
ITV*	Internal Target Volume
OAR	Organ at Risk
OBI	On-Board Imaging
PORT	Postoperative RT
PTV*	Planning Target Volume
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
RTOG	Radiation Therapy Oncology Group now part of NRG Oncology
SABR	Stereotactic Ablative RT, also known as Stereotactic Body RT (SBRT)
VMAT	Volumetric Modulated Arc Therapy

*Refer to ICRU Report 83 for detailed definitions.

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

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25–34 Gy	1	Peripheral, small
45–60 Gy	3	Peripheral tumors
48–50 Gy	4	Central or peripheral tumors <4–5 cm
50–55 Gy	5	Central or peripheral tumors
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^
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^
Great vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
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).
^For central tumor location. NS = not specified.

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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	50–54 Gy	1.8–2 Gy	5–6 weeks
• Extracapsular nodal extension or microscopic positive margins	54–60 Gy	1.8–2 Gy	6 weeks
• Gross residual tumor	60–70 Gy	2 Gy	6–7 weeks
Palliative RT			
• Obstructive disease (SVC syndrome or obstructive pneumonia)	30–45 Gy	3 Gy	2–3 weeks
• Bone metastases with soft tissue mass	20–30 Gy	4–3 Gy	1–2 weeks
• Bone metastases without soft tissue mass	8–30 Gy	8–3 Gy	1 day–2 weeks
• Brain metastases	CNS GLs*	CNS GLs*	CNS GLs*
• Symptomatic chest disease in patients with poor PS	17 Gy**	8.5 Gy**	1–2 weeks**
• Any metastasis in patients with poor PS	8–20 Gy	8–4 Gy	1 day–1 week

* NCCN Guidelines for Central Nervous System Cancers
** This regimen includes one dose per week, as the phase 3 study included day 1 & 8 treatments.

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%;[§] 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

Vxx = % of the whole OAR receiving ≥xx Gy.

[†] These constraints represent doses that generally should not be exceeded, based on a consensus survey of NCCN Member Institutions. 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.

[†] Speirs CK, et al. J Thorac Oncol 2017;12:293-301; Wang K, et al. J Clin Oncol 2017;35:1387-1394; Amini A, et al. Int J Radiat Oncol Biol Phys 2012;82:e391-398; Graham MV, et al. Int J Radiat Oncol Biol Phys 1999;45:323-329; Palma DA, et al. Int J Radiat Oncol Biol Phys 2013;85:444-450; Kamran SC, et al. JAMA Oncol 2021;7:910-914.

[§] 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).

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PRINCIPLES OF IMAGE-GUIDED THERMAL ABLATION THERAPY

General Principles

- **Interventional radiologists should actively participate in multidisciplinary discussions and meetings regarding patients with NSCLC (eg, multidisciplinary clinic and/or tumor board).**
- **Decisions about whether ablation is feasible should be performed by interventional radiologists who perform IGTA as a prominent part of their practice.**
- **IGTA includes radiofrequency ablation, microwave ablation, and cryoablation. IGTA is a form of "local therapy" or "local ablative therapy."[1]**
- **IGTA is a lung parenchymal sparing technique with at most a temporary decrement in FEV1 and DLCO, which is statistically indistinguishable from baseline after recovery.[2-6]**

Evaluation

- **IGTA may be considered for those patients who are deemed "high risk"—those with tumors that are for the most part surgically resectable but rendered medically inoperable due to comorbidities. In cases where IGTA is considered for high-risk or borderline operable patients, a multidisciplinary evaluation is recommended.**
- **IGTA has been successfully accomplished in patients considered "high risk," objectively defined with a single major and/or two or more minor criteria. Major criteria included an FEV1 or DCLO ≤50%, and minor criteria included a less depressed FEV1 or DLCO between 51%–60%, advanced age ≥75 years, pulmonary hypertension, LVEF ≤40%, resting or exercise PaO2 <55 mmHg, and pCO2 >45 mmHg.[4]**
- **If an interventional radiologist or center is uncertain about the feasibility or safety of IGTA or the use of IGTA for radiation failure, consider obtaining an additional interventional radiology opinion from a high-volume specialized center.**

Ablation

- **Each energy modality has advantages and disadvantages. Determination of energy modality to be used for ablation should take into consideration the size and location of the target tumor, risk of complication, as well as local expertise and/or operator familiarity.[7]**

Ablation for NSCLC

- **IGTA is an option for the management of NSCLC lesions <3 cm. Ablation for NSCLC lesions >3 cm may be associated with higher rates of local recurrence and complications.[8,9]**
- **There is evidence on the use of IGTA for selected patients with Stage 1A NSCLC, those who present with multiple lung cancers, or those who present with locoregional recurrence of symptomatic local thoracic disease.**
- **Like surgery, pneumothorax may occur after IGTA, particularly if multiple lesions are treated in a single session. Pneumothorax has been reported in 18.7%–45.7% of IGTA cases. Self-limited pneumothorax, not requiring chest tube placement, is an expected event and not considered a complication unless escalation of care is required. In 20.7% of IGTA cases, chest tube insertion may be required.[10]**

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SYSTEMIC THERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

Preferred (nonsquamous)
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[1]

Preferred (squamous)
- Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[2]
- Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[3]

Other Recommended
- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[4]
- Cisplatin 100 mg/m² day 1; vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5,6]
- Cisplatin 75–80 mg/m² day 1; vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1; etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[5]

Useful in Certain Circumstances

Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[7]
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[8]
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles[9]

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

Previous Adjuvant Chemotherapy or Ineligible for Platinum-Based Chemotherapy
- Osimertinib 80 mg daily[10]
  - Osimertinib for patients with completely resected stage IB–IIIA *EGFR* (*exon 19* deletion, *L858R*) NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab[11]
  - Atezolizumab for patients with completely resected stage IIB–IIIA or high risk stage IIA PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

References

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SYSTEMIC THERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY – REFERENCES

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CONCURRENT CHEMORADIATION REGIMENS

Concurrent Chemoradiation Regimens[€]

Preferred (nonsquamous)

- **Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT**[1,*,†,‡]
- **Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT**[2,3,*,†,‡] **± additional 4 cycles of pemetrexed 500 mg/m²**[†,§]
- **Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT**[4,*,†,‡] **± additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6**[†,§]
- **Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5 and 29–33; concurrent thoracic RT**[5,6,*,†,‡]

Preferred (squamous)

- **Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT**[6,*,†,‡] **± additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6**[†,§]
- **Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5 and 29–33; concurrent thoracic RT**[5,6,*,†,‡]

Consolidation Immunotherapy for Patients with Unresectable Stage II/III NSCLC, PS 0–1, and No Disease Progression After Definitive Concurrent Chemoradiation

Durvalumab 10 mg/kg IV every 2 weeks or 1500 mg every 4 weeks for up to 12 months (patients with a body weight of ≥30 kg)[7,8]
(category 1 for stage III; category 2A for stage II)

[€] For patients with superior sulcus tumors, the recommendation is for 2 cycles concurrent with radiation therapy and 2 more cycles after surgery. 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.

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

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

[‡] For eligible patients, durvalumab may be used after noted concurrent chemo/RT regimens.

[§] If using durvalumab, an additional 2 cycles of chemotherapy is not recommended.

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CONCURRENT CHEMORADIATION REGIMENS – REFERENCES

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CANCER SURVIVORSHIP CARE

NSCLC Long-Term Follow-up Care

- Cancer Surveillance (See NSCL-16)
- Immunizations
  - Annual influenza vaccination
  - Herpes zoster vaccine
  - Pneumococcal vaccination with revaccination as appropriate
- See NCCN Guidelines for Survivorship

Counseling Regarding Health Promotion and Wellness[1]

- 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 https://www.cancer.gov/publications/patient-education/facing-forward

Cancer Screening Recommendations[2,3]

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 and Diagnosis

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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
- Tissue Specimen Acquisition and Management:
  - Although tumor testing has been primarily focused on use of 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 tissue 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. Peripheral blood (plasma circulating tumor DNA) can be a surrogate sample (NSCL-H 7 of 7).

Continued

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- 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.
    - ◊ It is recommended at this time that when feasible, testing be performed via a broad, panel-based approach, most typically performed by NGS. For patients who, in broad panel testing don't have identifiable driver oncogenes (especially in never smokers), consider RNA-based NGS if not already performed, to maximize detection of fusion events.
      - – Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-19 in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable.
    - ◊ 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.
    - ◊ Any method that interrogates sequences other than a subset of highly specific alterations (eg, NGS, Sanger) has the potential to identify variants of uncertain significance (VUS). Any variant classified as a VUS, even if in a gene in which other variants are clinically actionable, should not be considered as a basis for targeted therapy selection.
    - ◊ Other methodologies may be utilized, including multiplex approaches not listed above.
    - ◊ Fluorescence in situ hybridization (FISH) analysis is utilized for many assays examining copy number, amplification, and structural alterations such as gene rearrangements.

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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 oral 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.
    - ◊ Molecular testing for *EGFR* mutations should be performed when adjuvant TKI therapy is a consideration for NSCLC stage IB–IIIA. While the testing process may be technically easier on a resection specimen, initial diagnostic biopsy specimens are also acceptable for testing for this indication.
    - ◊ Many of the less commonly observed alterations in EGFR, which cumulatively account for ~10% of *EGFR*-mutation positive NSCLC (ie, *exon 19* insertions, *p.L861Q, p.G719X, p.S768I*) are also associated with responsiveness to certain EGFR TKIs, such as osimertinib and afatinib, and should be considered on a mutation-specific basis, when possible.
    - ◊ *EGFR p.T790M* is most commonly observed as a mutation that arises in response to and as a mechanism of resistance to first- and second-generation EGFR TKI. In patients with progression on first- or second-generation TKI with *p.T790M* as the primary mechanism of resistance, third-generation TKIs are typically efficacious.
      - – If *EGFR p.T790M* is identified in the absence of prior EGFR TKI therapy, genetic counseling and possible germline genetic testing are warranted. Identification of germline *EGFR p.T790M* confers a high risk for lung cancer regardless of smoking status.
    - ◊ *EGFR exon 20 (EGFRex20)* mutations (other than *EGFR p.T790M*) are a heterogeneous group, some of which are responsive to targeted therapy and that require detailed knowledge of the specific alteration.
      - – Most *EGFRex20* alterations are a diverse group of in-frame duplication or insertion mutations.
        - ▪ These are generally associated with lack of response to first-, second-, and third-generation EGFR TKI therapy, with select exceptions: *p.A763_Y764insFQEA* is associated with sensitivity to TKI therapy and *p.A763_Y764insLQEA* may be associated with sensitivity to first- and third-generation TKI therapy.
        - ▪ *EGFRex20* insertions/duplications are associated with responsiveness to specific targeted subsequent therapy agents. The most commonly represented *EGFRex20* insertions/duplications in the clinical studies have been insASV, insSVD, and insNPH, although a wide spectrum of other alterations were included. There is currently no evidence that the specific alteration type impacts the probability of responsiveness to this class of kinase inhibitor.
        - ▪ Because some *EGFRex20* mutations are or may be sensitive to first- and third-generation inhibitors, the specific sequence of *EGFRex20* insertion mutations remains important. Some assays will identify the presence of an *EGFRex20* insertion without specifying the sequence, and additional testing to further clarify the *EGFRex20* insertion may be indicated for therapy selection.
        - ▪ Targeted PCR-based approaches for detection of EGFR variants may under-detect *EGFRex20* insertion events; therefore, NGS-based strategies are preferred.
    - ◊ 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.

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Molecular Targets for Analysis (continued)**
  - ***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 oral ALK TKIs.**
    - **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 can be utilized as a stand-alone test, not requiring confirmation by FISH. Numerous NGS methodologies can detect *ALK* fusions. Targeted real-time PCR assays are used in some settings, although it is unlikely to detect fusions with novel partners.**
  - ***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 GOPC (*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, although DNA-based NGS may under-detect *ROS1* fusions. Targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners.**

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- Molecular Targets for Analysis (continued)
  - *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 known activating mutation in *KRAS* identifies patients who are unlikely to benefit from further molecular testing.
    - ◊ The presence of *KRAS* p.G12C is associated with responsiveness to an oral KRAS G12C inhibitor used for subsequent therapy, which was designed specifically for this mutation. Responsiveness to this class of inhibitor has not been prospectively evaluated with mutations other than *KRAS* p.G12C.
    - ◊ Testing methodologies: NGS, real-time PCR, and Sanger sequencing (ideally paired with tumor enrichment) are the most commonly deployed methodologies for examining *KRAS* mutation status.
  - *MET* (mesenchymal-epithelial transition) *exon 14 (METex14)* skipping variants: MET is a receptor tyrosine kinase. A mutation that results in loss of *exon 14* can occur in NSCLC. Loss of *METex14* leads to dysregulation and inappropriate signaling.
    - ◊ The presence of *METex14* skipping mutation is associated with responsiveness to oral MET TKIs.
    - ◊ A broad range of molecular alterations lead to *METex14* skipping.
    - ◊ Testing Methodologies: NGS-based testing is the primary method for detection of *METex14* skipping events; RNA-based NGS may have improved detection. IHC is not a method for detection of *METex14* skipping.
  - *RET* (rearranged during transfection) Gene Rearrangements: RET is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the RET kinase domain.
    - ◊ Common fusion partners are *KIF5B, NCOA4*, and *CCDC6*; however, numerous other fusion partners have been identified.
    - ◊ The presence of a *RET* rearrangement is associated with responsiveness to oral RET TKIs regardless of fusion partner.
    - ◊ Testing Methodologies: FISH break-apart probe methodology can be deployed; however, it may under-detect some fusions. Targeted real-time reverse-transcriptase PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners. NGS-based methodology has a high specificity, and RNA-based NGS is preferable to DNA-based NGS for fusion detection.

Continued

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- Molecular Targets for Analysis (continued)
  - *NTRK1/2/3* (neurotrophic tyrosine receptor kinase) gene fusions
    - The presence of *NTRK1/2/3* gene fusions is associated with responsiveness to oral TRK inhibitors.
    - *NTRK1/2/3* are tyrosine receptor kinases that are rarely rearranged in NSCLC as well as in other tumor types, resulting in dysregulation and inappropriate signaling.
    - Numerous fusion partners have been identified.
    - To date, no specific clinicopathologic features, other than absence of other driver alterations, have been identified in association with these fusions.
    - Point mutations in *NTRK1/2/3* are generally non-activating and have not been studied in association with targeted therapy.
    - Testing Methodologies: Various methodologies can be used to detect *NTRK1/2/3* gene fusions, including: FISH, IHC, PCR, and NGS; false negatives may occur. IHC methods are complicated by baseline expression in some tissues. FISH testing may require at least 3 probe sets for full analysis. NGS testing can detect a broad range of alterations. DNA-based NGS may under-detect *NTRK1* and *NTRK3* fusions.
- In the event that a complete assessment for all biomarkers cannot be reasonably accomplished prior to initiation of therapy, consider repeat panel testing or selected biomarker testing at progression on first-line therapy if a lesion can be accessed for sampling and 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 from a tumor 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.
      - 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.
    - Broad genomic profiling may be the most informative approach to examining potential mechanisms of resistance, which may require more than one instance of such profiling over the course of an individual patient's therapy.
- Testing in the setting of a limited number of pulmonary nodules can aid in distinguishing separate primary lung carcinoma versus intrapulmonary metastatic disease.
  - Studies to explore tumor relatedness by testing tissue from separately sampled lesions using a broad gene coverage NGS approach suggest it may be superior to histopathologic assessment.
  - Tumor pairs exhibiting entirely non-overlapping, unique mutations are considered clonally unrelated separate primary lung cancers, even if histologically similar. Tumors that share multiple (≥2) mutations are more likely to be clonally related; however, this may depend on the extent to which any individual mutation is extremely common in NSCLC and whether identified alterations are driver or passenger alterations. Results in which no mutations or only one mutation are identified are not informative for this evaluation.

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- 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 are comparable regarding intensity and proportion of cells stained, some are not.
      - – The definition of positive and negative testing is dependent on the individual antibody, clone, and platform deployed, which may be unique to each checkpoint inhibitor therapy. The approval of multiple different assays for PD-L1 has raised concern among both pathologists and oncologists.
      - – While some clones for PD-L1 IHC are FDA-approved for specific indications, use of multiple IHC tests is not necessary, provided any individual IHC test has been internally validated for comparability for categorical results against the FDA-approved clone.
      - – Interpretation of PD-L1 IHC in NSCLC is typically focused on the proportion of tumor cells expressing membranous staining at any level and therefore is a linear variable; scoring systems may be different in other tumor types.
    - ◊ Although PD-L1 expression can be elevated in patients with an oncogenic driver, targeted therapy for the oncogenic driver should take precedence over treatment with an immune checkpoint inhibitor.
- Plasma Cell-Free/Circulating Tumor DNA Testing:
  - ▸ Cell-free/circulating tumor DNA testing should not be used in lieu of a histologic 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 a 30% false-negative rate; however, data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection.
  - ▸ Published guidelines elaborating 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 (see NSCL-18 for oncogenic drivers with available targeted therapy options).
    - ◊ In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available, consider repeat biopsy and/or cell-free/circulating tumor DNA testing.

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EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	**Available Targeted Agents with Activity Against Driver Event in Lung Cancer**
High-level *MET* amplification*	**Crizotinib**[1-2] **Capmatinib**[3] **Tepotinib**[4]
ERBB2 (HER2)* mutations*	**Ado-trastuzumab emtansine**[5] **Fam-trastuzumab deruxtecan-nxki**[6]

* The definition of high-level *MET* amplification is evolving and may differ according to the assay used for testing. For NGS-based results, a copy number greater than 10 is consistent with high-level *MET* amplification.

** For oncogenic or likely oncogenic *HER2* mutations, refer to definitions at oncokb.org.

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TARGETED THERAPY OR IMMUNOTHERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

EGFR Exon 19 Deletion or *L858R*

- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Erlotinib + ramucirumab[7]
  - Erlotinib + bevacizumab[c] (nonsquamous)[8]
- Subsequent therapy
  - Osimertinib[9]

EGFR S768I, L861Q, and/or *G719X*

First-line therapy
  - Afatinib[1,10]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,11]
- Subsequent therapy
  - Osimertinib[9]

EGFR Exon 20 Insertion Mutation Positive

- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

KRAS G12C Mutation Positive

- Subsequent therapy
  - Sotorasib[14]

ALK Rearrangement Positive

- First-line therapy
  - Alectinib[15,16]
  - Brigatinib[17]
  - Ceritinib[18]
  - Crizotinib[15,19]
  - Lorlatinib[20]
- Subsequent therapy
  - Alectinib[21,22]
  - Brigatinib[23]
  - Ceritinib[24]
  - Lorlatinib[25]

ROS1 Rearrangement Positive

- First-line therapy
  - Ceritinib[24]
  - Crizotinib[27]
  - Entrectinib[28]
- Subsequent therapy
  - Lorlatinib[29]
  - Entrectinib[28]

BRAF V600E Mutation Positive

- First-line therapy
  - Dabrafenib/trametinib[30]
  - Dabrafenib[30]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[31,32]

NTRK1/2/3 Gene Fusion Positive

- First-line/Subsequent therapy
  - Larotrectinib[33]
  - Entrectinib[34]

MET Exon 14 Skipping Mutation

- First-line therapy/Subsequent therapy
  - Capmatinib[35]
  - Crizotinib[36]
  - Tepotinib[37]

RET Rearrangement Positive

- First-line therapy/Subsequent therapy
  - Selpercatinib[38]
  - Pralsetinib[39]
  - Cabozantinib[40.41]

PD-L1 ≥1%

- First-line therapy[d]
  - Pembrolizumab[43-45]
  - (Carboplatin or cisplatin)/pemetrexed/ pembrolizumab (nonsquamous)[46]
  - Carboplatin/paclitaxel/bevacizumab[c]/ atezolizumab (nonsquamous)[47]
  - Carboplatin/(paclitaxel or albumin-bound paclitaxel)/pembrolizumab (squamous)[48]
  - Carboplatin/albumin-bound paclitaxel/ atezolizumab (nonsquamous)[48]
  - Nivolumab/ipilimumab[49]
  - Nivolumab/ipilimumab/pemetrexed/ (carboplatin or cisplatin) (nonsquamous)[50]
  - Nivolumab/ipilimumab/paclitaxel/carboplatin (squamous)[50]

PD-L1 ≥50% (in addition to above)

- First-line therapy[d]
  - Atezolizumab[51]
  - Cemiplimab-rwlc[52]

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[a] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.

[b] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

[d] 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.

References

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

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred
- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,e]

Other Recommended
- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,f,g,h,i]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
- Nivolumab/ipilimumab[5,d]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (category 1) [6,e]

Contraindications to PD-1 or PD-L1 inhibitors[d]

Useful in Certain Circumstances
- Bevacizumab[e]/carboplatin/paclitaxel (category 1)[7,g,h,i]
- Bevacizumab[e]/carboplatin/pemetrexed[7,8,g,h,i]
- Bevacizumab[e]/cisplatin/pemetrexed[9,g,h,i]
- Carboplatin/albumin-bound paclitaxel (category 1)[10]
- Carboplatin/docetaxel (category 1)[11]
- Carboplatin/etoposide (category 1)[12,13]
- Carboplatin/gemcitabine (category 1)[14]
- Carboplatin/paclitaxel (category 1)[15]
- Carboplatin/pemetrexed (category 1)[16]
- Cisplatin/docetaxel (category 1)[11]
- Cisplatin/etoposide (category 1)[17]
- Cisplatin/gemcitabine (category 1)[15,18]
- Cisplatin/paclitaxel (category 1)[19]
- Cisplatin/pemetrexed (category 1)[18]
- Gemcitabine/docetaxel (category 1)[20]
- Gemcitabine/vinorelbine (category 1)[21]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 2)

Preferred
- Carboplatin/pemetrexed[16]

Other Recommended
- Carboplatin/albumin-bound paclitaxel[23,24]
- Carboplatin/docetaxel[11]
- Carboplatin/etoposide[12,13]
- Carboplatin/gemcitabine[14]
- Carboplatin/paclitaxel[15]

Useful in Certain Circumstances
- Albumin-bound paclitaxel[22]
- Docetaxel[25,26]
- Gemcitabine[27-29]
- Gemcitabine/docetaxel[20]
- Gemcitabine/vinorelbine[21]
- Paclitaxel[30-32]
- Pemetrexed[33]

Maintenance Therapy NSCL-K 3 of 5
Subsequent Therapy NSCL-K 4 of 5
References

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 3–4)

Best supportive care See NCCN Guidelines for Palliative Care

[a] 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.

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

[c] If first-line systemic therapy completed before treatment for an actionable mutation, and disease has progressed, see Subsequent Therapy NSCL-K 4 of 5.

[d] 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 (ie, *EGFR exon 19* deletion *or L858R*, *ALK* rearrangements), which would predict lack of benefit.

[e] If progression on PD-1/PD-L1 inhibitor, using a PD-1/PD-L1 inhibitor is not recommended.

[f] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

[g] Bevacizumab should be given until progression.

[h] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.

[i] 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.

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.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

SQUAMOUS CELL CARCINOMA (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred
- Pembrolizumab/carboplatin/paclitaxel (category 1)[34,e]
- Pembrolizumab/carboplatin/albumin-bound paclitaxel (category 1)[34,e]

Other recommended
- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[6,e]

Contraindications to PD-1 or PD-L1 inhibitors[d]

Useful in Certain Circumstances
- Carboplatin/albumin-bound paclitaxel (category 1)[9]
- Carboplatin/docetaxel (category 1)[11]
- Carboplatin/gemcitabine (category 1)[14]
- Carboplatin/paclitaxel (category 1)[15]
- Cisplatin/docetaxel (category 1)[11]
- Cisplatin/etoposide (category 1)[17]
- Cisplatin/gemcitabine (category 1)[15,18]
- Cisplatin/paclitaxel (category 1)[19]
- Gemcitabine/docetaxel (category 1)[20]
- Gemcitabine/vinorelbine (category 1)[21]

SQUAMOUS CELL CARCINOMA (PS 2)

Preferred
- Carboplatin/albumin-bound paclitaxel[23,24]
- Carboplatin/gemcitabine[14]
- Carboplatin/paclitaxel[15]

Other Recommended
- Carboplatin/docetaxel[11]
- Carboplatin/etoposide[12,13]

Useful in Certain Circumstances
- Albumin-bound paclitaxel[22]
- Docetaxel[25,26]
- Gemcitabine[27-29]
- Gemcitabine/docetaxel[20]
- Gemcitabine/vinorelbine[21]
- Paclitaxel[30-32]

SQUAMOUS CELL CARCINOMA (PS 3–4)

Best supportive care See NCCN Guidelines for Palliative Care

Maintenance Therapy NSCL-K 3 of 5
Subsequent Therapy NSCL-K 4 of 5
References

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[a] 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.
[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c] If first-line systemic therapy completed before treatment for an actionable mutation, and disease has progressed, see Subsequent Therapy NSCL-K 4 of 5.
[d] 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 (ie, EGFR *exon 19* deletion *or L858R*, *ALK* rearrangements), which would predict lack of benefit.
[e] If progression on PD-1/PD-L1 inhibitor, using a PD-1/PD-L1 inhibitor is not recommended.

Note: All recommendations are category 2A unless otherwise indicated.
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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – MAINTENANCE

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.
- Patients should receive maintenance therapy for 2 years if they received front-line immunotherapy.
- Patients should receive maintenance therapy until progression if they received second-line immunotherapy.

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)

Continuation maintenance
- Bevacizumab (category 1)
- Pemetrexed (category 1)
- Bevacizumab/pemetrexed[j]
- Pembrolizumab/pemetrexed (category 1)[k]
- Atezolizumab/bevacizumab (category 1)[l]
- Nivolumab/ipilimumab[m]
- Atezolizumab[n]
- Gemcitabine (category 2B)

Switch maintenance
- Pemetrexed

SQUAMOUS CELL CARCINOMA (PS 0–2)

Continuation maintenance
- Pembrolizumab[o]
- Nivolumab/ipilimumab[m]
- Gemcitabine (category 2B)

ADENOCARCINOMA, LARGE CELL, NSCLC NOS, SQUAMOUS CELL CARCINOMA (PS 3–4)

Best supportive care See NCCN Guidelines for Palliative Care

Subsequent Therapy NSCL-K 4 of 5
References

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[j] If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
[k] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[l] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
[m] If nivolumab + ipilimumab ± chemotherapy given.
[n] If atezolizumab/carboplatin/albumin-bound paclitaxel given.
[o] If pembrolizumab/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.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – SUBSEQUENT

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)

Preferred (no previous IO):

Systemic immune checkpoint inhibitors[e]
- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]
- Docetaxel
- Pemetrexed
- Gemcitabine
- Ramucirumab/docetaxel
- Albumin-bound paclitaxel

SQUAMOUS CELL CARCINOMA (PS 0–2)

Preferred (no previous IO):

Systemic immune checkpoint inhibitors[e]
- Nivolumab (category 1)
- Pembrolizumab (category 1)[q]
- Atezolizumab (category 1)

Other Recommended (no previous IO or previous IO):[r]
- Docetaxel
- Gemcitabine
- Ramucirumab/docetaxel
- Albumin-bound paclitaxel

ADENOCARCINOMA, LARGE CELL, NSCLC NOS, SQUAMOUS CELL CARCINOMA (PS 3–4)

Best supportive care See NCCN Guidelines for Palliative Care

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – PROGRESSION

ADENOCARCINOMA, LARGE CELL, NSCLC NOS[e,r]

- PS 0–2: nivolumab, pembrolizumab, or atezolizumab, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), ramucirumab/docetaxel (category 2B), or albumin-bound paclitaxel (category 2B)
- PS 3–4: Best supportive care
- Options for further progression are best supportive care or clinical trial.

SQUAMOUS CELL CARCINOMA[e,r]

- PS 0–2: nivolumab, pembrolizumab, or atezolizumab, docetaxel (category 2B), gemcitabine (category 2B), ramucirumab/docetaxel (category 2B), or albumin-bound paclitaxel (category 2B)
- PS 3–4: Best supportive care
- Options for further progression are best supportive care or clinical trial.

References

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[e] If progression on PD-1/PD-L1 inhibitor, using a PD-1/PD-L1 inhibitor is not recommended.
[q] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.
[r] If not previously given.

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

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – REFERENCES

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Note: All recommendations are category 2A unless otherwise indicated.
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Table 1. Definitions for T, N, M

T		**Primary Tumor**
TX		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
T0		No evidence of primary tumor
Tis		Carcinoma *in situ* Squamous cell carcinoma *in situ* (SCIS) Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1		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
T2		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
T3		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
T4		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 an ipsilateral lobe different from that of the primary

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

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M		Distant Metastasis
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion[a]
	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

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

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[a] 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.

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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
T component		
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	—
N component		
No assessment, no involvement, or involvement of regional lymph nodes	NX, N0, N1, N2, N3	No change
M component		
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.

**The staging of tumor size in the AJCC Cancer Staging Manual, 7th Edition is based on the total tumor size (invasive and lepidic/noninvasive); whereas, in the AJCC Cancer Staging Manual, 8th Edition, staging is based on invasive size only for non-mucinous adenocarcinoma. However, in mucinous adenocarcinoma, the total tumor size is used.

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.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Non-Small Cell Lung Cancer. Last updated on September 15, 2020.

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Overview

Lung cancer is the leading cause of cancer death in the United States.[1] In 2020, an estimated 228,820 new cases (116,300 in men and 112,520 in women) of lung and bronchial cancer will be diagnosed, and 135,720 deaths (72,500 in men and 63,220 in women) are estimated to occur because of the disease.[2] Only 19% of all patients with lung cancer are alive 5 years or more after diagnosis, which includes patients with both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[3] From 2009 to 2015, the overall 5-year relative survival rate for NSCLC was 25% in the United States.[3] 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.[4-9] Patients with metastatic lung cancer who are eligible for targeted therapies or immunotherapies are now surviving longer; 5-year survival rates range from 15% to 50%, depending on the biomarker.[9-19] Thus, death rates for lung cancer have been declining, although there are still more deaths from lung cancer than from breast, prostate, colorectal, and brain cancers combined together.[2] Common symptoms of lung cancer include cough, hemoptysis, dyspnea, weight loss, and chest pain; patients with symptoms are more likely to have chronic obstructive pulmonary disease (COPD).[20]

These NCCN Guidelines® for NSCLC were first published in 1996.[21] Subsequently, the NCCN Guidelines® have been updated at least once a year by the NCCN NSCLC Panel; there were 8 updates for the 2020 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). For example, the NCCN NSCLC Panel has preference stratified the systemic therapy regimens for the 2020 update (Version 1) based on the biomedical literature and experience of the panel members using the following categories: 1) preferred interventions; 2) other recommended interventions; and 3) interventions that are useful in certain circumstances (see the NCCN Guidelines for NSCLC).[22] These new preference categories are intended to emphasize the preferred regimens in clinical practice and are not intended to replace the NCCN categories of evidence and consensus, such as category 1 or category 2A.

The NCCN Guidelines also provide specific category designations for all treatment interventions in the guidelines, which are based on evidence from the biomedical literature and consensus among the panel members. Category 1 recommendations indicate uniform NCCN consensus (at least 85% of the panel vote) that the intervention is appropriate based on high-level evidence, such as randomized phase 3 trials. Category 2A recommendations indicate uniform NCCN consensus that the intervention is appropriate based on lower level evidence, such as phase 2 trials. It is important to note that all recommendations are category 2A in the NCCN Guidelines unless otherwise indicated. Category 2B recommendations indicate NCCN consensus (50% to <85% of the panel vote) that the intervention is appropriate based on lower level evidence. Category 3 recommendations indicate major NCCN disagreement (at least 50% of the panel vote) that the intervention is appropriate based on any level of evidence. For a category 3 recommendation to remain in the guideline, at least 25% of the panel must vote 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.

Risk Factors

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths.[1,23-27] Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).[26,28] 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).[24,28-31]

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).[32,33] 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.[34-36] 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.[37] Asbestos also causes malignant pleural mesothelioma (see the NCCN Guidelines for Malignant Pleural Mesothelioma, available at 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, no increase in the incidence of lung cancer was found among postmenopausal women treated with estrogen plus progestin HRT; however, the risk of death increased in those with NSCLC.[38] In women who received estrogen alone, the incidence or risk of death from lung cancer did not increase.[39]

Smoking Cessation

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.[25] Active smoking causes lung cancer; former smokers are at increased risk for lung cancer compared with never smokers. 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.[25] Smoking harms nearly every organ in the body; smokers have increased mortality compared with nonsmokers.[40] Those who live with someone who smokes have an increased risk for lung cancer.[29] 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).[41-44] The 5 A's framework is a useful tool (that is, Ask, Advise, Assess, Assist, Arrange).[45] It is in the best interest of patients to quit smoking. Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival.[46] Some surgeons will not operate on a current smoker, because active smoking may increase postoperative pulmonary complications.[47] 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.[48] 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.[49,50] A study suggests that cytisine is more efficacious than nicotine replacement therapy, although more side effects were reported with cytisine such as nausea, vomiting, and sleep disorders.[51] Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.[52-54] The effectiveness of varenicline for preventing relapse has not been clearly established.[55] 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.[56-59] Other side effects with varenicline include nausea, abnormal dreams, insomnia, and headache.[54,60,61] Bupropion may also be associated with similar serious neuropsychiatric symptoms. Nicotine replacement has fewer adverse effects than varenicline or bupropion.[62] In spite of the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.[62]

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.[1,63,64] 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.[65] 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%.[66] 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.[65,67] 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).[68-71] 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).

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 SCLC (see the NCCN Guidelines for Small Cell Lung Cancer, available at www.NCCN.org).[72,73] NSCLC accounts for more than 80% of all lung cancer cases, and it includes 2 major types: 1) nonsquamous (including adenocarcinoma, large-cell carcinoma, and other subtypes); and 2) squamous cell (epidermoid) carcinoma.[3] 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.[72-74] All NSCLC should be classified according to subtype using the WHO Guidelines.[73] 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.[75]

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.[76] 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.[77] The NCCN Guidelines for Lung Cancer Screening have been 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.[78]

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).[79-83] 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.[80,81] 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.[81,84-86] 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.[74,81,84,85,87-89] 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.[87,90,91] 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).[77,80,81]

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). 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.[66] 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.[92-94]

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.[95] 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 in this Discussion and *Principles of Diagnostic Evaluation* in the NCCN Guidelines for NSCLC). Clinicians use both noninvasive and invasive methods when staging patients.[96] 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, Staging,* and *Clinical Evaluation* 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 variants are present (eg, epidermal growth factor receptor [*EGFR*] mutations) (see *Principles of Pathologic Review* in the NCCN

Guidelines for NSCLC).[97] Data show that targeted therapy is potentially very effective in patients with specific gene variants such as *EGFR* mutations or *ALK* fusions; therefore, tissue needs to be conserved for molecular testing (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[7,98-107]

Preoperative evaluations include examination of the following: bronchial brushings, bronchial washings, sputum, FNA biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy.[95,108] Minimally invasive techniques can be used to obtain specimens in patients with advanced unresectable NSCLC;[109,110] however, diagnosis may be more difficult when using small biopsies and cytology.[88] Rapid on-site evaluation (ROSE) may be used to ensure transbronchial needle aspirates or EBUS specimens are adequate for molecular testing.[111,112] 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).[113-115] 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.[72,73,116] 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).[72-74] The revised classification recommends immunohistochemical (IHC) and molecular studies (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).[117] 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.[73] 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 specified. 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 (see the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org). 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.[72-74] 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).[117]

The categories of BAC or mixed subtype adenocarcinoma are no longer used to classify adenocarcinoma.[74] 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.[74]

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 biomarker testing for anaplastic lymphoma kinase (*ALK*) gene rearrangements (also known as *ALK* fusions), *ROS1* rearrangements (also known as *ROS1* fusions), *BRAF* mutations, c-mesenchymal-epithelial transition factor (c-*MET*) exon 14 (*METex14*) skipping mutations, rearranged during transfection (*RET*) rearrangements, and programmed death ligand 1 (PD-L1) expression levels, because FDA-approved agents for lung cancer are available for these biomarkers. Testing for other genetic variants may also be done—such as neurotrophin tyrosine receptor kinase (*NTRK)* gene fusions, *MET* amplification, and *ERBB2 (*also known as *HER2)* mutations—to identify these rare oncogenic driver variants for which effective therapy may be available, although there is less evidence to support testing (see *Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC* in the NCCN Guidelines for NSCLC).[118-120] The NCCN NSCLC Panel also recommends PD-L1 IHC testing (category 1) in patients with metastatic NSCLC based on phase 3 randomized trial data.[121]

Immunohistochemical Staining

Judicious use of IHC in small tissue samples to determine a diagnosis of NSCLC 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).[110,122,123] 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-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.[124] If necessary, IHC should be used to distinguish adenocarcinoma, squamous cell carcinoma, metastatic malignancy, and primary pleural mesothelioma (particularly for pleural samplings).[122] IHC is useful for poorly differentiated NSCLC in small biopsy and/or cytology specimens.[74,125] Squamous cell carcinomas are often TTF-1 negative and p40 (or alternatively p63) positive, whereas adenocarcinomas are usually TTF-1 positive.[74] These 2 markers may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.[74,125] Other markers (eg, p40, Napsin A) may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.[126,127] 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.[125] However, TTF-1 is also positive in tumors such as thyroid cancer and rarely in a few other organ systems.[128] 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 (ERα, PR, GCDFP-15, mammaglobin, GATA-3), 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.[129,130] 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, Claudin-4, 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).[129-131] 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 (see the NCCN Guidelines for Small Cell Lung Cancer, available at www.NCCN.org).[95,125,132] 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.[133,134] 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.[135,136] The lung cancer staging system was revised by the International Association for the Study of Lung Cancer (IASLC)[137-139] and was adopted by the AJCC.[135,136,140,141] 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*).[142] 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+);[143] 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).[144]

From 2009 to 2015, the overall 5-year relative survival rate for NSCLC was 25% in the United States.[3] 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 61.4% for localized, 34.5% for regional, 6.1% for distant, and 14.6% for unstaged.[3]

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.[145] 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%.[146] 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). The NSCLC Panel recommends testing for certain molecular and immune biomarkers in all appropriate patients with metastatic NSCLC to assess whether patients are eligible for targeted therapies or immunotherapies based on data showing improvement in overall survival for patients receiving targeted therapies or immunotherapies compared with traditional chemotherapy regimens.[10-17]

Predictive biomarkers include the *ALK* fusion oncogene (fusion between *ALK* and other genes [eg, echinoderm microtubule-associated protein-like 4]), *ROS1* gene fusions, sensitizing *EGFR* gene mutations, *BRAF* V600E point mutations, *NTRK* gene fusions, *METex14* skipping mutations*, RET* rearrangements, and PD-L1 expression (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). Emerging predictive biomarkers include *ERBB2* mutations, high-level *MET* amplifications, 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, osimertinib); therefore, these mutations are referred to as *sensitizing EGFR* mutations (see *EGFR Mutations* in this Discussion).[147,148] 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.[149]

ALK fusion oncogenes (ie, *ALK* gene fusions) and *ROS1* fusions 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 fusions have recently been identified, such as *ERBB2 (HER2)* mutations 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).[150-155]

Testing for *ALK* gene fusions 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 variants can receive effective treatment with targeted agents (see *Targeted Therapies* in this Discussion and the NCCN Guidelines for NSCLC).[156-160] Testing for *ROS1* fusions 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* fusions or *EGFR* mutations can have mixed squamous cell histology.[161,162] Therefore, testing for *ALK* fusions 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.[161] Thus, testing for *EGFR* mutations and *ALK* fusions 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.[160] The incidence of *EGFR* mutations is very low in patients with pure squamous cell histology (<4%).[163] Testing for *ROS1* fusions or *BRAF* mutations is also recommended (category 2A) in patients with squamous cell carcinoma who have small biopsy specimens or mixed histology.

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* fusions, *ROS1* fusions, *METex14* skipping mutations, *RET* rearrangements, and PD-L1 expression levels. This list of recommended biomarkers may be revised as new oncogenic driver variants are identified and new agents are approved. Patients with NSCLC may have other genetic variants (see *Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC* in the NCCN Guidelines for NSCLC).[102,164,165] The NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays.[166] 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). *EGFR*, *KRAS*, *ROS1*, *BRAF*, *METex14* skipping mutations, *RET* rearrangements, and *ALK* genetic variants do not usually overlap; thus, testing for *KRAS* mutations may identify patients who will not benefit from further molecular testing.[150,167-171] 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).[172] *KRAS* mutations are also predictive of lack of benefit from EGFR TKI therapy.[147,173,174]

Other oncogenic driver variants are being identified such as high-level *MET* amplification, *ERBB2* mutations, and TMB.[175-178] TMB is an 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 With or Without Ipilimumab* in this Discussion).[179,180] However, there is no consensus on how to measure TMB. Targeted agents are available for patients with NSCLC who have these other genetic variants, 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).[181,182] Thus, the NCCN NSCLC Panel recommends molecular testing but strongly advises broader molecular profiling to identify these other rare driver variants for which targeted therapies may be available to ensure that patients receive the most appropriate treatment; patients may be eligible for clinical trials for some of these targeted agents.[159] Several online resources are available that describe NSCLC driver events such as *My Cancer Genome*.

Information about biomarker testing and plasma cell-free/circulating tumor DNA testing (so-called “liquid biopsy”) for genetic variants is included in the algorithm (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). Briefly, the panel feels that plasma cell-free/circulating tumor DNA testing should not be used to diagnose NSCLC; tissue should be used to diagnose NSCLC. Standards and guidelines for cell-free DNA (cfDNA)/circulating tumor DNA testing for genetic variants have not been established, there is up to a 30% false-negative rate, and variants can be detected that are not related to the tumor (eg, clonal hematopoiesis of indeterminate potential [CHIP]).[183,184] 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.[185] In addition, CHIP can be identified following prior chemotherapy or radiotherapy, further confounding interpretation of variants such as in *TP53*.[186] Given the previous caveats, careful consideration is required to determine whether cfDNA findings reflect a true oncogenic driver or an unrelated finding.

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.[187,188] Recent data suggest that plasma cell-free/circulating tumor DNA testing can be used to identify *EGFR*, *ALK*, and other oncogenic biomarkers that would not otherwise be identified in patients with metastatic NSCLC.[189-191]

Testing for Molecular Biomarkers

Molecular testing is used to test for genomic variants associated with oncogenic driver events for which targeted therapies are available; these genomic variants (also known as molecular biomarkers) include gene mutations and fusions. 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 fusions if the NGS platforms have been designed and validated to detect these genetic variants.[181,192-199] 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 fusions, 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. However, these multiplex polymerase chain reaction (PCR) systems do not typically detect gene fusions. *ROS1* and *ALK* gene fusions 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 broad molecular profiling be done as part of biomarker testing using a validated test(s) that assesses a minimum of the following potential genetic variants: *EGFR* mutations, *BRAF* mutations, *METex14* skipping mutations*, RET* rearrangements, *ALK* fusions, and *ROS1* fusions. 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 *NTRK* gene fusions, high-level *MET* amplification, *ERBB2* mutations, and TMB. Although clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with specific genetic variants (eg, *EGFR* mutations), these features should not be used to select patients for testing. Although the NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques, the guidelines do not endorse any specific commercially available biomarker assays.

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).[200] Thus, these drug-sensitive *EGFR* 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).[201,202] 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.[203]

Most patients with sensitizing *EGFR* mutations are nonsmokers or former light smokers with adenocarcinoma histology. Data suggest that *EGFR* mutations can occur in patients with adenosquamous carcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.[161] Patients with pure squamous cell carcinoma are unlikely to have sensitizing *EGFR* mutations; those with adenosquamous carcinoma may have mutations.[161] However, smoking status, ethnicity, and histology should not be used in selecting patients for testing. *EGFR* mutation testing is not usually recommended in patients who appear to have 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.[161] The ESMO Guidelines specify that only patients with nonsquamous NSCLC (eg, adenocarcinoma) should be assessed for *EGFR* mutations.[159,204] ASCO recommends that patients be tested for *EGFR* mutations.[205]

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.[200] Data show that EGFR TKI therapy should be used as first-line monotherapy in patients with advanced NSCLC and sensitizing *EGFR* mutations documented before first-line systemic therapy (eg, carboplatin/paclitaxel) (see *Targeted Therapies* in this Discussion).[206-211] Progression-free survival (PFS) is longer with use of EGFR TKI monotherapy in patients with sensitizing *EGFR* mutations when compared with cytotoxic systemic therapy, although overall survival is not statistically different.[206,207,212]

Non-responsiveness to EGFR TKI therapy is associated with *KRAS* and *BRAF* mutations and *ALK* or *ROS1* gene fusions. Patients with *EGFR* exon 20 insertion mutations are usually resistant to erlotinib, gefitinib, afatinib, or dacomitinib, although there are rare exceptions (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[213-217] Patients typically progress after first-line EGFR TKI monotherapy; 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]. 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.[197,218-224] Most patients with sensitizing *EGFR* mutations become resistant to erlotinib, gefitinib, or afatinib; PFS is about 9.7 to 13 months.[207,212,219,225,226] Studies suggest T790M may rarely occur in patients who have not previously received erlotinib, gefitinib, or afatinib.[227] 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.[228,229] Acquired resistance to EGFR TKIs may also be associated with histologic transformation from NSCLC to SCLC and with epithelial to mesenchymal transition.[230-233] For the 2020 update (Version 1), the NCCN NSCLC Panel suggests that a biopsy can be considered at progression to rule out SCLC transformation. Acquired resistance can also be mediated by other molecular events, such as acquisition of *ALK* rearrangement, *MET*, or *ERBB2* amplification.[234]

The NCCN NSCLC Panel recommends testing for sensitizing *EGFR* mutations in patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of osimertinib, erlotinib, gefitinib, afatinib, or dacomitinib and on FDA approvals (see *Osimertinib, Erlotinib and Gefitinib, Afatinib*, and *Dacomitinib* in this Discussion).[206,208-211] DNA mutational analysis is the preferred method to assess for EGFR status; IHC is not recommended for detecting *EGFR* mutations.[235-238] 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).[160,235] 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.[203,237,239-241] Mutation screening assays using multiplex PCR (eg, Sequenom's MassARRAY® system, SNaPshot® Multiplex System) can simultaneously detect more than 50 point mutations.[242] NGS can also be used to detect *EGFR* mutations.[198]

Osimertinib is a preferred first-line EGFR TKI option for patients with *EGFR* positive metastatic NSCLC (see *Osimertinib* in this Discussion). For the 2020 update (Version 1), the NCCN Panel preference stratified first-line therapy for patients with *EGFR* mutation positive metastatic NSCLC. Erlotinib, gefitinib, afatinib, or dacomitinib are "other recommended" EGFR TKI options for first-line therapy. Osimertinib is recommended (category 1) as second-line and beyond (subsequent) therapy for patients with *EGFR* T790M–positive metastatic NSCLC who have progressed on erlotinib, gefitinib, afatinib, or dacomitinib (see *Osimertinib* in this Discussion).[226,243] Sensitizing *EGFR* mutations and *ALK* or *ROS1* fusions are generally mutually exclusive.[171,244,245] Thus, crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib are not recommended as subsequent therapy for patients with sensitizing *EGFR* mutations who relapse on EGFR TKI therapy. 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.

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.[168,246] 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* fusions who are typically nonsmokers.[247] Mutations in *BRAF* typically do not overlap with *EGFR* mutations, *METex14* skipping mutations*, RET* rearrangements, *ALK* fusions, or *ROS1* fusions.[168,169] Testing for *BRAF* mutations is recommended (category 2A) in patients with metastatic nonsquamous NSCLC and may be considered in patients with squamous cell NSCLC (category 2A) if small biopsy specimens were used to assess histology or mixed histology was reported.[168,169] 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 in patients with metastatic nonsquamous NSCLC based on data showing the efficacy of dabrafenib plus trametinib for patients with *BRAF* V600E mutations and on the FDA approval (see *Dabrafenib and Trametinib* in this Discussion).[168] For the 2020 update (Version 1), the NCCN Panel preference stratified first-line therapy for patients with *BRAF* V600E mutation–positive metastatic NSCLC. Dabrafenib plus trametinib is recommended (category 2A; preferred) for patients with *BRAF* V600E mutations. If combination therapy with dabrafenib/trametinib is not tolerated, single-agent therapy with dabrafenib or vemurafenib are "other recommended" agents.[168,169,248] Chemotherapy regimens also used for initial systemic therapy (eg, carboplatin/pemetrexed for nonsquamous NSCLC) and are "useful in certain circumstances." Patients with *BRAF* mutations respond (24%) to immune checkpoint inhibitors (ICIs).[249]

ALK Gene Rearrangements

About 5% of patients with NSCLC have *ALK* gene rearrangements (also known as *ALK* fusions).[107] Patients with *ALK* fusions are resistant to EGFR TKIs but have similar clinical characteristics to those with *EGFR* mutations, such as adenocarcinoma histology and being light or never smokers.[165] *ALK* fusions are not routinely found in patients with squamous cell carcinoma. Patients with *ALK* gene fusions can have mixed squamous cell histology.[162,250] 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* fusions in patients with metastatic nonsquamous NSCLC based on data showing the efficacy of alectinib, brigatinib, ceritinib, and crizotinib for *ALK* fusions and on the FDA approvals.[251-254] If patients appear to have squamous cell NSCLC, then 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* fusions are described in the algorithm (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). A molecular diagnostic FISH test has been approved by the FDA for detecting *ALK* fusions. Rapid prescreening with IHC to assess for *ALK* fusions can be done.[160,171,255-262] An IHC assay for *ALK* fusions has also been approved by the FDA. NGS can also be used to assess whether *ALK* fusions are present, if the platform has been appropriately designed and validated to detect *ALK* fusions.[263-265]

Alectinib is recommended as a preferred first-line therapy for patients with *ALK* rearrangement–positive metastatic NSCLC (see *Alectinib* in this Discussion). For the 2020 update (Version 1), the NCCN Panel preference stratified first-line therapy with brigatinib, ceritinib, or crizotinib for patients with *ALK* rearrangement–positive metastatic NSCLC. Brigatinib and ceritinib are "other recommended" options, whereas crizotinib is "useful in certain circumstances" (see *Brigatinib*, *Ceritinib*, and *Crizotinib* in this Discussion). Patients with *ALK* rearrangements do not respond to ICIs.[249]

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]. *ALK* or *ROS1* fusions, *RET* rearrangements, *BRAF* mutations, *METex14* skipping mutations, and sensitizing *EGFR* mutations are generally mutually exclusive.[171,244,245] Specific targeted therapy for *RET* rearrangements, *BRAF* mutations, *METex14* skipping mutations, and sensitizing *EGFR* mutations is not recommended as subsequent therapy in patients with *ALK* or *ROS1* fusions who relapse on alectinib, brigatinib, crizotinib, ceritinib, or lorlatinib (see *ALK Positive*: *Subsequent Therapy* in the NCCN Guidelines for NSCLC).[164,165]

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).[151,266] It is estimated that *ROS1* gene rearrangements (also known as *ROS1* fusions) 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 fusions.[118,151,153,267] The NCCN NSCLC Panel recommends *ROS1* testing (category 2A) in patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of crizotinib, ceritinib, and entrectinib for patients with *ROS1* fusions (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[150,151,268,269] *ROS1* testing can be considered in patients with metastatic squamous cell NSCLC if small biopsy specimens were used to assess histology or mixed histology was reported. Similar to testing for *ALK* fusions, testing for *ROS1* fusions is done using FISH.[153,255,270-272] NGS can also be used to assess whether *ROS1* fusions are present, if the platform has been appropriately designed and validated to detect *ROS1* fusions.[151] Clinicians should use an appropriately validated test to detect *ROS1* fusions.[269]

Crizotinib is very effective for patients with *ROS1* fusions with response rates of about 70% to 80% including complete responses.[14,150,151,273,274] The NCCN NSCLC Panel recommends crizotinib, entrectinib, or ceritinib (all are category 2A) as first-line therapy options for patients with *ROS1*-positive metastatic NSCLC based on clinical trial data (see *Crizotinib*, *Entrectinib,* and *Ceritinib* in this Discussion). The NCCN NSCLC Panel voted that crizotinib and entrectinib are the preferred first-line therapy options 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).[268,269,275,276] Although entrectinib has better CNS penetration than crizotinib, it is more toxic. If *ROS1* fusions are discovered during first-line systemic therapy (eg, carboplatin/paclitaxel), then the planned therapy may be either completed or interrupted followed by crizotinib (preferred), entrectinib (preferred), or ceritinib.

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, entrectinib, or ceritinib (see *Lorlatinib* in this Discussion).[277] Initial systemic therapy options that are used for adenocarcinoma or squamous cell carcinoma are also an option in this setting (eg, carboplatin/paclitaxel). Patients with *ROS1* rearrangements have a slight response (17%) to ICIs.[249] Alectinib, brigatinib, and ceritinib are not recommended in patients with *ROS1* fusions whose disease becomes resistant to crizotinib.[151] Studies are ongoing regarding new agents for patients with *ROS1* fusions whose disease becomes resistant to crizotinib, ceritinib, or entrectinib.[278-281] 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.

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.[282-284] 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*.[283] Various methods can be used to detect *NTRK* gene fusions, including FISH, IHC, NGS, and PCR assays (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). DNA-based NGS may not detect some *NTRK1* and *NTRK3* fusions; RNA-based NGS may be considered to assess for fusions.[285] In a clinical trial, *NTRK* gene fusions were detected with NGS (50 patients) and FISH (5 patients).[284] 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.[276,284]

The NCCN NSCLC Panel recommends *NTRK* gene fusion testing in patients with metastatic NSCLC based on clinical trial data showing the efficacy of larotrectinib and entrectinib for patients with *NTRK* gene fusion–positive disease; however, clinical data are limited in NSCLC to support this recommendation.[284,286,287] 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).[275,276,286,288] For the

2020 update (Version 1), the NCCN Panel voted that larotrectinib and entrectinib are both preferred (category 2A) as first-line therapy for patients with *NTRK* gene fusion–positive metastatic disease. A new section about *NTRK* fusions was also added to the algorithm (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). For example, if *NRTK1/2/3* testing was not included as part of a broad upfront panel, then *NTRK1/2/3* testing can be considered if the patient's tumor is negative for the main oncogenic drivers (ie, pan-negative for EGFR, ALK, ROS1, BRAF drivers).

METex14 Skipping Mutations

C-MET, the hepatocyte growth factor (HGF) receptor, is a tyrosine kinase receptor that is involved in cell survival and proliferation; oncogenic driver genomic alterations in MET include *METex14* skipping mutations, MET gene copy number (GCN) gain or amplification, and MET protein overexpression.[167] MET genomic alterations do not typically overlap with *EGFR*, *ROS1*, *BRAF*, and *ALK* genetic variants.[289] However, *METex14* skipping mutations and MET amplification may occur together. *METex14* skipping mutations occur in 3% to 4% of patients with adenocarcinomas NSCLC and 1% to 2% of patients with other NSCLC histologies.[290,291] *METex14* skipping mutations are more frequent in older women who are nonsmokers.[292]

Several different types of *METex14* skipping mutations may occur, such as mutations, base substitutions, and deletions, which makes it difficult to test for all of the mutations. NGS and RT-PCR assays can be used to detect *METex14* skipping mutations and *MET* amplification. Patients with *METex14* skipping mutations have a modest response (16%) to immunotherapy, even those with high PD-L1 levels.[249,293]

For the 2020 update (Version 4), the NCCN NSCLC Panel recommends testing for *METex14* skipping mutations (category 2A) in eligible patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *METex14* skipping mutations and on the FDA approval for capmatinib (see *Oral TKIs that Inhibit MET Exon 14 Skipping Mutations* in this Discussion).[294,295]

RET Rearrangements

RET is a tyrosine kinase receptor that affects cell proliferation and differentiation. Rearrangements (fusions) may occur in NSCLC between the RET gene and other domains, especially kinesin family 5B (*KIF5B*) and coiled coil domain containing-6 (*CCDC6*), which lead to overexpression of the RET protein.[296,297] *RET* rearrangements occur in about 1% to 2% of patients with NSCLC and are more frequent in patients with adenocarcinoma histology.[155,296-299] In European patients, *RET* rearrangements occur in both smokers and nonsmokers.[298] *RET* rearrangements do not typically overlap with *EGFR*, *ROS1*, *BRAF*, *METex14* skipping, and *ALK* genetic variants.[297] However, a few studies suggest that *RET* rearrangements may infrequently overlap with *EGFR* and *KRAS* mutations.[300,301] FISH, RT-PCR, and NGS assays can be used to detect *RET* rearrangements.[297] Patients with *RET* rearrangements have minimal response (6%) to immunotherapy.[249]

For the 2020 update (Versions 4 and 7), the NCCN NSCLC Panel recommends testing for *RET* rearrangements (category 2A) in eligible patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *RET* rearrangements and on the FDA approvals for selpercatinib (LOXO-292) and pralsetinib (see *Oral TKIs that Inhibit RET Rearrangements* in this Discussion).[152,302-304]

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.[105,147,174,181,182] *KRAS* mutation prevalence is associated with cigarette smoking.[305] Patients with *KRAS* mutations appear to have a shorter survival than patients with wild-type KRAS; therefore, *KRAS* mutations are prognostic biomarkers.[172,174,306] *KRAS* mutational status is also predictive of lack of therapeutic efficacy with EGFR TKIs; it does not appear to affect chemotherapeutic efficacy.[105,147,173] *KRAS* mutations do not generally overlap with *EGFR*, *ROS1*, *BRAF*, and *ALK* genetic variants.[150,168-171,307] Therefore, KRAS testing may identify patients who may not benefit from further molecular testing.[159,173] *KRAS* mutations may infrequently overlap with *EGFR* mutations and *RET* rearrangements.[300,301] Targeted therapy is not currently available for patients with *KRAS* mutations, although immune checkpoint inhibitors (ICIs) appear to be effective.[249,308]

Testing for Immune Biomarkers: PD-L1 Expression Levels

Human ICI 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).[309-311] Nivolumab and pembrolizumab inhibit PD-1 receptors.[121,312] Atezolizumab and durvalumab inhibit PD-L1.[313,314] The NCCN NSCLC Panel recommends (category 1) IHC testing for PD-L1 expression ideally before first-line treatment (if clinically feasible) in all patients with metastatic NSCLC to assess whether the ICI regimens are an option based on clinical data showing the efficacy of these regimens (see *Pembrolizumab* in this Discussion).[121,315]

The FDA-approved companion diagnostic test for PD-L1 expression is based on tumor proportion score (TPS) and used to determine usage of pembrolizumab in patients with metastatic NSCLC. TPS is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. Testing for PD-L1 is not required for prescribing first-line therapy with the atezolizumab plus chemotherapy regimens or for subsequent therapy with single-agent nivolumab or atezolizumab.

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 (ICIs; also known as immuno-oncology [IO] agents, immunotherapy).[316,317] 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.[316] Unique anti-PD-L1 IHC assays have been developed for each one of the different ICIs.[316,318-320] The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.[320] Extensive effort has been undertaken to examine the cross-comparability of different clones with regard to each other to facilitate adoption of testing.

The NCCN NSCLC Panel emphasizes that clinicians should obtain molecular testing results for actionable biomarkers before administering first-line ICI therapy, if clinically feasible. Therefore, for the 2020 update (Version 1), the panel deleted “or unknown” regarding test results for certain actionable molecular biomarkers before administering PD-1 or PD-L1 inhibitors. Patients with metastatic NSCLC and PD-L1 expression levels of 1% or more—but who also have a targetable driver oncogene molecular variant (eg, *EGFR, ALK, ROS1*)—should receive first-line targeted therapy for that oncogene and not first-line ICIs because targeted therapies yield higher response rates (eg, osimertinib, 80%) than ICIs (poor response rates) in the first-line setting, targeted therapy is better tolerated, and these patients are unlikely to respond to ICIs.[249,321-324] For the 2020 updates (Versions 1 and 4), the NCCN NSCLC Panel also deleted “or unknown” regarding test results for PD-L1 expression levels; the panel also added “*ROS1* and *RET* fusions” along with “*BRAF* and *MET* exon 14 skipping mutations” to the list of actionable biomarkers that need to be negative before administering PD-1 or PD-L1 inhibitors.[183] At a minimum, EGFR and ALK status should be known before starting systemic therapy with ICI regimens; however, it is ideal if ROS1, BRAF, RET, and *MET* exon 14 status are also known. If it is not feasible to do molecular testing, then patients are treated as though they do not have driver oncogenes.

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). Older adults may be at risk for treatment-related adverse events.[325]

Surgery

In general, surgery provides the best chance for cure in patients with stage I or II disease.[326] 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.[326-330] Although frailty is an increasingly recognized predictor of surgical and other treatment morbidity, a preferred frailty assessment system has not been established.[331-333]

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 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).[334] Patients with pathologic stage II or greater disease can be referred to a medical oncologist for evaluation. For patients with stage IIIA NSCLC that is deemed resectable, 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.[326,335,336] 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).[337-341] Resection (including wedge resection) is preferred over ablation.[326,336] Wide wedge resection may improve outcomes.[342] Patients with medically inoperable early-stage NSCLC may be candidates for SABR, also known as stereotactic body RT (SBRT).[343,344] If SABR is considered for patients at high risk, a multidisciplinary evaluation is recommended (see *Stereotactic Ablative Radiotherapy* in this Discussion).[345-347]

Lymph Node Dissection

The ACOSOG Z0030 randomized trial compared systematic mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in patients with NSCLC who had 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) disease. In patients with early-stage NSCLC who had negative nodes by systematic lymph node dissection, complete mediastinal lymph node dissection did not improve survival.[348,349] 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.[348] 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.[135] The lymph node map from the IASLC may be useful.[350] 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.

Thoracoscopic Lobectomy

Video-assisted thoracic surgery (VATS), which is also known as thoracoscopic 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).[351,352] Published studies suggest that thoracoscopic lobectomy has several advantages over thoracotomy.[353-357] Acute and chronic pain associated with thoracoscopic lobectomy is minimal; thus, this procedure requires a shorter length of hospitalization.[358,359] Thoracoscopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.[360-364] Thoracoscopic lobectomy is associated with less morbidity, fewer complications, and more rapid return to function than lobectomy by thoracotomy.[365-368]

In patients with stage I NSCLC who had thoracoscopic lobectomy with lymph node dissection, the 5-year survival rate, long-term survival, and local recurrence rate were comparable to those achieved by routine open lung resection.[369-373] Thoracoscopic lobectomy has also been shown to improve discharge independence in older populations and patients at high risk.[374,375] Data show that thoracoscopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.[376,377] Based on its favorable effects on postoperative recovery and morbidity, thoracoscopic 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).[378-381] Robotic VATS seems to be more expensive with longer operating times than conventional VATS.[382,383]

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, thoracoscopic procedures) and to discuss whether surgery is appropriate in a multidisciplinary team, which should include a thoracic surgeon.[384,385] Randomized controlled trials suggest that surgery does not increase survival in these patients.[386,387] However, one of these trials (EORTC) only enrolled patients with unresectable disease.[387] 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.[388] 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.[389,390] In patients with N2 disease, 50% of the NCCN Member Institutions use preoperative chemoradiotherapy whereas 50% use preoperative chemotherapy.[391,392] 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.[390] 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).[384,393] It is controversial whether pneumonectomy after preoperative chemoradiotherapy is appropriate.[386,393-399] Patients with resectable stage IIIA (N2) disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.[393,400] For the 2020 update (Version 1), the NCCN NSCLC panel deleted the recommendation for postoperative chemotherapy in patients with T1–3 (other than invasive) N2 disease receiving induction chemotherapy with or without RT.

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.[401-406] These RT principles are summarized in this section. Whole brain RT and stereotactic radiosurgery (SRS) for brain metastases are also discussed in this section. The RT abbreviations are defined in the NSCLC algorithm (see Table 1 in *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC). Recently, 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 based on the biomedical literature (see Table 5).[407-412]

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 radiation oncologists who perform lung cancer RT as a prominent part of their practice should be part of the multidisciplinary evaluation 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.[347,413-420] 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.[421-427] A secondary analysis of the RTOG 0617 randomized trial 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).[428] 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.[429,430] Ideally, PET/CT should be obtained 4 weeks before treatment because of the potential for rapid progression of NSCLC.[431,432] 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).[426,433-436] 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).[437]

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).[402,404,417,438-443] 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;[444,445] the ACR Practice Parameters and Technical Standards are also a helpful reference.[423,446,447] 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*).[448] 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.[449-453]

Recently, 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).[407-412] These constraints are mainly empirical and have not, for the most part, been validated rigorously.[411,438,454-459] 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 also added 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 (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).[460,461] RTOG 0617, a phase 3 randomized trial, suggests 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.[408,462-466] Although optimal RT dose intensification remains a valid question, at higher RT doses, normal tissue constraints become even more important.[464] Although the RT dose to the heart was decreased in the RTOG 0617 trial, survival was decreased; thus, more stringent constraints may be appropriate.[466-472] The NCCN Panel does not currently recommend a high dose of 74 Gy for routine use.[463,465,466,468-475]

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).[343,344,347,420,476,477] Image-guided thermal ablation is an option for selected patients who are medically inoperable or those who need definitive local therapy.[326,478-482] By extrapolation from surgical data, chemotherapy may be considered after definitive RT/SABR in patients with high-risk factors for recurrence (eg, large tumors >4 cm in size); for the 2020 update (Version 1), the NCCN NSCLC Panel revised the chemotherapy recommendation to category 2A from 2B.[345,483] 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).[484] 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.[485]

Definitive chemoradiation is recommended for patients with stage II to III disease who are not appropriate surgical candidates.[486] 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.[487] Dose escalation is associated with better survival in non-randomized comparisons in RT alone, sequential chemo/RT, or concurrent chemo/RT.[468,475,488] A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens.[489] 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).[490-497]

The optimal management of patients with potentially operable stage IIIA (N2) NSCLC is controversial and is discussed in detail in the algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).[384,386,398,498] For patients undergoing preoperative therapy before surgical resection of stage IIIA NSCLC, some oncologists prefer chemotherapy alone rather than chemoradiotherapy for the preoperative treatment;[390] RT should generally be given postoperatively if not given preoperatively.[499] The NCCN NSCLC Panel recommends a preoperative RT dose of 45 to 54 Gy in 1.8 to 2 Gy fractions.[389,500] Definitive RT doses delivered as preoperative chemo/RT can safely be administered and achieve promising nodal clearance and survival rates;[441-443,501] the risk of surgical complications after high-dose RT can be minimized with expert thoracic surgical techniques. NCCN Member Institutions are split evenly in their use of preoperative chemotherapy versus preoperative chemoradiation in patients with stage IIIA N2 NSCLC.[384] 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,[386] 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.[502] 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.[403,503,504] Lung dose constraints should be more conservative, because tolerance appears to be reduced after surgery. The European LungART trial provides useful guidelines for postoperative RT technique.[505] 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 preoperative concurrent chemoradiation (ie, ≥60 Gy). Soft tissue flap coverage and reduced intraoperative fluid administration and ventilator pressures can reduce the risk of these complications.[441-443] 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).[420,506-508] 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).[509-512] 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.[506,513] 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).

Oligometastatic disease is heterogenous and refers to isolated or limited metastatic sites; management is evolving. Definitive local therapy to oligometastases (including brain, lung) achieves prolonged survival in a small proportion of well-selected patients with good PS who have also received radical therapy to the intrathoracic disease.[514] Definitive RT to oligometastases, particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.[515,516] In 2 randomized phase II trials, significantly longer 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.[517,518] Updated data from one of the trials also shows that median overall survival was longer for patients with oligometastatic NSCLC who received local consolidative therapy (median, 41.2 months; 95% CI, 18.9 months–not reached) compared with those receiving maintenance therapy or observation (median, 17.0 months; 95% CI, 10.1–39.8 months; P = .017).[519] A phase 2 trial of consolidative RT for oligometastatic NSCLC (n = 29) reported median overall survival of 28.4 months (95% CI, 14.5–45.8 months).[520] The NCCN Guidelines recommend that local therapy (RT, SABR, or surgery) to primary and oligometastatic lesions should be considered for patients without progression on systemic therapy.[517-519]

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.[343,521-524] 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.[347,525-529] 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%.[344] 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.[326,344,436,482,484,528,530-535] 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.[476] 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.[484,527,536-541] 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.[542] If possible, biopsy should confirm NSCLC before use of SABR.[543,544] A multidisciplinary evaluation is recommended to provide consensus that a biopsy is safe or too risky. Data suggest that survival outcomes may be biased in patients who do not receive pathologic confirmation of malignancy; some of these patients may not have NSCLC.[543]

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).[326,529,531,545,546] A combined analysis of 2 randomized trials (that individually did not complete accrual) compared SABR to lobectomy.[545] 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.[522,529,547-553] 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.[554,555] This careful follow-up is particularly relevant, because selected patients with localized recurrences after SABR may benefit from surgery or re-treatment with SABR.[556-560]

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).[343,526,528,535,561-571] 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.[571,572] Prescription doses do not completely describe the actual delivered doses.[573,574] 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).[345,564,575-577] Data from the RTOG 0813 trial suggest that 5-fraction regimens are safe.[578,579]

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).[334,515,516,529,580-583] 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.[580,581] Targeted therapy and consideration of local therapy (eg, surgery or SABR [or SRS] for isolated lesions) are recommended for patients with *ALK* fusions or sensitizing *EGFR* mutations who have progressed on targeted therapy, depending on the type of progression.[584-587] 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.[588-590] 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.[326,347,482]

Whole Brain RT and Stereotactic Radiosurgery

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.[20,591] Whole brain RT is associated with measurable declines in neurocognitive function in clinical trials, particularly with increasing dose and advanced age of the patient.[592-594] However, control of brain metastases confers improved neurocognitive function.[595,596] 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.[596,597] Thus, SRS alone is recommended for patients with limited volume metastases.[598] 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.[599] 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). 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.[600,601] A study suggests that using IMRT to avoid the hippocampus may help decrease memory impairment after whole brain RT.[602] 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.[603] 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. Two retrospective analyses have reported increased survival in patients with brain metastases who received SRS and concurrent ICI therapy.[604,605]

Options for treatment of limited brain metastases in patients with NSCLC include: 1) SRS alone; and 2) surgical resection for selected patients followed by SRS or whole brain RT (see the NCCN Guidelines for NSCLC). Selected patients include those with symptomatic metastases or whose tumor tissue is needed for diagnosis.[550,591,599,606-612] 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.[606,613-615] Treatment should be individualized for patients with recurrent or progressive brain lesions.[616] 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.[617] Clinicians are using whole brain RT less often in patients with NSCLC and limited brain metastases.[599] 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).[598,618-620]

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.[621-624] 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).[384,625-631] A randomized trial found no difference in survival with preoperative versus postoperative chemotherapy.[632] 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.[326,633] Concurrent chemoradiation is more efficacious than sequential chemoradiation for patients with unresectable stage III disease.[634-637] Cytotoxic chemotherapeutic agents can cause hair loss, which is distressing for patients. Hair loss varies depending on the regimen and other factors. Data in women with non-metastatic breast cancer suggest that a scalp cooling device may help reduce hair loss in patients receiving cytotoxic chemotherapy regimens.[638-642]

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.[643-648] 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.[649,650] Patients should receive treatment for debilitating symptoms.[20,651,652] A study also suggests that social support, such as being married, is as effective as systemic therapy.[653] Data suggest that systematic symptom monitoring during outpatient chemotherapy treatment increases overall survival when compared with usual care.[654-656] 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).[657] 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).[334,514,517,519,529,580,581] The trials supporting the recommendations for combined modality therapy are discussed in the following sections.

Surgery Followed by Chemotherapy: Trial Data

The International Adjuvant Lung Cancer Trial (IALT) assessed cisplatin-based postoperative therapy in patients with completely resected stage I, II, or III NSCLC.[622] 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. The survival rate at 5 years was 45% for cisplatin-based therapy versus 40% for observation (HR for death, 0.86; 95% CI, 0.76–0.98; *P* < .03); the disease-free survival rate was 39% versus 34% at 5 years (HR, 0.83; 95% CI, 0.74–0.94; *P* < .003). However, after 7.5 years of follow-up, there were more deaths in the chemotherapy group and the benefit of chemotherapy decreased over time.[658] 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.[623] Postoperative chemotherapy significantly prolonged overall survival compared with observation alone (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). 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.[659] 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.[624] 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.[624] 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;[660] however, most clinicians in the United States prefer to use regimens with less toxicity.[661,662]

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).[663] A subgroup analysis found that cisplatin/vinorelbine also increased survival.[660] 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.[329,664]

The CALGB 9633 trial assessed paclitaxel/carboplatin in patients with stage IB (T2a,N0,M0) lung cancer.[665-667] 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 (however, a subset analysis showed a benefit for tumors 4 cm or more), although 3-year survival was significant (80% vs. 73%, *P* = .02).[666,667] 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).[668] It is important to note that the CALGB trial was underpowered for patients with stage 1B disease.[669]

The TREAT study assessed cisplatin/pemetrexed versus cisplatin/vinorelbine as postoperative therapy for patients with completely resected stages IB to III NSCLC in a phase 2 randomized trial.[661] The trial showed that cisplatin/pemetrexed was an effective, less toxic regimen compared with cisplatin/vinorelbine; in addition, patients were able to receive more cycles of cisplatin/pemetrexed compared with cisplatin/vinorelbine.[661] Overall survival at 3 years was similar between the arms (75% vs. 77%; *P* = .858).[670]

In the NSCLC algorithm for resected stage IA disease, postoperative chemotherapy is not recommended based on the trials described in the previous paragraphs.[671] 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 chemotherapy for patients with patients with completely resected stages IB to III NSCLC are provided in the NCCN Guidelines; the regimens also include specific dosing (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy* in the NCCN Guidelines for NSCLC).[621,671] For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified all the systemic therapy regimens and decided that cisplatin/pemetrexed is the preferred preoperative and postoperative regimen for nonsquamous NSCLC.[661,670] Cisplatin/gemcitabine and cisplatin/docetaxel are the preferred preoperative and postoperative regimens for patients with squamous cell NSCLC.[672,673] Other recommended regimens include cisplatin/vinorelbine and cisplatin/etoposide.[622-624] Preoperative and postoperative therapy regimens for patients with comorbidities or those not able to tolerate cisplatin are designated as useful in certain circumstances and include: 1) carboplatin/paclitaxel; 2) carboplatin/gemcitabine; and 3) carboplatin/pemetrexed (but only for nonsquamous NSCLC).[674-677] Preoperative and postoperative therapy is also known as neoadjuvant and adjuvant therapy, respectively.

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 NATCH, a phase 3 randomized 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.[630] 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.[632] Postoperative chemotherapy (with or without RT or reresection) is recommended and typically used for early-stage disease in the NCCN Guidelines.[326]

Several trials suggest that preoperative therapy is beneficial in patients with N2 disease.[384,390,629] Other trials suggest that preoperative therapy is beneficial in patients with earlier stage disease.[626,627,631] 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.[631]

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).[626] 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 longer than the surgery alone arm (HR, 0.84; 95% CI, 0.77–0.92; *P* = .0001).[625] These results are similar to those reported in another meta-analysis (HR, 0.89; 95% CI, 0.81–0.98; *P* = .02).[626] The benefit from preoperative chemotherapy is similar to that attained with postoperative chemotherapy.[626,632,663]

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.[678-682] For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is more efficacious than radiation alone.[678,679,681-683] Concurrent chemoradiation is more efficacious than sequential chemoradiation.[634-637,684] 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.[489,685] Sequential chemoradiation or RT alone is recommended for frail patients who cannot tolerate concurrent chemoradiation.[327,686]

JCOG0301, a phase 3 randomized trial, assessed chemo/RT using low-dose carboplatin versus RT alone in elderly patients (>70 years) with unresectable NSCLC.[687] Median overall survival was 22.4 months (95% CI, 16.5–33.6) for chemoradiotherapy with carboplatin and 16.9 months (95% CI, 13.4–20.3) for RT alone (HR, 0.68; 95.4% CI, 0.47–0.98, *P*=.0179). In the chemo/RT group, 3% (3/100) of patients died, whereas 4% (4/100) of patients died in the RT group. Grade 3 to 4 hematologic effects occurred at a greater rate in the chemo/RT arm than in the RT alone arm, including leucopenia (61 [63.5%] vs. none), neutropenia (55 [57.3%] vs. none), and thrombocytopenia (28 [29.2%] vs. 2 [2.0%]). Long-term follow-up data show that overall survival is improved in elderly patients receiving chemo/RT versus RT alone (HR, 0.743; 95% CI, 0.552–0.998; *P* = .0239).[688] A 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).[499] 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.[402,404,405,689]

Concurrent chemoradiation regimens that may be used for all histologies for initial treatment include cisplatin/etoposide and carboplatin/paclitaxel (see *Chemotherapy Regimens Used with Radiation Therapy* in the NCCN Guidelines for NSCLC).[463,634,636,690-695] For nonsquamous NSCLC, additional concurrent chemoradiation regimens may be used including carboplatin/pemetrexed and cisplatin/pemetrexed.[696-698] A weekly paclitaxel/carboplatin regimen is another chemoradiation option.[463] The different options for preoperative, definitive, and postoperative chemotherapy/RT are described in detail in the algorithm. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified all the systemic therapy regimens and decided that the following concurrent chemoradiation regimens are preferred for patients with NSCLC: 1) carboplatin/pemetrexed and cisplatin/pemetrexed for nonsquamous NSCLC only; and 2) carboplatin/paclitaxel and cisplatin/etoposide for all histologies. For the 2020 update (Version 1), the panel also deleted the cisplatin/vinblastine concurrent regimen, because this regimen is rarely used in the United States. 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 ICI antibody that inhibits PD-L1 (see *PD-L1 Expression Levels* and *Immunotherapies* in this Discussion).[309-311,313] PACIFIC, a phase 3 randomized trial, compared adjuvant treatment with durvalumab (also known as consolidation immunotherapy in this setting) versus placebo in eligible patients with unresectable stage III NSCLC (PS 0–1) who had not progressed after treatment with 2 or more cycles of definitive concurrent platinum-based chemoradiation.[313,699] Eligible patients received adjuvant durvalumab after treatment with 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 (not reached [34.7 months–not reached] vs. 28.7 months [22.9– not reached]; stratified HR for death, 0.68; 99.73% CI, 0.47–0.997; $P = .0025$).[699] 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%).[699] 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). Overall survival data after 3 years continue to show improvement with durvalumab.[700] 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%). Durvalumab did not compromise patient-reported outcomes.[701]

The NCCN NSCLC Panel recommends durvalumab (category 1) as consolidation immunotherapy (regardless of PD-L1 status) for eligible patients (PS 0–1) with unresectable stage III NSCLC who have not progressed after treatment with 2 or more cycles of definitive concurrent platinum-based chemoradiation based on this trial and FDA approval.[313,699] It is important to note that adjuvant durvalumab is not recommended for patients who have had surgical resection. In addition, durvalumab is used as adjuvant treatment in this setting; it is not being used as second-line therapy. Durvalumab may be used as consolidation immunotherapy after treatment with 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).

If patients will be receiving durvalumab but have not received full-dose chemotherapy concurrently with RT, the NCCN NSCLC Panel does not recommend an additional 2 cycles of full-dose chemotherapy (ie, consolidation chemotherapy) based on concerns that adding 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). If patients will not be receiving durvalumab because of medical contraindications or other reasons, consolidation chemotherapy is an option after concurrent chemoradiation if patients have not received full-dose chemotherapy concurrently with RT.

Chemotherapy: Trial Data

Patients with metastatic (stage IV) NSCLC who have a good PS benefit from chemotherapy, usually with a platinum-based regimen, which was used for many years before the advent of targeted therapy and immunotherapy regimens.[645-647] Combination chemotherapy regimens produce 1-year survival rates of 30% to 40% and are more efficacious than single agents.[668,673,702-704] However, survival rates are higher for patients with stage IV NSCLC who are eligible for either the newer targeted therapy or immunotherapy regimens.[10-17] Phase 3 randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.[705,706] The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients.[707-710] Carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;[673,711-713] non–platinum-based regimens such as gemcitabine/vinorelbine and gemcitabine/docetaxel are also options.[714-717] The prognosis for stage IV inoperable lung cancer remains poor if patients are not candidates for targeted therapy.

In the United States, frequently used initial cytotoxic regimens for stage IV nonsquamous NSCLC include: 1) cisplatin (or carboplatin)/pemetrexed; or 2) carboplatin/paclitaxel with (or without) bevacizumab.[690,718,719] Gemcitabine plus cisplatin (or carboplatin) is often used for patients with stage IV squamous cell NSCLC.[704,709,718,719] These chemotherapy regimens are recommended based on phase 3 randomized trials (eg, cisplatin/pemetrexed, carboplatin/paclitaxel [with or without bevacizumab], gemcitabine/cisplatin) (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).[704,720] 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).[721,722]

A phase 3 randomized trial assessed cisplatin/pemetrexed versus cisplatin/gemcitabine as first-line therapy in patients with stage IIIB or IV NSCLC.[704] For patients with adenocarcinoma who received cisplatin/pemetrexed, median overall survival was 12.6 months compared with 10.9 months for those receiving cisplatin/gemcitabine (HR, 0.84; 95% CI, 0.71–0.99; $P = .03$). In contrast, for patients with squamous cell NSCLC who received cisplatin/pemetrexed, overall survival was 9.4 versus 10.8 months for those receiving cisplatin/gemcitabine (HR, 1.23; 95% CI, 1.00–1.51; $P = .05$). Patients with nonsquamous NSCLC receiving cisplatin/pemetrexed have less toxicity when compared with those receiving cisplatin/gemcitabine.[723] Median overall survival was similar for both regimens when histologies were combined (8.6 vs. 9.2 months, respectively; HR, 1.08; 95% CI, 0.81–1.45; *P* = .586).

TAX 326, a phase 3 randomized trial, assessed docetaxel plus cisplatin (or carboplatin) versus vinorelbine/cisplatin as first-line therapy for patients with stage IIIB or IV nonsmall cell lung cancer.[673] Docetaxel plus cisplatin was associated with similar overall survival (11.3 vs. 10.1 months (*P* =.044; HR, 1.183 [97.2% CI, 0.989–1.416]) and better response rate (31.6%) when compared with cisplatin/vinorelbine (24.5%; *P* =.029); docetaxel/cisplatin was associated with better quality of life and was better tolerated.

Many oncologists use pemetrexed-based regimens for stage IV adenocarcinomas (if patients are not candidates for targeted therapy or PD-1/PD-L1 inhibitors), because taxane-based regimens are associated with more toxicity (eg, neurotoxicity).[704,724] There are no agents for the prevention of peripheral neuropathy, and few agents are useful for treatment.[725] The POINTBREAK trial showed that carboplatin/pemetrexed/bevacizumab is a reasonable option for patients with metastatic NSCLC and confirmed that taxane-based regimens are more toxic than pemetrexed-based regimens.[726] 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 (≥65 years) with advanced nonsquamous NSCLC.[727] However, another retrospective cohort study reported increased survival in older patients.[728] 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.[729]

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.[730,731] A phase 3 randomized trial in patients with advanced NSCLC 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.[732] 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.

Chemotherapy is recommended for patients with stage IV NSCLC and negative test results for *EGFR, ALK, ROS1, METex14* skipping, or *BRAF* genetic variants; PD-L1 expression less than 1%; and contraindications to PD-1 or PD-L1 inhibitors. 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).

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.[204] For nonsquamous NSCLC or NSCLC NOS, single-agent chemotherapy includes gemcitabine, pemetrexed, or taxanes; combination chemotherapy regimens include carboplatin/paclitaxel or carboplatin/pemetrexed.[733-735] Patients with a PS of 2 are often just treated with single-agent chemotherapy because of concerns about toxicity.[736] 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.[733,737]

For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified all the systemic therapy regimens. The newer chemotherapy/pembrolizumab regimens are preferred for eligible patients with metastatic NSCLC who do not have contraindications to immunotherapy and are not candidates for targeted therapy (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC and *Pembrolizumab* in this Discussion). For patients with metastatic nonsquamous NSCLC and PS 0 to 1 who have contraindications to immunotherapy, the panel decided that the following chemotherapy regimens are "useful in certain circumstances," including 1) carboplatin with paclitaxel (or albumin-bound paclitaxel), docetaxel, etoposide, gemcitabine, or pemetrexed; all are category 1; 2) cisplatin with paclitaxel (or albumin-bound paclitaxel), docetaxel, etoposide, gemcitabine, or pemetrexed; all are category 1; 3) bevacizumab with carboplatin and either paclitaxel or pemetrexed; and 4) gemcitabine with either docetaxel or vinorelbine. The panel also preference stratified the regimens for patients with metastatic nonsquamous NSCLC and PS 2; carboplatin/pemetrexed is preferred for patients with adenocarcinoma. The regimens for patients with metastatic squamous cell NSCLC have also been preference stratified.

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). For patients with metastatic nonsquamous NSCLC and NSCLC NOS, panel members deleted carboplatin/vinorelbine, cisplatin/vinorelbine, etoposide, irinotecan, and vinorelbine. For patients with metastatic squamous cell NSCLC, panel members deleted carboplatin/etoposide, carboplatin/vinorelbine, cisplatin/gemcitabine/necitumumab, cisplatin/vinorelbine, etoposide, irinotecan, and vinorelbine.

The NCCN NSCLC Panel 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).[738] 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.[739]

Targeted Therapies

Specific targeted therapies are available for the treatment of eligible patients with metastatic NSCLC.[158,740,741] Afatinib, alectinib, brigatinib, ceritinib, crizotinib, erlotinib, gefitinib, osimertinib, dacomitinib, dabrafenib, trametinib, entrectinib, larotrectinib, and lorlatinib are oral TKIs. Bevacizumab and ramucirumab are recombinant monoclonal antibodies that target the 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* fusions, *ROS1* fusions, and *MET* tyrosine kinases (ie, high-level *MET* amplification, *METex14* skipping mutation). Ceritinib inhibits *ALK* fusions and IGF-1 receptor. Alectinib inhibits *ALK* and *RET* fusions.[742] Brigatinib inhibits various *ALK* fusions and other targets.[743] Lorlatinib inhibits *ALK* and *ROS1* fusions.[275,277,744,745] Dabrafenib inhibits *BRAF* V600E mutations; trametinib inhibits MEK; both agents inhibit different kinases in the RAS/RAF/MEK/ERK pathway.[168,169] Entrectinib and larotrectinib inhibit *TRK* fusion proteins.[284,286,287] Capmatinib inhibits several MET tyrosine kinases including *METex14* skipping mutations.[294] Selpercatinib, pralsetinib, cabozantinib, and vandetanib inhibit *RET* rearrangements.[152,303,304,746] Other targeted therapies are being developed (see *Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC* in the NCCN Guidelines for NSCLC). Flare phenomenon may occur in some patients who discontinue targeted therapies for *EGFR*, *ALK*, or *ROS1* genetic variants. If disease flare occurs, then the targeted therapies should be restarted.[747-750]

It is important to note that targeted therapies are recommended for patients with metastatic NSCLC and specific oncogenic drivers, independent of PD-L1 levels. Patients with metastatic NSCLC and PD-L1 expression levels of 1% or more—but who also have a targetable driver oncogene molecular variant (eg, *EGFR, ALK, ROS1*)—should receive first-line targeted therapy for that oncogene and not first-line ICIs, because targeted therapies yield higher response rates (eg, osimertinib, 80%) than ICIs (poor response rates) in the first-line setting, targeted therapy is better tolerated, and these patients are unlikely to respond to ICIs.[249,321-323,751] For the 2020 update (Version 1), the NCCN NSCLC Panel emphasizes that clinicians should obtain molecular testing results for actionable biomarkers before administering first-line therapy, if clinically feasible. Therefore, the panel deleted “or unknown” regarding test results for actionable molecular biomarkers before administering PD-1 or PD-L1 inhibitors. At a minimum, EGFR and ALK status should be known before starting first-line systemic therapy, if clinically feasible; however, it is ideal if ROS1 and BRAF status are also known. If it is not feasible to do molecular testing, then patients are treated as though they do not have driver oncogenes.

VEGF or VEGF Receptor Inhibitors

Bevacizumab

Bevacizumab is a recombinant monoclonal antibody that targets VEGF. ECOG 4599, a phase 3 randomized trial, assessed bevacizumab added to paclitaxel/carboplatin versus chemotherapy alone in patients with recurrent or advanced nonsquamous NSCLC (stage IIIB–IV).[720] In the bevacizumab/chemotherapy group, median survival was 12.3 months versus 10.3 months with chemotherapy alone (HR for death, 0.79; *P*=0.003). Clinically significant bleeding occurred more often with bevacizumab/chemotherapy versus chemotherapy alone (4.4% vs. 0.7%, respectively; *P* < .001). Fifteen treatment-related deaths were reported with bevacizumab/chemotherapy.

Bevacizumab may be added to carboplatin/paclitaxel (category 1), carboplatin/pemetrexed, or cisplatin/pemetrexed. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that these specific bevacizumab plus chemotherapy first-line therapy options are “useful in certain circumstances” for eligible patients with metastatic NSCLC based on clinical data and the FDA approval.[720,752] These bevacizumab plus chemotherapy regimens are an option for patients with PS 0 to 1, nonsquamous NSCLC or NSCLC NOS, negative test results for *EGFR,* *ALK*, *ROS1*, *METex14* skipping, or *BRAF* variants, PD-L1 expression less than 1%, and contraindications to PD-1 or PD-L1 inhibitors (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, ABCP) is a first-line therapy option (category 1, other recommended) regardless of PD-L1 expression for patients with PS 0 to 1; nonsquamous NSCLC or NSCLC NOS; negative test results for *EGFR, ALK*, *ROS1*, *METex14* skipping, or *BRAF* variants; and no contraindications to PD-1 or PD-L1 inhibitors or bevacizumab (see *Atezolizumab* in this Discussion). 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.[753-757] 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 is not recommended for patients with squamous cell NSCLC.

Ramucirumab

Ramucirumab is a recombinant monoclonal antibody that targets VEGF receptors.

First-Line Therapy

RELAY, a phase 3 randomized trial, compared first-line therapy with ramucirumab/erlotinib versus erlotinib alone in patients with advanced NSCLC and sensitizing *EGFR* mutations.[758] PFS was 19.4 months (95% CI, 15.4–21.6) with ramucirumab/erlotinib versus 12.4 months (95% CI, 11.0–13.5) with erlotinib alone (HR, 0.59; 95% CI, 0.46–0.76; $P < .0001$). Serious adverse events (grade 3–4) occurred in 72% (159/221) of patients receiving erlotinib/ramucirumab (including hypertension) versus 54% (121/225) in those receiving erlotinib alone (including increased alanine aminotransferase [ALT]). One treatment-related death occurred in a patient receiving erlotinib/ramucirumab. For the 2020 update (Version 2), the NCCN NSCLC Panel recommends erlotinib/ramucirumab as a first-line therapy option for patients with *EGFR*-positive metastatic NSCLC (category 2A, other recommended intervention) based on clinical data.[758]

Subsequent Therapy

REVEL, a phase 3 randomized trial, assessed ramucirumab/docetaxel versus docetaxel alone in patients with metastatic NSCLC that had progressed.[759] The median overall survival was 10.5 months for ramucirumab/docetaxel versus 9.1 months for docetaxel alone (HR, 0.86; 95% CI, 0.75–0.98; $P < .023$). 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. The NCCN NSCLC Panel recommends ramucirumab/docetaxel (category 2A) as a subsequent therapy option for patients with metastatic NSCLC, regardless of histology, that has progressed after first-line chemotherapy based on the REVEL trial and the FDA approval.[759,760]

Oral TKIs that Inhibit EGFR Mutations

Osimertinib

Osimertinib (AZD9291) is an oral TKI that inhibits both *EGFR* sensitizing mutations and T790M. As previously mentioned, *EGFR* sensitizing mutations include Exon19del and L858R as well as other rarer mutations (see *EGFR Mutations* in this Discussion). Both mutations are associated with sensitivity to the small-molecule oral EGFR TKIs, such as osimertinib, erlotinib, gefitinib, afatinib, and dacomitinib.[200] The NCCN NSCLC Panel recommends *EGFR* mutation testing (category 1) in certain patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *EGFR* mutations and on the FDA approvals (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[321,761] *EGFR* T790M is a mutation associated with acquired resistance to first-line therapy with EGFR TKIs and has been reported in about 60% of patients with disease progression after initial response to sensitizing EGFR TKIs.[197,218-224] 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.[207,212,219,226] Data show that patients receiving osimertinib as first-line therapy have PFS of about 19 months.[321,762] Flare phenomenon may occur in some patients who discontinue EGFR TKIs. If disease flare occurs, then the EGFR TKIs should be restarted.[747-750]

First-Line Therapy

FLAURA, a phase 3 randomized trial, assessed first-line therapy with osimertinib compared with either erlotinib or gefitinib in patients with metastatic NSCLC and *EGFR* mutations regardless of T790M status.[10,321,761,762] PFS was longer with osimertinib (18.9 months; 95% CI, 15.2–21.4) 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 compared with erlotinib or gefitinib (median response, 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. An updated analysis showed that median overall survival was 38.6 months with osimertinib (95% CI, 34.5–41.8) compared with 31.8 months (95% CI, 26.6–36.0) for either erlotinib or gefitinib (HR, 0.8; 95% CI, 0.64–1.0; *P* = .046).[10]

The NCCN NSCLC Panel recommends osimertinib as a preferred first-line therapy option for patients with metastatic NSCLC who have sensitizing *EGFR* mutations based on the phase 3 trial and FDA approval.[10,321] Osimertinib is a category 1 (preferred) recommended option if an *EGFR* mutation is discovered before giving first-line systemic therapy (eg, pembrolizumab/chemotherapy), and osimertinib is a category 2A (preferred) option if an *EGFR* mutation is discovered during first-line systemic therapy.[10] For patients receiving first-line ICIs with or without chemotherapy, oncologists should be aware of the long half-life of the ICIs and potential adverse effects when combining ICIs with osimertinib.[763-765]

Subsequent Therapy

AURA3, a 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. PFS was longer with osimertinib compared with chemotherapy (10.1 vs. 4.4 months; HR, 0.30; 95% CI, 0.23–0.41; *P* < .001).[226] PFS was also longer in patients with CNS metastases who received osimertinib versus chemotherapy (8.5 vs. 4.2 months; HR, 0.32; 95% CI, 0.21–0.49). In addition, the objective response rate was increased with osimertinib (71%; 95% CI, 65%–76%) 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 was 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 compared with those receiving chemotherapy (23% vs. 47% [63/279 vs. 64/136]). There were 4 fatal events with osimertinib (respiratory failure [2 patients], pneumonitis, and ischemic stroke) and one with chemotherapy (hypovolemic shock).

The NCCN NSCLC Panel recommends osimertinib (category 1) as a subsequent therapy option for patients with metastatic *EGFR* T790M-positive NSCLC who have progressed on EGFR TKIs (including erlotinib with or without ramucirumab or bevacizumab) based on the phase 3 randomized trial and FDA approval [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion].[226] 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 (eg, SABR or surgery); 2) continuing osimertinib; or 3) a first-line systemic therapy regimen for metastatic NSCLC (such as carboplatin/paclitaxel). There are no data to support using erlotinib (with or without ramucirumab or bevacizumab), gefitinib, afatinib, or dacomitinib after progression on first-line therapy with osimertinib. 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.[766-768] The NCCN NSCLC Panel also recommends osimertinib (category 1) for patients with T790M who have symptomatic brain metastases after progression on erlotinib (with or without ramucirumab or bevacizumab), gefitinib, afatinib, or dacomitinib based on data showing an improvement.[226,769-772]

Updated data from the BLOOM study suggest that osimertinib is beneficial for patients with *EGFR* mutations (regardless of T790M status) who have progressive leptomeningeal disease.[773] In the BLOOM 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 had improved and one had stable disease. Of 15 asymptomatic patients, 87% (13/15) remained asymptomatic.[773] Several studies suggested that pulse erlotinib is beneficial for patients with *EGFR* mutations who have progressive leptomeningeal disease.[774-776] 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).[776] Based on these studies, the NCCN NSCLC Panel feels that osimertinib (regardless of T790M status) can be considered for patients with *EGFR* mutations who have progressive leptomeningeal disease. For the 2020 update (Version 1), pulse erlotinib was deleted as an option for progressive leptomeningeal disease because osimertinib is a better option in this setting.

Erlotinib and Gefitinib

Erlotinib and gefitinib are oral TKIs that inhibit sensitizing *EGFR* mutations. IPASS, a phase 3 randomized trial, assessed first-line therapy with gefitinib alone versus carboplatin/paclitaxel in Asian patients with *EGFR*-positive metastatic NSCLC.[212] Patients with sensitizing *EGFR* mutations who received gefitinib had longer PFS (24.9% vs. 6.7%), increased response rate (71.2% vs. 47.3%), and improved quality of life with fewer side effects (eg, neutropenia) compared with carboplatin/paclitaxel.[212] Updated results from the IPASS trial showed that overall survival was similar in patients receiving gefitinib or chemotherapy regardless of sensitizing *EGFR* mutation status.[777] 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.

EURTAC, a phase 3 randomized trial, assessed first-line therapy with erlotinib versus chemotherapy in European patients with metastatic NSCLC and sensitizing *EGFR* mutations.[207] PFS was longer and response rate was increased for those receiving erlotinib compared with chemotherapy.[207] 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.[778] 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.[157,779]

CALGB 30406, a phase 3 randomized trial, compared first-line erlotinib monotherapy versus erlotinib plus carboplatin plus paclitaxel in patients (mainly Caucasian) with advanced NSCLC and sensitizing *EGFR* mutations.[780] Erlotinib monotherapy was associated with fewer side effects in patients with sensitizing *EGFR* mutations 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 first-line chemotherapy (see *EGFR Mutation Positive/First-Line Therapy* in the NCCN Guidelines for NSCLC).[781] The NCCN Guidelines do not recommend adding EGFR TKIs to current chemotherapy based on this CALGB study.[780] 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).

WJOG 5108L, a phase 3 randomized trial, 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.[782] The median PFS was 8.3 months for gefitinib versus 10.0 months for erlotinib 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 ALT/aspartate aminotransferase (AST) levels (gefitinib: 6.1%/13.0% vs. erlotinib: 2.2%/3.3%).

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.[783] The TORCH trial suggested that *EGFR* mutation testing should be done in patients with advanced nonsquamous NSCLC.[784] Survival was longer 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.[210,211] 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.[785,786]

RELAY, a phase 3 randomized trial, compared first-line therapy with erlotinib/ramucirumab versus erlotinib alone in patients with advanced NSCLC and sensitizing *EGFR* mutations.[758] PFS was 19.4 months (95% CI, 15.4–21.6) with erlotinib/ramucirumab versus 12.4 months (95% CI, 11.0–13.5) with erlotinib (HR, 0.59; 95% CI, 0.46–0.76; $P < .0001$). The overall response rate was similar (erlotinib/ramucirumab: 76% versus erlotinib alone: 75%). Serious adverse events (grade 3–4) occurred in 72% (159/221) of patients receiving erlotinib/ramucirumab (including hypertension) versus 54% (121/225) in those receiving erlotinib alone (including increased ALT). One treatment-related death occurred in a patient receiving erlotinib/ramucirumab.

NEJ026, a phase 3 randomized trial, compared first-line erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced nonsquamous NSCLC.[787] At interim analysis, PFS was 16.9 months (95% CI, 14.2–21.0) for erlotinib/bevacizumab versus 13.3 months (95% CI, 11.1–15.3) for erlotinib alone (HR, 0.605; 95% CI, 0.417–0.877; *P* = .016). Grade 4 adverse events occurred in 8% (9/112) of patients receiving erlotinib/bevacizumab (including neutropenia, hepatic dysfunction) versus 4% (5/114) of patients receiving erlotinib alone (hepatic dysfunction); no treatment-related deaths were reported.

The NCCN NSCLC Panel recommends erlotinib and gefitinib as first-line therapy options in patients with 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).[105,212,788,789] Erlotinib and gefitinib are category 1 (other recommended) options if an *EGFR* mutation is discovered before giving first-line systemic therapy (eg, pembrolizumab/chemotherapy), and they are category 2A options if an *EGFR* mutation is discovered during first-line systemic therapy. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that erlotinib and gefitinib are “other recommended” options for patients with *EGFR* mutation--positive metastatic NSCLC; osimertinib is the preferred option in this setting. The NCCN NSCLC Panel recommends *EGFR* mutation testing (category 1) in certain patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *EGFR* mutations and on the FDA approvals (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[207,212] For the 2020 update (Version 2), the NCCN NSCLC Panel added erlotinib/ramucirumab as a first-line therapy option for patients with *EGFR* positive metastatic NSCLC (category 2A, other recommended intervention) based on clinical data.[758] The panel also added erlotinib/bevacizumab as a first-line therapy option for patients with *EGFR* positive metastatic NSCLC (category 2B, useful in certain circumstances) based on clinical data.[787]

Afatinib

Afatinib is a second-generation oral TKI that irreversibly inhibits the ErbB/HER family of receptors including EGFR and ERBB2.[790,791] LUX-Lung 3, a phase 3 randomized 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).[206] The NCCN NSCLC Panel recommends afatinib as a first-line therapy option in patients with metastatic nonsquamous NSCLC who have sensitizing *EGFR* mutations based on the clinical trial and FDA approval (see the NCCN Guidelines for NSCLC).[206,790,792-794] Afatinib is a category 1 (other recommended) option if an *EGFR* mutation is discovered before giving first-line systemic therapy (eg, pembrolizumab/chemotherapy). Afatinib is a category 2A option if an *EGFR* mutation is discovered during first-line systemic therapy. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that afatinib is an “other recommended” option; osimertinib is the preferred option in this setting. 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).[200] However, afatinib is not recommended as subsequent therapy based on a phase 3 randomized trial showing low response rates; it is less efficacious and safe compared to other available options [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion].[795]

A phase 2B trial assessed afatinib compared with gefitinib for first-line therapy in patients with metastatic adenocarcinoma and sensitizing *EGFR* mutations.[796] 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. Updated results indicate that overall survival was not significantly different between afatinib and gefitinib (27.9 vs. 24.5 months [HR, 0.86; 95% CI, 0.66–1.12; *P* = .2580]).[797] 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%). The NCCN Guidelines do not state that afatinib is more efficacious than gefitinib (see the NCCN Guidelines with Evidence Blocks™ for NSCLC, available at www.NCCN.org).[782] 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).

Dacomitinib

Like afatinib, dacomitinib is a second-generation oral TKI that irreversibly inhibits ErbB/HER receptors including EGFR, HER1, HER2, and HER4. ARCHER 1050, a phase 3 randomized trial, compared dacomitinib versus gefitinib as first-line therapy for patients with sensitizing EGFR-positive metastatic NSCLC.[798,799] 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). An updated analysis reported that the median overall survival was 34.1 months (95% CI, 29.5–37.7) in patients receiving dacomitinib compared with 26.8 months (95% CI, 23.7–32.1) in those receiving gefitinib (HR, 0.760; 95% CI, 0.582–0.993; two-sided *P* = .044).[798]

The NCCN NSCLC Panel recommends dacomitinib as a first-line treatment option for patients with sensitizing EGFR-positive metastatic NSCLC based on these clinical trial data and the FDA approval.[770,798] Dacomitinib is a category 1 (other recommended) option if an *EGFR* mutation is discovered before giving first-line systemic therapy (eg, pembrolizumab/chemotherapy); dacomitinib is a category 2A option if an *EGFR* mutation is discovered during first-line systemic therapy. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that dacomitinib is an “other recommended” option; osimertinib is the preferred option in this setting.

Oral TKIs that Inhibit ALK and ROS1 Fusions

Alectinib

Alectinib is an oral TKI that inhibits *ALK* and *RET* rearrangements (also known as fusions) but not *ROS1* fusions.[742]

First-Line Therapy

ALEX, a phase 3 randomized trial, assessed first-line therapy with alectinib versus crizotinib in 303 patients with *ALK*-positive advanced NSCLC including those with asymptomatic CNS disease.[251] 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). Fewer deaths were reported with alectinib (3.3% [5/152]) versus crizotinib (4.6% [7/151]); 2 treatment-related deaths were reported in the crizotinib arm and none in the alectinib arm.

J-ALEX, a phase 3 randomized trial, assessed first-line therapy with alectinib versus crizotinib in 207 Japanese patients with *ALK*-positive advanced NSCLC.[800] Median PFS was not 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 first-line therapy option for patients with *ALK*-positive metastatic NSCLC based on clinical trial data and the FDA approval.[251,800,801] Panel members voted that alectinib is the preferred first-line therapy option for patients with metastatic NSCLC who are positive for *ALK*-positive metastatic NSCLC based on these trials. Alectinib is a category 1 (preferred) option if an *ALK* rearrangement is discovered before giving first-line systemic therapy (eg, pembrolizumab plus chemotherapy); alectinib is a category 2A (preferred) option if an *ALK* rearrangement is discovered during first-line systemic therapy. Brigatinib, ceritinib, and crizotinib are also recommended as first-line therapy options in patients with *ALK*-positive NSCLC (see *Brigatinib* and *Crizotinib* and *Ceritinib* in this Discussion). For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the first-line therapy regimens and decided that brigatinib and ceritinib are "other recommended" options for patients with *ALK*-positive metastatic NSCLC; the panel decided that crizotinib is useful in certain circumstances.

Subsequent Therapy

Phase 2 trials assessed alectinib in patients with *ALK*-positive metastatic NSCLC who had progressed on crizotinib; overall response rates were 48% to 50%.[156,802] In the larger trial (138 patients), 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).[156] 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. The NCCN NSCLC Panel recommends alectinib as a subsequent therapy option for patients with *ALK*-positive NSCLC who have progressed after crizotinib based on these trials and the FDA approval.[156,801,802] Patients who do not tolerate crizotinib may be switched to alectinib, ceritinib, or brigatinib (if not previously given).

Crizotinib

Crizotinib inhibits *ALK* fusions, *ROS1* fusions, and some *MET* tyrosine kinases (high-level *MET* amplification or *METex14* skipping mutation); it is approved by the FDA for patients with metastatic NSCLC who have *ALK* gene fusions (ie, *ALK*-positive disease) or *ROS1* fusions.[150,252,289,803-807] The NCCN NSCLC Panel recommends 4 agents for patients with ALK-positive metastatic NSCLC—alectinib, crizotinib, brigatinib, and ceritinib—based on clinical trial data and FDA approvals (see the *Alectinib, Brigatinib, Ceritinib,* and *ALK Rearrangements* in this Discussion and the NCCN Guidelines for NSCLC). The NCCN NSCLC Panel recommends crizotinib and entrectinib (both are preferred) for patients with *ROS1*-positive metastatic NSCLC based on trial data and FDA approvals (see *Entrectinib* in this Discussion). The NCCN NSCLC Panel recommends ALK and ROS1 testing in certain patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *ALK* and *ROS1* fusions and on the FDA approvals (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).

ALK Rearrangements

Randomized phase 3 trials have compared crizotinib with first-line chemotherapy (PROFILE 1014) and with subsequent chemotherapy (PROFILE 1007).[7,252,808] 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).[252] Crizotinib yields high response rates (>60%) when used in patients with advanced NSCLC who have *ALK* fusions, including those with brain metastases.[107,252,809-811] 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.[812,813] Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in renal function).[810,814,815] However, some patients have had pneumonitis; crizotinib should be discontinued in these patients.[805] 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).

The NCCN NSCLC Panel recommends crizotinib as a first-line treatment option for patients with ALK-positive metastatic NSCLC based on clinical trial data and the FDA approval.[252] Crizotinib is a category 1 (useful in certain circumstances) option if an *ALK* rearrangement is discovered before giving first-line systemic therapy (eg, pembrolizumab/chemotherapy); it is a category 2A option if an *ALK* rearrangement is discovered during first-line systemic therapy. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the first-line therapy regimens and decided that crizotinib is useful in certain circumstances for patients with *ALK*-positive metastatic NSCLC. Alectinib is the preferred first-line therapy option for patients with *ALK*-positive metastatic NSCLC; brigatinib and ceritinib are “other recommended” options for *ALK*-positive metastatic NSCLC.

Crizotinib may also be continued for patients with *ALK* fusions who have progressed on crizotinib, depending on the type of progression.[804] Recently, 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).[816-819] 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 and had not previously received ALK inhibitors.[804]

ROS1 Rearrangements

Crizotinib is also very effective for patients with *ROS1* fusions with response rates of about 70% to 80% including complete responses (see other section on *ROS1 Rearrangements* in this Discussion).[150,151,269,273,274] 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).[274]

PROFILE 1001, a phase 2 study, assessed crizotinib in 50 patients with advanced NSCLC who were positive for *ROS1* fusions.[151] Crizotinib yielded an objective response rate of 72% (95% CI, 58%–84%); there were 3 complete responses and 33 partial responses.[151] 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). Updated results from PROFILE 1001 reported an overall response rate of 72% (95% CI, 58%–83%) with crizotinib including 6 confirmed complete responses in 53 patients with *ROS1*-positive advanced NSCLC.[14] The median overall survival was 51.4 months (95% CI, 29.3–not reached). No grade 4 or higher treatment-related adverse events were reported.

The EUCROSS study reported crizotinib yielded an overall response rate of 70% (21/30; 95% CI, 51%–85%) in 30 patients with *ROS1*-positive advanced NSCLC.[273] Adverse events related to treatment occurred in 97% (33/34) of patients. A retrospective European study in patients (n = 30 evaluable) with stage IV NSCLC and *ROS1* fusions also assessed crizotinib.[150] 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 in certain patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *ROS1* fusions and on the FDA approval (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[150,151,269] Crizotinib is a category 2A option (preferred) if a *ROS1* rearrangement is discovered before giving first-line systemic therapy (eg, pembrolizumab plus chemotherapy); crizotinib is a category 2A option (preferred) if an *ROS1* rearrangement is discovered during first-line systemic therapy. The NCCN NSCLC Panel decided that crizotinib and entrectinib are the preferred agents for first-line therapy in patients with *ROS1* fusions, 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 (see *Lorlatinib* in this Discussion).[277]

Ceritinib

Ceritinib is an oral TKI that inhibits *ALK* and *ROS1* fusions.[820]

ALK Rearrangements

ASCEND-4, a phase 3 randomized trial, assessed ceritinib versus platinum-based chemotherapy as first-line therapy for patients with *ALK*-positive metastatic NSCLC.[253] PFS was improved when using ceritinib 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 ceritinib as a first-line therapy option for patients with *ALK*-positive metastatic NSCLC based on clinical trial data and the FDA approval.[253,821-823] Ceritinib is a category 1 (other recommended) option if an *ALK* rearrangement is discovered before giving first-line systemic therapy (eg, pembrolizumab/chemotherapy); ceritinib is a category 2A option if an *ALK* rearrangement is discovered during first-line systemic therapy. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the first-line therapy regimens and decided that ceritinib and brigatinib are “other recommended” options for patients with *ALK*-positive metastatic NSCLC; alectinib is the preferred first-line therapy option for *ALK*-positive metastatic NSCLC. The panel also decided that crizotinib is useful in certain circumstances.

ASCEND-5, a phase 3 randomized trial, 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.[818] 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 [95% CI, 1.4–2.8] for chemotherapy; HR, 0.49; 95% CI, 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. ASCEND-2, a phase 2 study, assessed ceritinib in patients who had previously received at least 2 or more treatments, had progressed on crizotinib, and had brain metastases.[817] The overall response rate was 38%; the duration of response was 9.7 months (95% CI, 7.1–11.1).[817] The intracranial overall response rate was 45.0% (95% CI, 23.1%–68.5%), the NCCN NSCLC Panel recommends ceritinib as a subsequent therapy option (category 2A) for patients with *ALK*-positive NSCLC who have progressed after crizotinib based on clinical trial data and the FDA approval.[817,818,821-823] Patients who do not tolerate crizotinib may be switched to alectinib, ceritinib, or brigatinib (if not previously given).

ROS1 Rearrangements

A phase 2 trial assessed ceritinib as first-line therapy in patients (n = 28 evaluable) with NSCLC and *ROS1* fusions.[820] 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-naıve 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 metastatic NSCLC based on this trial. Ceritinib is a category 2A (other recommended) option if an *ROS1* rearrangement is discovered before giving first-line systemic therapy (eg, pembrolizumab/chemotherapy); ceritinib is a category 2A option if a *ROS1* rearrangement is discovered during first-line systemic therapy. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the first-line therapy regimens and decided that ceritinib is an “other recommended” option for patients with *ROS1*-positive metastatic NSCLC. The NCCN NSCLC Panel decided that crizotinib and entrectinib are the preferred agents for first-line therapy for patients with advanced NSCLC and *ROS1* fusions 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.[277]

Brigatinib

Brigatinib is an oral TKI that inhibits *ALK* fusions.

First-Line Therapy

ALTA-1L, a phase 3 randomized trial, assessed brigatinib versus crizotinib as first-line therapy for patients with *ALK*-positive metastatic NSCLC.[254] 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%). The NCCN NSCLC Panel recommends brigatinib as a first-line therapy option for patients with *ALK*-positive NSCLC based on clinical trial data and FDA approval.[254] Brigatinib is a category 1 (other recommended) option if an *ALK* rearrangement is discovered before giving first-line systemic therapy (eg, pembrolizumab plus chemotherapy); brigatinib is a category 2A option if an *ALK* rearrangement is discovered during first-line systemic therapy. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the first-line therapy regimens and decided that brigatinib and ceritinib are “other recommended” options for patients with *ALK*-positive metastatic NSCLC; alectinib is the preferred first-line therapy option for *ALK*-positive metastatic NSCLC. The panel decided that crizotinib is useful in certain circumstances.

Subsequent Therapy

ALTA, a phase 2 study, assessed 2 different doses of brigatinib: 90 mg (arm A) or 180 mg (arm B) every day—in patients with *ALK*-positive metastatic NSCLC who had progressed on or were intolerant to crizotinib.[824,825] 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). The NCCN NSCLC Panel recommends brigatinib (category 2A) as a subsequent therapy option for patients with *ALK*-positive NSCLC who have progressed after crizotinib based on clinical trial data and the FDA approval.[824,825] Patients receiving brigatinib should be carefully monitored for respiratory symptoms, especially during the first week of treatment. Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, or ceritinib (if not previously given).

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.[744,745]

Subsequent Therapy

Data show that lorlatinib is effective in select patients who have progressed after treatment with ALK inhibitors, including those with CNS metastases.[744,745] 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.[744] 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.

A phase 1 to 2 trial assessed lorlatinib in patients with *ROS1*-positive metastatic NSCLC.[277] Many patients (58% [40/69]) had previously received crizotinib; some patients were TKI naïve (30% [21/69]). Objective responses were achieved in 35% (14/40) of patients who had previously received crizotinib and 62% (13/21) of TKI-naïve patients. An intracranial response was observed in 50% (12/24) of patients who had previously received crizotinib and 64% (7/11) of TKI-naïve patients. Serious treatment-related adverse events occurred in 7% (5/69) of patients; no treatment-related deaths were reported.

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.[277,745] Lorlatinib is a subsequent therapy option for select patients with *ALK*-positive NSCLC after progression on either alectinib, brigatinib, or ceritinib depending on the type of progression. Lorlatinib is also a subsequent therapy option for select patients with *ALK*-positive NSCLC after progression on crizotinib followed by progression on either alectinib, brigatinib, or ceritinib. 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, entrectinib, or ceritinib.[277]

Oral TKIs That Inhibit BRAF Mutations

Dabrafenib and Trametinib

Dabrafenib and trametinib inhibit kinases in the RAS/RAF/MEK/ERK pathway.[168,169] Dabrafenib inhibits *BRAF* harboring V600E mutations; trametinib inhibits MEK 1/2, which is downstream of BRAF signaling.

A phase 2 trial assessed first-line combination therapy with dabrafenib/trametinib for 36 patients with metastatic NSCLC and *BRAF V600E* mutations.[826] 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.[168,827] 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).[828]

The NCCN NSCLC Panel recommends *BRAF* mutation testing in certain patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *BRAF* mutations and on the FDA approvals (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[826-829] The NCCN NSCLC Panel recommends combination therapy with dabrafenib/trametinib as preferred first-line therapy for patients with metastatic NSCLC and *BRAF* V600E mutations based on these trials and the FDA approval.[826,828,829] Single-agent therapy with dabrafenib or vemurafenib is also an option (other recommended) for patients with *BRAF* V600E mutations who do not tolerate combination therapy with dabrafenib/trametinib.[169,828,830] Other systemic therapy regimens are also recommended (useful in certain circumstances) for patients with *BRAF* V600E mutations; the same initial systemic regimens used for patients with metastatic NSCLC may be used (eg, carboplatin/paclitaxel). For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the first-line therapy regimens for patients with *BRAF* V600E mutation-positive metastatic NSCLC and decided that: 1) dabrafenib/trametinib is the preferred option; 2) dabrafenib or vemurafenib are "other recommended" options; and 3) other systemic therapy regimens (eg, carboplatin/paclitaxel) are useful in certain circumstances. If patients with *BRAF* V600E mutations have not received dabrafenib/trametinib as first-line therapy and have progressed after first-line systemic therapy regimens (eg, carboplatin/paclitaxel), then the NCCN NSCLC Panel recommends dabrafenib/trametinib as subsequent therapy.[168,827]

Oral TKIs that Inhibit NTRK and ROS1 Fusions

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).[284] 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.[284] 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%).[284] An updated analysis 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.[287] An additional 35 patients with *NTRK* gene fusion–positive disease had an overall response rate of 74%.[287] Fewer than 3% of patients had adverse events of grade 3 to 4.

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.[284,287] For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that larotrectinib and entrectinib are preferred first-line therapy options for *NTRK* gene fusion–positive metastatic NSCLC. Other systemic therapy regimens are also recommended (useful in certain circumstances) as first-line therapy options for patients with *NTRK* gene fusions; the same initial systemic regimens used for patients with metastatic NSCLC may be used (eg, carboplatin/paclitaxel). Larotrectinib may be used as subsequent therapy if it or entrectinib were not previously given as first-line therapy for *NTRK* gene fusion–positive metastatic NSCLC.

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).[276,831] 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, and phase 1 ALKA-372-001 trial).[268,832] 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% (41/53; 95% CI, 64%–88%; 3 complete responses).[268] The intracranial overall response rate was 55% (95% CI, 32%–77%; 4 complete responses, 7 partial responses).[268,832] In the larger *ROS1* population (n = 134), grade 3 to 4 adverse events were seen in 34% of patients. Fifteen patients had serious adverse events such as nervous system disorders (4 patients [3%]) and cardiac disorders (3 patients [2%]). No treatment-related deaths were reported. 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 fusion–positive metastatic NSCLC (phase 2 STARTRK-2 trial, phase 1 STARTRK-1 trial, and phase 1 ALKA-372-001 trial).[268,286,832] 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% (95% CI, 35%–93%; 7/10: 7/7 adenocarcinoma NSCLC, 0/3 squamous cell carcinoma, unclassified, or undifferentiated NSCLC); there was one complete response.[275] 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). Grade 3 adverse events with entrectinib across a range of solid tumors included anemia and increased weight. Grade 4 adverse events occurred in 3 patients (ie, increased AST, increased ALT, blood uric acid, hyperuricemia). Nervous system disorders were the most common serious treatment-related adverse event (4% [3/68] and 3% [10/355]). No treatment-related deaths were reported.

The NCCN NSCLC Panel recommends entrectinib as a first-line therapy 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 FDA approval.[268,275,276,832] For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that entrectinib and larotrectinib are preferred first-line therapy options for *NTRK* gene fusion–positive metastatic NSCLC. Other systemic therapy regimens are also recommended (useful in certain circumstances) for patients with *NTRK* gene fusions; the same initial systemic regimens used for patients with metastatic NSCLC may be used (eg, carboplatin/paclitaxel). 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. Entrectinib may be used as subsequent therapy if it or larotrectinib were not previously given as first-line therapy for *NTRK* gene fusion–positive metastatic NSCLC.

Oral TKIs that Inhibit MET Exon 14 Skipping Mutations

Capmatinib

Capmatinib is an oral TKI that selectively inhibits MET genomic alterations. Oncogenic driver genomic alterations in MET include *METex14* skipping mutations, MET gene copy number (GCN) gain or amplification, and MET protein overexpression (see *MET Genomic*

Alterations in this Discussion). Capmatinib has been assessed in phase 1 and 2 studies of patients with advanced NSCLC.[294,833,834]

GEOMETRY, a phase 2 study, assessed capmatinib in different cohorts of patients with *MET* genomic alterations, including those with *METex14* skipping mutations; patients had stage IIIB/IV NSCLC and were wild-type for *EGFR* and *ALK* genomic alterations.[294] Preliminary data from GEOMETRY show that first-line therapy with capmatinib yielded an overall response rate of 71.4% (95% CI, 51.3%–86.8%) in 28 patients with *METex14* skipping mutations; the median PFS was 9.13 months (5.52–13.9 months) for first-line therapy. Subsequent therapy with capmatinib yielded an overall response rate of 39.1% (95% CI, 27.6%–51.6%) in 69 patients with *METex14* skipping mutations; the median PFS was 5.42 months (95% CI, 4.17–6.97 months) for subsequent therapy. Common adverse events across all cohorts included peripheral edema (49%), nausea (43%), and vomiting (28%), but most events were grades 1 to 2. Updated results from GEOMETRY suggest that capmatinib is effective for patients with brain metastases.[833] Of patients with brain metastases, 54% (7/13) responded to capmatinib; 4 patients had a complete response in the brain.

For the 2020 update (Version 4), the NCCN NSCLC Panel recommends capmatinib as either a first-line therapy or subsequent therapy option (category 2A; preferred) for patients with metastatic NSCLC who are positive for *METex14* skipping mutations based on preliminary data and the FDA approval.[294,833] The NCCN NSCLC Panel also preference stratified regimens that are recommended for *METex14* skipping mutations and decided that capmatinib is a preferred first-line therapy or subsequent therapy option for *METex14* skipping mutation–positive metastatic NSCLC based on clinical trial data. Capmatinib may be used as subsequent therapy if it or crizotinib were not previously given as first-line therapy for *METex14* skipping mutation–positive metastatic NSCLC. The panel decided that crizotinib is useful in certain circumstances as either a first-line therapy or subsequent therapy option for *METex14* skipping mutation–positive metastatic NSCLC (see next paragraph on *Crizotinib*).[295] Other systemic therapy regimens are also recommended as useful in certain circumstances for first-line therapy for patients with metastatic NSCLC who are positive for *METex14* skipping mutation; these systemic regimens include platinum doublets, such as carboplatin/paclitaxel. These platinum doublets may be used as subsequent therapy for patients who have progressed on capmatinib or crizotinib. Patients with *METex14* skipping mutations and high PD-L1 expression do not respond to immunotherapy, even those with high PD-L1 levels.[249,293]

Crizotinib

Crizotinib is an oral TKI that inhibits some MET tyrosine kinases (high-level *MET* amplification or *METex14* skipping mutation), *ALK* fusions, and *ROS1* fusions; it is approved by the FDA for patients with metastatic NSCLC who have *ALK* or *ROS1* fusions. A phase 2 study assessed crizotinib in 69 patients with advanced NSCLC who were positive for *METex14* skipping mutations.[295] The objective response rate was 32% (95% CI, 21%–45%). Median PFS was 7.3 months (95% CI, 5.4–9.1 months). For the 2020 update (Version 4), the NCCN NSCLC Panel recommends crizotinib as a first-line therapy or subsequent therapy option (category 2A; useful in certain circumstances) for patients with metastatic NSCLC who are positive for *METex14* skipping mutations based on this data.[295] Crizotinib may be used as subsequent therapy if it or capmatinib were not previously given as first-line therapy for *METex14* skipping mutation–positive metastatic NSCLC. However, the panel voted that capmatinib is preferred in the first-line setting for *METex14* skipping mutation–positive metastatic NSCLC (see previous paragraph on *Capmatinib*).[294]

Oral TKIs that Inhibit RET *Rearrangements*

Selpercatinib

Selpercatinib (LOXO-292) is an oral TKI that selectively inhibits *RET* rearrangements. Libretto-001, a phase 1/2 study, assessed selpercatinib in patients with metastatic NSCLC and *RET* rearrangements.[303] Preliminary data from Libretto-001 show that first-line therapy with selpercatinib yielded an overall response rate of 85% (29/34; 95% CI, 69%–95%). Second-line therapy with selpercatinib yielded an overall response rate of 68% (71/105; 95% CI, 58%–76%); the median PFS was 18.4 months (95% CI, 12.9–24.9). Of patients with brain metastases, 91% (10/11) responded to selpercatinib. Common adverse events with selpercatinib include dry mouth (32%), diarrhea (31%), hypertension (29%), and increased liver enzyme levels (27%). Only 1.7% of patients (9/531) had to stop taking selpercatinib because of side effects.

For the 2020 update (Version 4), the NCCN NSCLC Panel recommends selpercatinib as a first-line or subsequent therapy option (category 2A; preferred) for patients with metastatic NSCLC who are positive for *RET* rearrangements based on this preliminary data and the FDA approval for selpercatinib.[303,833] Selpercatinib may be used as subsequent therapy if it or other RET inhibitors were not previously given as first-line therapy for *RET* rearrangement–positive metastatic NSCLC.

Pralsetinib

Pralsetinib is an oral TKI that selectively inhibits *RET* rearrangements. ARROW, a phase 1/2 study, assessed pralsetinib in patients with metastatic NSCLC and *RET* rearrangements.[302] Preliminary data from ARROW show that first-line therapy with pralsetinib yielded an overall response rate of 66% (19/29; 95% CI, 46%–82%); 10% of patients had a complete response. Second-line therapy with pralsetinib yielded an overall response rate of 55% (50/92; 95% CI, 45%–66%); 6% of patients had a complete response. Nine patients had measurable brain metastases, and 56% responded to pralsetinib; 3 patients had an intracranial complete response. Grade 3 or higher adverse events with pralsetinib include anemia (8%), neutropenia (10%), and hypertension (10%). Common adverse events with pralsetinib included increased AST levels (31%), increased ALT levels (21%), anemia (22%), hypertension (20%), constipation (21%), and neutropenia (19%). Only 4% of patients (5/132) had to stop taking pralsetinib because of side effects.

For the 2020 update (Version 7), the NCCN NSCLC Panel recommends pralsetinib as a first-line or subsequent therapy option (category 2A; preferred) for patients with metastatic NSCLC who are positive for *RET* rearrangements based on this preliminary data and the FDA approval for pralsetinib.[302] Pralsetinib may be used as subsequent therapy if it or other RET inhibitors were not previously given as first-line therapy for *RET* rearrangement–positive metastatic NSCLC.

Cabozantinib and Vandetanib

Cabozantinib and vandetanib are oral TKIs that inhibit *RET* rearrangements but also inhibit other kinases. A phase 2 study assessed cabozantinib in 26 patients.[152,304,835] 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 cabozantinib as a first-line therapy or subsequent therapy option (category 2A; useful in certain circumstances) for *RET* rearrangement–positive metastatic NSCLC based on this data.[152,304]

A phase 2 study assessed vandetanib in 18 patients with NSCLC with *RET* rearrangements who had received 2 or more previous chemotherapy regimens.[746,836] 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 NCCN NSCLC Panel recommends vandetanib as a first-line therapy or subsequent therapy option (category 2B; as useful in certain circumstances) for *RET* rearrangement–positive metastatic NSCLC based on this data.[746] Cabozantinib or vandetanib may be used as subsequent therapy if they or other RET inhibitors were not previously given as first-line therapy for *RET* rearrangement–positive metastatic NSCLC.

Preference Stratification

The NCCN NSCLC Panel preference stratified the regimens that are recommended for *RET* rearrangements and decided that selpercatinib and pralsetinib are preferred first-line therapy or subsequent therapy options for *RET* rearrangement–positive metastatic NSCLC based on clinical trial data.[302,303,833] The panel decided that cabozantinib (category 2A) and vandetanib (category 2B) are both useful in certain circumstances as either first-line therapy or subsequent therapy options for *RET* rearrangements based on clinical trial data [152,304,835] Selpercatinib, pralsetinib, cabozantinib, or vandetanib may be used as subsequent therapy if they were not previously given as first-line therapy for *RET* rearrangement–positive metastatic NSCLC. Other systemic therapy regimens (category 2A; other recommended regimens) are also recommended as first-line therapy options for patients with metastatic NSCLC who are positive for *RET* rearrangements; these systemic regimens include platinum doublets, such as carboplatin/paclitaxel. These platinum doublets may be used as subsequent therapy for patients who have progressed on selpercatinib, pralsetinib, cabozantinib, or vandetanib. Patients with *RET* rearrangements have minimal response (6%) to immunotherapy.[249]

EGFR *Inhibitor:* Monoclonal Antibody

Cetuximab

Cetuximab is a monoclonal antibody that targets EGFR. FLEX, a large phase 3 randomized trial, assessed cisplatin/vinorelbine with (or without) cetuximab for patients with advanced NSCLC; most patients had stage IV disease.[837] 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 NCCN NSCLC Panel does not recommend the cetuximab plus cisplatin plus vinorelbine regimen based on the clinical data.[837] 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.[643] 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.[643,661,837] Although the FLEX trial results were reported to be statistically significant, they were not clinically significant.[643] The NCCN NSCLC Panel recently deleted the cisplatin/vinorelbine and carboplatin/vinorelbine regimens from the list of recommended cytotoxic therapy options for patients with metastatic NSCLC with all histologies.

Immune Checkpoint Inhibitors

Human ICI antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.[309-311] ICIs (also known as immunotherapy or immuno-oncology [IO] agents) 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, which may include active or previously documented autoimmune disease, current use of immunosuppressive agents, or presence of an oncogene that would predict lack of benefit. Nivolumab and pembrolizumab inhibit PD-1 receptors;[312,121] atezolizumab and durvalumab inhibit PD-L1.[313,314]

The NCCN NSCLC Panel recommends (category 1) IHC testing for PD-L1 expression before first-line treatment in all patients with metastatic NSCLC based on the efficacy of pembrolizumab with or without chemotherapy (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC and *Pembrolizumab* in this Discussion).[315] Ideally, PD-L1 expression levels are assessed before first-line therapy in patients with metastatic NSCLC, if clinically feasible. Every effort also needs to be made to assess for oncogenic driver variants for which targeted therapies are available (eg, *EGFR* mutations, *ALK* fusions). It is important to note that targeted therapies are recommended for patients with metastatic NSCLC and specific oncogenic drivers, independent of PD-L1 levels. Patients with metastatic NSCLC and PD-L1 expression levels of 1% or more—but who also have a targetable driver oncogene molecular variant (eg, *EGFR, ALK, ROS1*)—should receive first-line targeted therapy for that oncogene and not first-line ICIs because targeted therapies yield higher response rates (eg, osimertinib, 80%) than ICIs (poor response rates) in the first-line setting, targeted therapy is better tolerated, and these patients are unlikely to respond to ICIs.[249,321-323,751] For patients receiving first-line ICIs with or without chemotherapy, oncologists should be aware of the long half-life of the ICIs and potential adverse effects when combining ICIs with osimertinib.[763-765]

The following content briefly summarizes the use of ICIs as first-line or subsequent therapy in eligible patients with metastatic NSCLC; detailed information, including clinical trial data, is provided in subsequent sections (see *Pembrolizumab*, *Atezolizumab,* and *Nivolumab with or Without Ipilimumab* in this Discussion); durvalumab is discussed in a different section, because it is used for eligible patients with unresectable stage III NSCLC (see *Durvalumab* in this Discussion).

Single-agent pembrolizumab is recommended (category 1; preferred) as first-line therapy for eligible patients with metastatic NSCLC regardless of histology, PD-L1 expression levels of 50% or more, and with negative test results for *EGFR*, *ALK*, *ROS1, METex14* skipping, and *BRAF* V600E (specific molecular) variants. The NCCN NSCLC Panel also recommends single-agent pembrolizumab as a first-line therapy option in eligible patients with metastatic NSCLC regardless of histology, PD-L1 levels of 1% to 49% (category 2B; useful in certain circumstances), and negative test results for specific molecular variants (see *Pembrolizumab* in this Discussion).[838] Combination therapy with pembrolizumab plus chemotherapy is recommended (category 1; preferred) as a first-line therapy option in eligible patients with metastatic NSCLC and negative test results for specific molecular variants, regardless of PD-L1 expression levels. Combination therapy with the ABCP regimen is recommended (category 1; other recommended intervention) as a first-line therapy option for eligible patients with metastatic NSCLC and negative test results for specific molecular variants, regardless of PD-L1 expression levels. Maintenance immunotherapy is recommended, if tolerated, for 2 years for all the first-line regimens. Durvalumab is recommended (category 1) as consolidation immunotherapy by the NCCN NSCLC Panel for eligible patients with unresectable stage III NSCLC who have not progressed after treatment with definitive concurrent chemoradiation; clinical trial data and appropriate use for durvalumab are described in greater detail elsewhere (see *Durvalumab* in this Discussion).[313]

If patients have progressed on PD-1/PD-L1 inhibitor therapy (with or without chemotherapy), then switching to a different PD-1/PD-L1 inhibitor is not recommended for subsequent therapy. Single-agent pembrolizumab is recommended (category 1; preferred) as a subsequent therapy option for select patients with metastatic NSCLC and PD-L1 levels greater than 1%; nivolumab or atezolizumab is recommended (category 1; preferred) as a subsequent monotherapy option for select patients with metastatic NSCLC regardless of PD-L1 levels (see *Pembrolizumab, Atezolizumab*, and *Nivolumab with or Without Ipilimumab* 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* fusions regardless of PD-L1 expression levels.[309,312,751,839,840] 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%.[322] Patients with *ALK*-positive NSCLC and very high PD-L1 expression levels do not respond to pembrolizumab.[751] In the trials assessing the efficacy of first-line therapy with pembrolizumab with (or without) chemotherapy, most of the patients were wild type for *EGFR* or *ALK* variants. Maintenance immunotherapy is recommended, if tolerated, until progression for all the subsequent therapy regimens.

ICIs are associated with unique immune-mediated adverse events, such as endocrine disorders, that are not seen with traditional cytotoxic chemotherapy; 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).[841,842] Pembrolizumab, atezolizumab, nivolumab, or 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). Pseudoprogression has been reported; therefore, traditional RECIST criteria may not be applicable.[843]

Pembrolizumab

Pembrolizumab is a human ICI antibody that inhibits PD-1 receptors, which improves antitumor immunity.[312,121] The NCCN NSCLC Panel recommends (category 1) IHC testing for PD-L1 expression before first-line treatment in all patients with metastatic NSCLC based on the efficacy of pembrolizumab (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[315] 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.[316,317] 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.[316] Unique anti-PD-L1 IHC assays have been developed for each one of the different ICIs currently available.[316,320] The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.[320]

Ideally, PD-L1 expression levels are assessed before first-line therapy in patients with metastatic NSCLC, if clinically feasible. Every effort also needs to be made to assess for specific oncogenic driver variants for which targeted therapies are available such as *EGFR* mutations and *ALK* variants. Plasma-based testing can be used to evaluate for *EGFR* mutations and *ALK* fusions, although these assays are less sensitive than tissue assays. It is important to note that targeted therapies are recommended for patients with metastatic NSCLC and specific oncogenic drivers, independent of PD-L1 levels. Patients with metastatic NSCLC and

PD-L1 expression levels of 1% or more—but who also have a targetable driver oncogene molecular variant (eg, *EGFR, ALK, ROS1*)—should receive first-line targeted therapy for that oncogene and not first-line ICIs because targeted therapies yield higher response rates (eg, osimertinib, 80%) than ICIs (poor response rates) in the first-line setting, targeted therapy is better tolerated, and these patients are unlikely to respond to ICIs.[249,321-324]

Immune-mediated adverse events may occur with pembrolizumab.[844-846] For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered based on the severity of the reaction (see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org). 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).

First-Line Monotherapy

KEYNOTE-024, a phase 3 randomized trial, 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* fusions.[9,121] At 6 months, the rate of overall survival was 80.2% with pembrolizumab monotherapy versus 72.4% with chemotherapy (HR for death, 0.60; 95% CI, 0.41–0.89; *P* = .005). Reponses were higher for pembrolizumab than for chemotherapy (44.8% vs. 27.8%).[121] An updated analysis of KEYNOTE-024 showed that median overall survival was increased with pembrolizumab monotherapy (30.0 months; 95% CI, 18.3 months–not reached) compared with chemotherapy (14.2 months; 95% CI, 9.8–19.0 months; HR, 0.63; 95% CI, 0.47–0.86).[9] Fewer severe treatment-related adverse events (grades 3–5) were reported in patients receiving pembrolizumab monotherapy compared with those receiving chemotherapy (31.2% vs. 53.3%). Treatment-related deaths occurred in 1.3% (2/154) of patients receiving pembrolizumab monotherapy versus 2% (3/150) of patients receiving chemotherapy alone.

KEYNOTE-042, a phase 3 randomized trial, 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* fusions.[838] Overall survival was longer 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; 95% CI, 10.4–14.2; HR, 0.69; 95% CI, 0.56–0.85; *P* = .0003). In a subgroup analysis, overall survival was 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) (HR, 0.92; 95% CI, 0.77–1.11). Long-term data from KEYNOTE-001 show that 5-year survival for patients with metastatic NSCLC is approximately 23% for patients who received first-line pembrolizumab monotherapy and 15.5% for patients who received subsequent pembrolizumab monotherapy; for patients with PD-L1 levels of 50% or more, 5-year overall survival is about 29.6% and 25%, respectively.[11] Median overall survival was 22.3 months (95% CI, 17.1–32.3) for treatment-naïve patients and 10.5 months (95% CI, 8.6–13.2) for patients previously treated with pembrolizumab monotherapy. For patients with metastatic NSCLC receiving chemotherapy alone, 5-year overall survival is approximately 6%.[11]

The NCCN NSCLC Panel recommends single-agent pembrolizumab (category 1; preferred) as a first-line therapy option for eligible patients with advanced nonsquamous or squamous NSCLC, PD-L1 expression levels of 50% or more, no contraindications to PD-1 or PD-L1 inhibitors, and negative test results for *EGFR, ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants based on clinical trial data and FDA approval.[121,838,847] Maintenance therapy with pembrolizumab is also a recommended option in this setting (category 1). 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.

The NCCN NSCLC Panel also recommends single-agent pembrolizumab as a first-line therapy option (category 2B; useful in certain circumstances) for eligible patients with metastatic NSCLC, PD-L1 expression levels of 1% to 49%, no contraindications to PD-1 or PD-L1 inhibitors, and negative test results for *EGFR, ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants based on clinical trial data and FDA approval.[838,847] The NCCN NSCLC Panel decided that single-agent pembrolizumab is a useful intervention in patients with PD-L1 levels of 1% to 49% who cannot tolerate or refuse platinum-based chemotherapy (category 2B; useful in certain circumstances). In patients with PD-L1 levels of 1% to 49%, the HR of 0.92 is not statistically or clinically significant for pembrolizumab monotherapy versus chemotherapy; therefore, pembrolizumab plus chemotherapy is recommended (category 1; preferred) if patients can tolerate the therapy. Maintenance therapy with pembrolizumab is also a recommended option in this setting (category 2B).

First-Line Combination Therapy

KEYNOTE-189, a phase 3 randomized trial, compared pembrolizumab added to carboplatin (or cisplatin)/pemetrexed versus chemotherapy in patients with metastatic nonsquamous NSCLC.[848] Most patients received pembrolizumab/carboplatin/pemetrexed (72% [445/616]) in this trial, but some received pembrolizumab plus cisplatin plus pemetrexed (28% [171/616]); patients did not have *EGFR* mutations or *ALK* fusions. The estimated rate of overall survival at one 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; TMB did not predict for response.[849] For the pembrolizumab plus 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%).

The NCCN NSCLC Panel recommends pembrolizumab plus pemetrexed and either carboplatin or cisplatin (category 1; preferred) as a first-line therapy option for eligible patients with metastatic nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or NSCLC NOS based on clinical trial data and on FDA approval.[848,850] For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that these pembrolizumab/chemotherapy regimens are preferred first-line options for eligible patients with metastatic nonsquamous NSCLC, regardless of their PD-L1 expression levels. These pembrolizumab/chemotherapy regimens are recommended (category 1; preferred) as first-line therapy options for patients with metastatic nonsquamous NSCLC, no contraindications to PD-1 or PD-L1 inhibitors, and negative test results for *EGFR*, *ALK*, *BRAF* V600E, *METex14* skipping, *RET,* and *ROS1* variants, regardless of their PD-L1 expression levels. Maintenance therapy with pembrolizumab/pemetrexed is also a recommended option (category 1) in this setting. For patients with metastatic NSCLC 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.

KEYNOTE-407, a phase 3 randomized trial, compared pembrolizumab added to carboplatin and either paclitaxel or albumin-bound paclitaxel in patients with metastatic squamous cell NSCLC; 32% of patients received albumin-bound paclitaxel (also known as nab-paclitaxel).[851] Median overall survival was 15.9 months (95% CI, 13.2–not reached) with pembrolizumab plus chemotherapy versus 11.3 months (95% CI, 9.5–14.8) with chemotherapy alone (HR for death, 0.64; 95% CI, 0.49–0.85; *P* < .001). Patients receiving pembrolizumab/chemotherapy had an overall response rate of 57.9% compared to 38.4% for those receiving chemotherapy alone. Only 38% of patients had a PD-L1 TPS less than 1%. Grade 3 or higher adverse events were similar in both groups (pembrolizumab/chemotherapy, 69.8% vs. chemotherapy alone, 68.2%). Because of adverse events, more patients discontinued treatment with pembrolizumab/chemotherapy than with chemotherapy (13.3% vs. 6.4%, respectively).

The NCCN NSCLC Panel recommends pembrolizumab plus carboplatin and either paclitaxel or albumin-bound paclitaxel (category 1; preferred) as a first-line therapy option for patients with metastatic squamous cell NSCLC based on clinical trial data from and FDA approval.[851,852] Maintenance therapy with pembrolizumab is also a recommended option in this setting (category 1). For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that these pembrolizumab/chemotherapy regimens are preferred for eligible patients with metastatic squamous cell NSCLC, regardless of their PD-L1 expression levels. These pembrolizumab plus chemotherapy regimens are recommended (category 1; preferred) as first-line therapy options for patients with metastatic squamous cell NSCLC, no contraindications to PD-1 or PD-L1 inhibitors, and negative test results for *EGFR*, *ALK*, *BRAF* V600E, *METex14* skipping, *RET,* and *ROS1* variants, regardless of their PD-L1 expression levels. For the 2020 update (Version 1), the NCCN NSCLC Panel deleted the recommendation for the pembrolizumab/cisplatin with either paclitaxel or albumin-bound paclitaxel regimen, because there are less data for this regimen.

Subsequent Therapy

KEYNOTE-010, a phase 3 randomized trial, compared single-agent pembrolizumab in patients with previously treated advanced nonsquamous and squamous NSCLC who were PD-L1 positive (≥1%); most patients were current or former smokers.[840] There were 3 arms in this trial: pembrolizumab at 2 mg/kg, pembrolizumab at 10 mg/kg, and docetaxel at 75 mg/m² 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; 95% 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.

If patients have not previously received a PD-1/PD-L1 inhibitor, the NCCN NSCLC Panel recommends single-agent pembrolizumab (category 1; preferred) as a subsequent therapy option for patients with metastatic nonsquamous or squamous NSCLC and PD-L1 expression levels of 1% or more based on clinical trial data and FDA approval.[840,853,854] Testing for

PD-L1 expression levels is recommended before prescribing pembrolizumab monotherapy (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).

Atezolizumab

Atezolizumab is a human ICI antibody that inhibits PD-L1, which improves antitumor immunity.[314] Immune-mediated adverse events may occur with atezolizumab.[839,855] For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered based on the severity of the reaction (see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org). 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).

First-Line Therapy

IMpower150, a phase 3 randomized trial, compared first-line therapy with the ABCP regimen for patients with metastatic nonsquamous NSCLC versus bevacizumab plus chemotherapy.[855] Median overall survival was 19.2 months (95% CI, 17.0–23.8) in the ABCP arm versus 14.7 months (95% CI, 13.3–16.9) in the carboplatin/paclitaxel/bevacizumab arm; the HR for death was 0.78 (95% CI, 0.64–0.96; *P* = .02). PFS was longer in the ABCP 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* fusions (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 variants. In these patients with *EGFR* mutations or *ALK* fusions, PFS was also increased with ABCP compared with chemotherapy/bevacizumab (9.7 vs. 6.1 months; HR, 0.59; 95% CI, 0.37–0.94). A subgroup analysis of IMpower150 reported that subsequent therapy with the ABCP regimen increased median overall survival in a few patients with *EGFR* mutation–positive metastatic NSCLC (n = 34) compared with those receiving carboplatin plus paclitaxel plus bevacizumab (n = 45).[856] Therefore, the ABCP regimen may be an option for patients with *EGFR* mutations or *ALK* fusions who have progressed after initial therapy with TKIs.

IMpower130, a phase 3 randomized trial, compared atezolizumab plus carboplatin plus nab-paclitaxel versus chemotherapy alone as first-line therapy in patients with metastatic nonsquamous NSCLC with no *EGFR* mutations or *ALK* fusions.[857] Median overall survival was 18.6 months (95% CI, 16.0–21.2) in the atezolizumab plus chemotherapy arm versus 13.9 months (95% CI, 12.0–18.7) with carboplatin/nab-paclitaxel (HR, 0.79; 95% CI, 0.64–0.98; *P* = .033). Treatment-related deaths were reported in 2% (8/473) of patients in the atezolizumab plus chemotherapy arm and in less than 1% (1/232) of patients in the chemotherapy only arm.

The NCCN NSCLC Panel recommends the ABCP regimen (category 1; other recommended intervention) as a first-line therapy option for eligible patients with metastatic nonsquamous NSCLC (including adenocarcinoma) based on clinical trial data and FDA approval.[855] The ABCP regimen (also known as the quadruplicate regimen) is recommended as a first-line therapy option for patients with negative test results for *EGFR, ALK, ROS1, METex14* skipping, *RET,* or *BRAF* variants, regardless of PD-L1 expression levels. Maintenance therapy with atezolizumab and bevacizumab is also recommended in this setting (category 1; other recommended intervention) (see *Maintenance Therapy* in this Discussion). For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that the ABCP regimen is an other recommended intervention, because the NCCN NSCLC Panel prefers the pembrolizumab plus chemotherapy regimens based on tolerability and experience with these regimens. The NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the systemic therapy regimens containing bevacizumab, such as ABCP, that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.[753-757]

For the 2020 update (Version 2), the NCCN NSCLC Panel recommends atezolizumab/carboplatin/nab-paclitaxel (category 2A; other recommended intervention) as a first-line therapy option for eligible patients with metastatic NSCLC based on clinical trial data.[857] Atezolizumab/carboplatin/nab-paclitaxel is recommended as a first-line therapy option for patients with metastatic NSCLC and negative test results for *EGFR, ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants, regardless of histology or PD-L1 levels. Maintenance therapy with atezolizumab is also recommended in this setting (category 2A).

IMpower110, a phase 3 randomized trial, compared first-line therapy with atezolizumab monotherapy versus platinum-based chemotherapy in three different subgroups of patients with metastatic NSCLC, including those with high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]); patients were wild type for *EGFR* or *ALK* variants and most were either former smokers or current smokers.[858] Patients receiving first-line atezolizumab monotherapy also received maintenance therapy with atezolizumab. Chemotherapy regimens for patients with nonsquamous NSCLC included cisplatin (or carboplatin)/pemetrexed and maintenance therapy with pemetrexed; patients with squamous cell NSCLC received cisplatin/gemcitabine and best supportive care as maintenance therapy.

It is important to note that a different IHC assay was used to test for PD-L1 levels in IMpower110 (SP142 PD-L1 IHC assay) compared with IHC assays used for pembrolizumab monotherapy in KEYNOTE-024 (PD-L1 IHC 22C3 pharmDx assay); however, the results were similar regardless of which PD-L1 IHC assay was used.[859] Data suggest that different methods of testing for PD-L1 levels are not equivalent.[318,319] Based on an interim analysis using the SP142 PD-L1 IHC assay, median OS was 20.2 months (95% CI,16.5–not estimable) with atezolizumab monotherapy (n = 107) versus 13.1 months (95% CI, 7.4–16.5 months) with chemotherapy (n = 98) (HR, 0.59; 95% CI, 0.40–0.89; *P*=.0106) in patients with high PD-L1 expression. Based on an interim analysis using the 22C3 pharmDx assay, median OS was 20.2 months with atezolizumab monotherapy (n = 134) versus 11.0 months with chemotherapy (n = 126) (HR, 0.60; 95% CI, 0.41–0.86).[859] There was no survival advantage in the other two subgroups of patients with lower PD-L1 expression (ie, TC ≥ 5% or IC ≥ 5%; TC ≥ 1% or IC ≥ 1%). Atezolizumab monotherapy was associated with fatal adverse reactions in 3.8% of all patients (11/ 286, all 3 groups) including aspiration, chronic obstructive pulmonary disease, pulmonary embolism, acute myocardial infarction, cardiac arrest, mechanical ileus, sepsis, cerebral infraction, and device occlusion; 4.2% of patients (11/263) receiving chemotherapy also died. Grade 3 to 4 treatment-related adverse events occurred in 12.9% of patients receiving atezolizumab monotherapy versus 44.1% with chemotherapy. The most frequent serious adverse reactions with atezolizumab monotherapy were pneumonia (2.8%), chronic obstructive pulmonary disease (2.1%), and pneumonitis (2.1%); 28% of patients had serious adverse reactions.

For the 2020 update (Version 5), the NCCN NSCLC Panel recommends atezolizumab monotherapy (category 2A; preferred) as a first-line therapy option for eligible patients with metastatic NSCLC based on preliminary clinical trial data and on the FDA approval.[858] Atezolizumab monotherapy is recommended as a first-line therapy option for patients with metastatic NSCLC, PD-L1 levels of 50% or more, and negative test results for *EGFR, ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants, regardless of histology; maintenance therapy with atezolizumab is also recommended in this setting. For the Version 5 update, the NCCN NSCLC Panel preference stratified the regimen and voted that atezolizumab monotherapy is a preferred recommended option in this setting based on clinical trial data.[858]

Subsequent Therapy

OAK, a phase 3 randomized trial, compared atezolizumab versus docetaxel in patients with metastatic NSCLC who had progressed during or after systemic therapy.[839,860] Most patients were current or former smokers and had received platinum-based chemotherapy; 10% of patients were not reported because they had *EGFR* mutations and *ALK* fusions.[839,860] Patients with nonsquamous NSCLC who received atezolizumab had longer overall survival (15.6 months; 95% CI, 13.3–17.6) when compared with those receiving docetaxel (11.2 months; 95% CI, 9.3–12.6; HR, 0.73; 0.6–0.89; *P* = .0015). In patients with squamous cell NSCLC, overall survival was 8.9 months (95% CI, 7.4–12.8) in patients receiving atezolizumab versus 7.7 months (95% CI, 6.3–8.9) with docetaxel (HR, 0.73; 0.54–0.98; *P* = .038). Fewer patients were in the squamous group compared with the nonsquamous group (222 vs. 628). Fewer treatment-related severe adverse events (grades 3–4) were reported for atezolizumab versus docetaxel (15% vs. 43% [90/609 vs. 247/578]).

If patients have not previously received a PD-1/PD-L1 inhibitor, the NCCN NSCLC Panel recommends atezolizumab (category 1; preferred) as a subsequent therapy option for patients with metastatic nonsquamous or squamous cell NSCLC based on clinical trial data and FDA approval.[314,839,860] Testing for PD-L1 expression levels is not required for prescribing atezolizumab but may provide useful information.

Nivolumab with or Without Ipilimumab

Nivolumab and ipilimumab are ICIs that have complementary mechanisms of action on T-cells; nivolumab is used either with or without ipilimumab. Nivolumab inhibits PD-1 receptors, which improves antitumor immunity.[309,312,121] PD-1 receptors are expressed on activated cytotoxic T cells.[309-311] Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)–blocking antibody that binds to CTLA-4 and prevents the interactions with CD80/CD86, which induces de novo T-cell responses against tumors; CTLA-4 inhibits T-cell activation.[861] Immune-mediated adverse events may occur with nivolumab or nivolumab/ipilimumab.[862] For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered based on the severity of the reaction (see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org). Nivolumab either with or without ipilimumab 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). If patients are receiving nivolumab plus ipilimumab and have treatment-related adverse events, it may be reasonable to discontinue ipilimumab and continue the nivolumab.[862]

First-Line Therapy

CheckMate 227, a phase 3 randomized trial in patients with metastatic nonsquamous or squamous NSCLC who had PS 0 to 1 and no EGFR mutations or ALK fusions, compared nivolumab/ipilimumab, nivolumab monotherapy, and chemotherapy for patients with PD-L1 expression levels of 1% or more. Nivolumab/ipilimumab, nivolumab/chemotherapy, and chemotherapy alone were also compared for patients with PD-L1 expression levels less than 1%. In addition, first-line nivolumab/ipilimumab and chemotherapy were compared as one of the co-primary analyses in the patients who had high TMB levels (≥10 mutations/megabase).[179] 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). Updated results from CheckMate 227 for patients with PD-L1 expression of 1% or more, reported that the median overall survival was 17.1 months (95% CI, 15.0–20.1) for nivolumab plus ipilimumab versus 14.9 months (95% CI, 12.7–16.7) for chemotherapy (HR = 0.79; 95% CI, 0.65–0.96; *P* = .007).[862]

For the 2020 update (Version 2), the NCCN NSCLC Panel recommends nivolumab plus ipilimumab (category 2A) as a first-line therapy option for eligible patients with metastatic NSCLC based on clinical trial data.[179,180,862] Nivolumab/ipilimumab is recommended for patients with metastatic NSCLC, regardless of PD-L1 levels or histology; negative test results for *EGFR, ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants; and no contraindications to immunotherapy. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified the systemic therapy regimens and decided that first-line therapy with nivolumab/ipilimumab is "useful in certain circumstances" (eg, renal impairment) for patients with PD-L1 levels of 1% or more and is an "other recommended" first-line therapy option for patients with PD-L1 levels less than 1%.TMB is considered to be an emerging biomarker that may be useful in selecting patients for nivolumab with or without ipilimumab; however, there is no consensus on how to measure TMB.

CheckMate 9LA, a phase 3 randomized trial, compared first-line nivolumab/ipilimumab and 2 cycles of platinum-doublet chemotherapy versus 4 cycles of chemotherapy alone in patients with metastatic nonsquamous or squamous NSCLC, regardless of PD-L1 expression levels, who had PS 0 to 1 and no *EGFR* mutations or *ALK* fusions.[863] For metastatic nonsquamous NSCLC, the chemotherapy was pemetrexed with either cisplatin or carboplatin; for metastatic squamous NSCLC, the chemotherapy was paclitaxel with carboplatin. Preliminary data show that the median overall survival with nivolumab/ipilimumab/chemotherapy was 15.6 months (95% CI, 13.9–20.0 months) versus 10.9 months (95% CI, 9.5–12.5 months) with chemotherapy regardless of histology or PD-L1 expression levels (HR, 0.66; 95% CI, 0.55–0.80). Overall survival was also significantly different between the groups based on histology or PD-L1 expression levels. The overall response rate was 38% with nivolumab plus ipilimumab plus chemotherapy versus 25% with chemotherapy alone. Serious grade 3 or 4 adverse events occurred in 25.4% of patients receiving nivolumab/ipilimumab/chemotherapy versus 15% in those receiving chemotherapy alone. The death rate was 2% in each arm (nivolumab/ipilimumab/chemotherapy: 7/358; chemotherapy alone: 6/349). In the nivolumab/ipilimumab/chemotherapy arm, treatment-related deaths were from acute renal failure due to chemotherapy, thrombocytopenia, pneumonitis, hepatic toxicity, hepatitis, diarrhea, sepsis, and acute renal insufficiency; treatment-related deaths in the chemotherapy arm were from anemia, pancytopenia, febrile neutropenia, respiratory failure, pulmonary sepsis, and sepsis. The most common treatment-related adverse events (≥15%) were nausea, anemia, asthenia, and diarrhea.

For the 2020 update (Version 6), the NCCN NSCLC Panel recommends nivolumab/ipilimumab/chemotherapy (category 2A; other recommended) as a first-line therapy option for eligible patients with metastatic NSCLC based on preliminary clinical trial data and the FDA approval.[863] For metastatic nonsquamous NSCLC, the recommended chemotherapy is pemetrexed with either cisplatin or carboplatin; for metastatic squamous NSCLC, the recommended chemotherapy is paclitaxel with carboplatin. Nivolumab/ipilimumab/chemotherapy is recommended for patients with metastatic NSCLC, regardless of PD-L1 levels; negative test results for *EGFR, ALK, ROS1, BRAF*, *METex14* skipping, or *RET* variants; and no contraindications to PD-1/PD-L1 inhibitors. For the Version 6 update, the panel preference stratified the regimen and voted that first-line therapy with nivolumab plus ipilimumab plus chemotherapy is an "other recommended" first-line therapy option for eligible patients with metastatic NSCLC.

Subsequent Therapy

CheckMate-057, a phase 3 randomized trial, compared nivolumab versus docetaxel as subsequent therapy for patients with metastatic nonsquamous NSCLC who had progressed on or after first-line chemotherapy.[309] Median overall survival was 12.2 months (95% CI, 9.7–15.0) for patients receiving nivolumab compared with 9.4 months (95% CI, 8.1–10.7) for docetaxel (HR, 0.73; 95% CI, 0.59–0.89; *P* = .002).[309] 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.

CheckMate-017, a phase 3 randomized trial, compared nivolumab versus docetaxel as subsequent therapy for patients with metastatic squamous cell NSCLC who had progressed on or after first-line chemotherapy.[312] Median overall survival was 9.2 months (95% CI, 7.3–13.3) with nivolumab compared with 6.0 months (95% CI, 5.1–7.3) for docetaxel (HR, 0.59; 95% CI, 0.44–0.79; *P* < .001).[312] 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. Fewer grade 3 to 4 adverse events were reported with nivolumab (7%) compared with docetaxel (55%). No patients died in the nivolumab arm versus 3 deaths in the docetaxel arm.

In a long-term analysis of CheckMate-057 and CheckMate-017, 2-year survival and durable responses were increased in patients with advanced NSCLC receiving nivolumab when compared with docetaxel.[864] 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%).

If patients have not previously received a PD-1/PD-L1 inhibitor, the NCCN NSCLC Panel recommends single-agent nivolumab (category 1; preferred) as a subsequent therapy option for patients with metastatic nonsquamous or squamous NSCLC who have progressed on or after first-line chemotherapy based on clinical trial data and the FDA approvals.[309,312,864,865] The NCCN NSCLC Panel recommends nivolumab, atezolizumab, or pembrolizumab as preferred subsequent therapy options (category 1 for all) based on improved overall survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy.[309,312,840,866]

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.[867] Testing for PD-L1 is not required for prescribing nivolumab but may provide useful information.[320] Current or former smoking status correlated with the response rate to ICIs.[309,868] Data suggest that mismatch repair deficiency is associated with response to ICIs.[869,870]

Immune-related adverse events, such as pneumonitis, may occur with nivolumab.[311,844,846,871-875] Intravenous high-dose corticosteroids should be administered for patients with immune-mediated adverse events based on the severity of the reaction (see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org). 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).

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 therapy.[876] Patients are only candidates for maintenance therapy if their tumors have responded to their previous treatment (ie, tumor response) or they 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 fusions, PS). Maintenance therapy is recommended 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) (see the NCCN Guidelines for NSCLC).[877] For the 2020 update (Version 1), the NCCN Panel deleted the recommendation for close observation instead of maintenance therapy.

Continuation Maintenance Therapy

For continuation maintenance therapy, select agents (which were initially given with first-line therapy) may be continued until evidence of disease progression or unacceptable toxicity based on the design of the clinical trials that led to their approval. This section mainly discusses continuation maintenance with chemotherapy; continuation maintenance with ICIs is discussed in another section (see *Immune Checkpoint Inhibitors* in this Discussion). Single-agent bevacizumab (category 1) may be continued beyond 4 to 6 cycles of initial therapy (ie, platinum-doublet chemotherapy given with bevacizumab) in patients with nonsquamous NSCLC.[720,878,879] 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.[753-757] Therefore, if a bevacizumab biosimilar was initially used as part of first-line combination therapy, the biosimilar should be continued as maintenance therapy in eligible patients.

PARAMOUNT, a phase 3 randomized trial, reported that continuation maintenance therapy with pemetrexed slightly increased PFS when compared with placebo (4.1 vs. 2.8 months).[880] Updated results from PARAMOUNT reported that continuation maintenance therapy with pemetrexed also improves overall survival (13.9 vs. 11.0 months).[881] The NCCN NSCLC Panel recommends single-agent pemetrexed as continuation maintenance therapy (category 1) in patients with nonsquamous NSCLC based on clinical trial data and FDA approval.[878,880,881]

POINTBREAK, a phase 3 randomized trial, assessed bevacizumab plus carboplatin/pemetrexed or bevacizumab plus carboplatin/paclitaxel in patients with metastatic NSCLC; patients received maintenance therapy with either bevacizumab/pemetrexed or bevacizumab alone.[726] PFS was 6 months with pemetrexed plus carboplatin/bevacizumab versus 5.6 months with paclitaxel plus carboplatin/bevacizumab.[726] 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.

AVAPERL, a phase 3 randomized trial, assessed maintenance therapy with bevacizumab/pemetrexed versus bevacizumab alone in patients with advanced nonsquamous NSCLC; the initial regimen was bevacizumab/cisplatin/pemetrexed.[882,883] An updated analysis reported that overall survival was 17.1 months with bevacizumab/pemetrexed maintenance versus 13.2 months with bevacizumab alone (HR, 0.87; 95% CI, 0.63–1.21; *P* = .29).[882] The NCCN NSCLC Panel recommends continuation maintenance therapy with bevacizumab/pemetrexed (category 2A) in patients with nonsquamous NSCLC who initially received bevacizumab/pemetrexed/platinum regimen based on clinical trial data.[882,883]

IFCT-GFPC 0502, a phase 3 randomized trial, compared using maintenance therapy with either gemcitabine or erlotinib after first-line therapy with cisplatin-gemcitabine in patients with advanced NSCLC. 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).[672,884] A phase 3 randomized trial from the CECOG assessed continuation maintenance therapy with gemcitabine versus best supportive care after an initial regimen of cisplatin/gemcitabine.[885] The data showed a slight difference in PFS but no difference in overall survival (13 vs. 11 months, respectively; *P* = .195). The NCCN NSCLC Panel recommends gemcitabine (category 2B) as continuation maintenance therapy regardless of histology in patients with metastatic NSCLC, negative test results for *EGFR, ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants, and PD-L1 expression less than 1%.

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.[724] 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.[722,724] 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).[721,722]

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.[724,886] 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.[887,888] The NCCN NSCLC Panel recommends switch maintenance therapy with pemetrexed in patients with nonsquamous cell carcinoma; negative test results for *EGFR, ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants; and PD-L1 expression less than 1% based on clinical trial data and FDA approval.[888,889]

The NCCN NSCLC Panel does not recommend erlotinib as switch maintenance therapy (or as subsequent therapy) for patients with nonsquamous NSCLC, good PS, negative test results for *EGFR, ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants based on results from

IUNO, a randomized trial, and a revised indication from the FDA.[890] 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.[672,891] A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.[892] Switch maintenance therapy with docetaxel is a category 2B recommendation in the NCCN Guidelines for patients with squamous cell NSCLC, good PS, and negative test results for *EGFR, ALK, ROS1, METex14* skipping, *RET,* or *BRAF* variants, because many patients in the delayed chemotherapy arm did not receive docetaxel.[892]

Clinical Evaluation

The workup and evaluation of incidental lung nodules that are detected on imaging for other conditions are described in the NSCLC algorithm (see *Incidental Lung Nodules* in this Discussion and the NCCN Guidelines for NSCLC). The cutoff thresholds are 6 mm for a positive scan result for incidental solid and subsolid lung nodules detected on chest CT based on the Fleischner criteria (see the NCCN Guidelines for NSCLC).[79-83] As previously described, low-dose CT screening is recommended for asymptomatic select patients who are at high risk for lung cancer and management of any nodules detected in these patients is described elsewhere (see the NCCN Guidelines for Lung Cancer Screening, available at 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.[42,893-895] 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.[96,896-898] 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.[96] 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.[899] 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.[900] 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.[901] 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.[896] 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.[96,902,903] However, FDG PET/CT is even more sensitive and is recommended by NCCN.[904-906] 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.[907] Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported.[908] 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.[909] 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%.[910] Kernstine et al compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.[911] 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.[912,913]

When patients with early-stage disease are accurately staged using FDG PET/CT, inappropriate surgery is avoided.[904] 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.[96,914] 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.[915-918] 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.[919] In patients with positive nodes on CT or PET, EBUS-TNBA can be used to clarify the results.[920,921] In patients with negative findings on EBUS-TNBA, conventional mediastinoscopy can be done to confirm the results.[916,921-923] 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.[924] 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).

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 variants, and PS. Before treatment, it is strongly recommended that determination of tumor resectability be made by 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). RT doses are also recommended in the algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC). In addition, the NCCN Guidelines also recommend regimens for targeted therapy, immunotherapy, 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 eligible patients with metastatic NSCLC and positive test results for *EGFR, ALK, ROS1, BRAF, METex14* skipping, *RET,* or *NTRK* variants.

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).[326,344,347,420,477,925] 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 before treatment. 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.[334] 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.[334,440,442,926-929] The overall 5-year survival rate is approximately 40%.[440,930] 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.[694,931] The NCCN NSCLC Panel recommends durvalumab (category 1) as consolidation immunotherapy after treatment with definitive concurrent chemoradiation for eligible patients with unresectable stage III NSCLC based on data from a phase 3 randomized trial and FDA approval (see *Chemoradiation: Trial Data* and *Durvalumab* in this Discussion and the NCCN Guidelines for NSCLC).[313] 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).[386,634] Recently, the NCCN NSCLC 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 and will be receiving durvalumab, 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 will not be receiving durvalumab.

Multimodality therapy is recommended for most patients with stage III NSCLC.[686] 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 their 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).[419,635] 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).[932] 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%.[933] 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.[689] 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).[934]

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).[935,936] It is important to determine whether the multiple lung cancers are metastases or separate lung primaries (synchronous or metachronous); most multiple lung tumors are metastases.[74,334,937,938] 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).[939,940] Although criteria have been established for diagnosing multiple lung cancers, no definitive method has been established before treatment.[940-943] 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.[943]

Treatment of multiple lung cancers depends on the status of the lymph nodes (eg, N0–1) and on whether patients are asymptomatic, symptomatic, or at high or low risk of becoming symptomatic (see *Multiple Lung Cancers* in the NCCN Guidelines for NSCLC).[937,944-946] Patients should be evaluated in a multidisciplinary setting by surgeons, radiation oncologists, and 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).[936,937] VATS or SABR are reasonable options depending on the number and distribution of the tumors requiring local treatment.[947] 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).[948]

Stage IIIB and IIIC NSCLC

Stage IIIB NSCLC comprises 2 unresectable groups, including: 1) T1–2,N3 tumors; and 2) T3–4,N2 tumors; stage IIIC NSCLC includes contralateral mediastinal nodes (T4,N3), which are also unresectable. 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).[949,950] 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 followed by durvalumab (category 1).[386,634,694,699,951-953] Durvalumab is recommended (category 1) as consolidation immunotherapy after treatment with definitive concurrent chemoradiation for eligible patients with unresectable stage III NSCLC (see *Durvalumab* and *Chemoradiation: Trial Data* in this Discussion and the NCCN Guidelines for NSCLC).[313] Durvalumab is not recommended for patients who have had definitive surgical resection. If patients will be receiving durvalumab but have not received full-dose chemotherapy concurrently with RT, the NCCN NSCLC Panel does not recommend an additional 2 cycles of full-dose chemotherapy (ie, consolidation chemotherapy) based on concerns that adding consolidation chemotherapy will increase the risk of pneumonitis if patients are also receiving durvalumab. If patients will not be receiving durvalumab because of medical contraindications or other reasons, consolidation chemotherapy is an option after concurrent chemoradiation if patients have not received full-dose chemotherapy concurrently with RT. 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 (stages IIIB and IIIC), 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 durvalumab (see the NCCN Guidelines for NSCLC).[386,634,694,699,951-954] Again, durvalumab is recommended (category 1) as consolidation immunotherapy after treatment with definitive concurrent chemoradiation for eligible patients with unresectable stage III NSCLC.[313] Two additional cycles of full-dose chemotherapy (consolidation chemotherapy) may be given if full-dose chemotherapy was not given concurrently with RT; however, consolidation chemotherapy is not recommended if patients will be receiving durvalumab.

Limited Metastatic 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).[781] 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).[141] 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.[955] 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).[956]

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.[514,957] Clinicians are not using whole brain RT as often in patients with limited brain metastases because of concerns about neurocognitive problems.[599] Therefore, the NCCN NSCLC Panel has decreased the recommendations for whole brain RT to treat limited brain metastases (see *Whole Brain RT and Stereotactic Radiosurgery* in this Discussion text). 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* mutation–positive metastatic NSCLC 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).[958,959]

Preoperative and Postoperative Treatment

Chemotherapy or Chemoradiation

On the basis of clinical studies,[622-624] the NCCN NSCLC Panel recommends cisplatin combined with docetaxel, etoposide, gemcitabine, or vinorelbine for preoperative and postoperative chemotherapy for all histologies in the NCCN Guidelines. For the 2020 update (Version 1), the NCCN NSCLC Panel preference stratified all the systemic therapy regimens and decided that cisplatin combined with pemetrexed is preferred for nonsquamous NSCLC, whereas cisplatin combined with either gemcitabine or docetaxel is preferred for squamous cell NSCLC (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy* in the NCCN Guidelines for NSCLC).[668,673,704] Cisplatin combined with either vinorelbine or etoposide are “other recommended” options. For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin may be combined with pemetrexed (nonsquamous only), paclitaxel, or gemcitabine; thus, these regimens are useful in certain circumstances.[668,960] These regimens that are used for preoperative and postoperative chemotherapy may also be used for sequential chemoradiation.[674-677]

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. Three phase 3 trials have assessed preoperative chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.[629,961-963] All 3 studies showed a survival advantage for patients who received preoperative chemotherapy. SWOG S9900—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.[962,963] 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.[964-966]

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 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).[667,967] 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).[403,667]

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.[663,968] 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.[689] 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 (adding RT is for N2 only).[663]

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, then adjuvant treatment with durvalumab (category 1) is recommended for eligible patients. 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.[689] 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) (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.

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 (population-based analysis of data from SEER) of small randomized trials using older techniques and dosing regimens .[969] There was an apparent survival benefit of postoperative RT in patients with N2 nodal stage diagnosed surgically.[504] The analysis of the ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received chemotherapy.[403] 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.[970] A meta-analysis also concluded that postoperative RT improves survival for patients with N2 disease.[971] A meta-analysis assessed postoperative chemotherapy with (or without) postoperative RT in patients with mainly stage III disease.[968] 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.[972,973]

Postoperative sequential chemotherapy with RT is recommended for patients with T1–3, N2 disease and negative margins (see the NCCN Guidelines for NSCLC). 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.[689] Cisplatin/etoposide 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).[693] Pemetrexed with either cisplatin or carboplatin may be used for concurrent chemoradiation in patients with nonsquamous NSCLC.[696,974,975] When chemoradiation is recommended in the NCCN Guidelines, these regimens may be used for stage II to III disease.[404,405,634,635,694,697,698]

PROCLAIM, a phase 3 randomized trial, assessed concurrent thoracic RT with cisplatin/pemetrexed versus cisplatin/etoposide followed by consolidation chemotherapy in patients with unresectable stage III nonsquamous NSCLC.[691] 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 deleted the cisplatin/etoposide consolidation regimen based on the PROCLAIM trial.[691] In addition, the NCCN NSCLC Panel clarified that the cisplatin/pemetrexed and carboplatin/paclitaxel regimens may be followed by consolidation chemotherapy alone for eligible patients receiving definitive chemoradiation; however, these consolidation chemotherapy regimens should not be used if the patient will be receiving durvalumab.

Surveillance

Because recurrence is common after treatment for NSCLC, initial 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.[976-980] The surveillance guidelines were compiled 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). Surveillance schedules for most patients with metastatic disease are individualized for each patient, although the NCCN Guidelines provide a surveillance schedule for certain patients with stage IV oligometastatic disease.

NLST, a large randomized trial, assessed lung screening with low-dose CT screening versus chest radiography in individuals at high risk for lung cancer.[66] Low-dose CT screening decreased mortality from lung cancer (mainly adenocarcinoma) compared with chest radiography (247 vs. 309 deaths, respectively; 20% relative reduction in mortality; 95% CI, 6.8–26.7; *P* = .004).[66] Low-dose CT is recommended for screening individuals at high risk for lung cancer (see the NCCN Guidelines for Lung Cancer Screening). The NCCN NSCLC Panel feels that low-dose CT is beneficial for identifying recurrences in patients previously treated for NSCLC. It is important to note that the surveillance recommendations for patients who have been treated for NSCLC are different from the screening recommendations for individuals at high risk for lung cancer (see the NCCN Guidelines for Lung Cancer Screening).

The NCCN Guidelines recommend a chest CT scan with (or without) contrast and an H&P for the initial surveillance schedules (2–5 years) followed by an annual low-dose non-contrast–enhanced CT and an H&P (see *Surveillance* in the NCCN Guidelines for NSCLC).[978,979,981-984] Patients treated with chemotherapy with (or without) RT who have residual abnormalities may require more frequent imaging. 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.[985] For the 2020 update (Version 1), the NCCN NSCLC Panel now recommends assessing patients with recurrences using PET/CT and brain MRI with contrast. 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.[986]

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases. Management of locoregional recurrences or symptomatic local disease—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).[20] 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 their quality of life.[987] 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 variants 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.[225,988-990]

Management of distant metastases—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).[417,509,991] 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).[547,548,551,581,992-995] 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.[414,558-560,996-999]

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).[1000] Denosumab and bisphosphonate therapy can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk for hypocalcemia. Denosumab or intravenous bisphosphonate therapy can be considered in patients with bone metastases to decrease bone complications (eg, decrease pain, delay skeletal-related events) based on clinical trial data.[158,1000-1004] The FDA has approved the use of zoledronic acid and denosumab in patients with bone metastases from solid tumors.[1005,1006]

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).[704] In addition, biomarker testing for genetic variants (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 variants. The number of available targeted agents is increasing. In the NCCN Guidelines, several targeted agents are recommended for first-line therapy in patients with specific genetic variants such as erlotinib, gefitinib, afatinib, osimertinib, dacomitinib, alectinib, ceritinib, brigatinib, and crizotinib.[781] Additional targeted therapies for patients with other genetic variants 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). Certain targeted therapies—such as ceritinib, alectinib, brigatinib, lorlatinib, and osimertinib—are recommended as subsequent therapies (if not previously given) for patients with the indicated genetic variants whose disease becomes resistant to first-line targeted therapies; other targeted therapies are being investigated for resistance.

Biomarker testing for genetic variants is recommended in the NCCN Guidelines based on the improved outcomes associated with use of targeted therapy in eligible patients with metastatic NSCLC (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC and *Predictive and Prognostic Biomarkers* in this Discussion). 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).[105,200,209,212,1007] Testing for *ALK* fusions (category 1) is also recommended in patients with nonsquamous NSCLC, because ALK inhibitors are recommended for patients with metastatic NSCLC who are positive for *ALK* fusions.[160,1008] The NCCN NSCLC Panel also recommends testing for *ROS1* fusions (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.[271] 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 fusions can be done with FISH or with NGS if the platform is validated and can identify gene fusions.[181,198,199] The NCCN NSCLC Panel also recommends upfront PD-L1 expression testing (category 1) 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 emerging genetic variants: 1) crizotinib (for high-level *MET* amplification 2) ado-trastuzumab for *ERBB2* mutations; 3) nivolumab with or without ipilimumab for patients with TMB.[102,107,151-153,168,169,177,181,206,289-291,304,746,788,791,827,830,835,836,1009-1020] The NCCN NSCLC Panel recommends crizotinib for high-level *MET* amplification based on data from several studies.[289,1021,1022] The NCCN NSCLC Panel recommends ado-trastuzumab emtansine (category 2A) for patients with *ERBB2* (also known as *HER2*) mutations based on results from a phase 2 basket trial.[178,1011] 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%), nonsmokers, and all had adenocarcinomas. The NCCN NSCLC Panel does not recommend single-agent therapy with trastuzumab or afatinib (both for *ERBB2* mutations), because response rates are lower and treatment is less effective when these agents are used for patients with *ERBB2* mutations.[1023,1024]

As previously mentioned, recommendations from an international panel suggest that general histologic categories be avoided in patients with NSCLC (eg, NSCLC), because more effective treatment can be selected when the histology is known.[74] Patients with pure squamous cell carcinoma do not seem to have *ALK* fusions, *ROS1* fusions, *RET* rearrangements, sensitizing *EGFR* mutations, *METex14* skipping mutations, or *BRAF* V600E mutations; therefore, routine molecular testing is not recommended in these patients.[161,163,1025,1026] However, molecular testing for *ALK* fusions, *ROS1* fusions, *RET* rearrangements, *BRAF* mutations, *METex14* skipping 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.[161] Molecular testing for *EGFR* mutations or *ALK* fusions 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 test results for *ALK* fusions or sensitizing *EGFR* mutations and with PD-L1 expression less than 1%. 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 recommended for patients without genetic variants (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). Single-agent targeted therapy is recommended for patients with *EGFR, ALK, BRAF* V600E*, METex14* skipping*, RET,* or *ROS1* variants or other emerging driver mutations (see *Targeted Therapy for Advanced or Metastatic Disease* and *Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC* in the NCCN Guidelines for NSCLC).

Chemotherapy/immunotherapy regimens, such as pembrolizumab/carboplatin (or cisplatin)/pemetrexed, are recommended for patients with nonsquamous NSCLC and negative test results for *EGFR*, *ALK, ROS1, METex14* skipping*, RET,* or *BRAF* genetic variants (also known as wild-type), regardless of PD-L1 expression (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).[704]

For patients with metastatic NSCLC and contraindications to pembrolizumab or other ICIs, 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, and *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).[781,1027] Chemotherapy with or without bevacizumab is an option if eligibility criteria are met for patients with nonsquamous NSCLC and negative test results for *EGFR*, *ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants and with PD-L1 expression less than 1%.[1028] 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.[1029] 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).[1030] Systemic therapy for elderly patients with advanced NSCLC needs to be carefully selected to avoid adverse reactions.[1031] 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 for mutations, fusions, 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 test results for *EGFR*, *ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants and with PD-L1 expression less than 1%, chemotherapy/immunotherapy regimens—such as pembrolizumab/carboplatin with either paclitaxel or albumin-bound paclitaxel—are recommended (category 1; preferred). For patients with metastatic squamous cell NSCLC who have contraindications to pembrolizumab, recommended options include cisplatin/gemcitabine (category 1).[704] 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 NSCLC and negative test results for *EGFR, ALK, ROS1, METex14* skipping*, RET,* or *BRAF* variants and with PD-L1 expression less than 1%. 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, fewer treatment options are available for patients with squamous cell carcinoma compared with nonsquamous NSCLC. Research is ongoing to find newer options.[7,102,199,1032,1033]

Trial Data

Data show that platinum-based combination therapy is superior to best supportive care for patients with advanced, incurable disease who are not eligible for targeted therapy or immunotherapy. 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).[668,673,702-704,711,712,732] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.[1034] Non-platinum regimens (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine) are reasonable alternatives, because data show they are active and less toxic than platinum-based regimens.[714-717,1035]

ECOG 4599, a phase 2/3 trial, randomly assigned 878 patients to either 1) bevacizumab in combination with paclitaxel/carboplatin; or 2) paclitaxel/carboplatin alone.[720,1036] 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.[720] The overall 1-year and 2-year survival were 51% versus 44% and 23% versus 15%, respectively, in favor of the bevacizumab/paclitaxel/carboplatin arm.[720] 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).[1028] AVAiL, a phase 3 randomized trial, compared cisplatin/gemcitabine with (or without) bevacizumab; survival was not increased with the addition of bevacizumab.[1037,1038] 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.[753-757]

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.[704] 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.[1039]

Number of Cycles of First-Line Systemic Therapy

Data from the PARAMOUNT trial suggest that 4 cycles of platinum-based therapy is not optimal;[880] 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.[724] A meta-analysis suggests that continuing the initial regimen beyond 4 to 6 cycles is associated with increased PFS; however, patients have more adverse events.[1040] 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.[721,722] In this phase 3 trial, taxane-based regimens were used and patients had increasing neurotoxicity as more cycles were used.[721]

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.[724] 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.[721,878]

The NCCN Guidelines recommend that 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.[225,988-990] 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.[644,721,1041] The NCCN Guidelines do not recommend continuing chemotherapy beyond 4 to 6 cycles. Generally, patients with metastatic NSCLC receive 4 cycles of initial systemic chemotherapy (eg, carboplatin/pemetrexed/pembrolizumab for nonsquamous NSCLC) before starting maintenance therapy. However, if patients are tolerating the therapy, then 6 cycles of systemic therapy can be considered.

Maintenance Therapy

Maintenance therapy is an option for patients with metastatic nonsquamous NSCLC, with responsive or stable disease after first-line systemic chemotherapy or immunotherapy (see the NCCN Guidelines for NSCLC). Continuation maintenance therapy includes bevacizumab (category 1), pemetrexed (category 1), bevacizumab/pemetrexed (category 2A), pembrolizumab/pemetrexed (category 1), pembrolizumab (category 1), atezolizumab/bevacizumab (category 1), atezolizumab (category 2A), or gemcitabine (category 2B) (see the NCCN Guidelines for NSCLC).[672,720,726,837,880,883,884] Switch maintenance therapy for these patients includes pemetrexed (category 2A).[672,884,887,888]

A phase 3 randomized trial in 663 patients with advanced NSCLC assessed the effect of best supportive care with (or without) switch maintenance pemetrexed in patients who had received platinum-based chemotherapy but had not progressed.[888] Overall survival was 13.4 months (95% CI, 11.9–15.9) with pemetrexed compared with 10.6 months (95% CI, 8.7–12.0) with placebo (HR, 0.50; 95% CI, 0.42–0.61; $P <$ .0001). Maintenance therapy is discussed in greater detail earlier in this Discussion (see *Combined Modality Therapy: Maintenance Therapy*).

IUNO, a phase 3 randomized trial, assessed erlotinib as switch maintenance therapy (and as subsequent therapy) for patients with nonsquamous NSCLC and PS 0 to 2 but without *EGFR* mutations.[890] Overall survival and PFS were not improved in patients receiving erlotinib when compared with placebo. The NCCN NSCLC Panel previously 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 IUNO and a revised indication by the FDA.[890]

IFCT-GFPC 0502, a phase 3 randomized trial, compared maintenance therapy with either gemcitabine or erlotinib after initial cytotoxic therapy with cisplatin-gemcitabine in patients with advanced NSCLC.[672,884] 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) compared with observation (1.9 months).[672,884] For patients with squamous cell NSCLC, gemcitabine (category 2B) is recommended as continuation maintenance therapy based on this trial (see the NCCN Guidelines for NSCLC).[884,887] The benefits of continuation 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 in patients with advanced NSCLC.[892] Docetaxel is recommended (category 2B) as switch maintenance therapy for with squamous cell NSCLC based on this trial. 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.[1042] For patients with squamous cell NSCLC, pembrolizumab is recommended as continuation maintenance therapy if patients received either pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) or pembrolizumab alone (see *Pembrolizumab* in this Discussion).

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) that is termed the *flare phenomenon*.[747-750] This strategy mirrors the experience in other oncogene-addicted cancers, such as ALK inhibitors.[748] 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).[586,958,959,1043,1044]

Accumulating data suggest how cancers become resistant to EGFR inhibitors.[1045] 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.[1046,1047]

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 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.[747,749] Thus, continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.[1044]

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).[1017,1043,1048-1050] Osimertinib is recommended (category 1) for patients with symptomatic brain metastases and T790M who have progressed on erlotinib, gefitinib, dacomitinib, or afatinib.[226] 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, crizotinib, or ceritinib, patients with *ALK* fusions 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 previously 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 variant, the histologic subtype, and whether the patient has symptoms (see the NCCN Guidelines for NSCLC).[1051-1060] 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 PD-1 or PD-L1 inhibitors.[225,988,990,1061,1062]

If patients have not previously received an ICI, the NCCN NSCLC Panel recommends (category 1) pembrolizumab, nivolumab, or atezolizumab 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 *Pembrolizumab, Atezolizumab*, and *Nivolumab with or Without Ipilimumab* in this Discussion).[309,312,860] Human ICI antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.[309-311] The NCCN NSCLC Panel recommends nivolumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC based on the CheckMate 017 and CheckMate 057 clinical trials and FDA approvals.[309,864] The NCCN NSCLC Panel recommends pembrolizumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC and PD-L1 expression >1% based on the KEYNOTE-010 and KEYNOTE-001 trials, and on FDA approval.[840,853] The NCCN NSCLC Panel also recommends atezolizumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC based on the OAK and POPLAR trials, and FDA approval.[314,839,860] 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 clinical trial data and on the FDA approval (see *Osimertinib* in this Discussion).[226,243]

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 metastatic NSCLC and T790M who have brain metastases and have progressed on erlotinib, afatinib, dacomitinib, or gefitinib.[226,769-771] Data suggest that an afatinib/cetuximab regimen may be useful for patients who have progressed after receiving erlotinib, afatinib, or gefitinib and after chemotherapy.[1063] 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.

Subsequent therapy is recommended 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 EFGR 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.[309,751,840,860] The PD-1 or PD-L1 inhibitors were not worse than chemotherapy and were 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.[309,840,860] 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. A recent meta-analysis suggests that docetaxel improves overall survival when compared with pembrolizumab, nivolumab, or atezolizumab.[1064] Data suggest that patients with *EGFR* mutations or *ALK* fusions have a low response rate to PD-1 or PD-L1 inhibitors when compared with patients without these genetic variants (response rate, 3.6% vs. 23%, respectively).[751,1064] Therefore, subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with *EGFR* mutations or *ALK* fusions. Patients with *ALK*-positive NSCLC and very high PD-L1 expression do not respond to pembrolizumab.[751] In addition, those with *METex14* mutations and high PD-L1 expression do not respond to immunotherapy.[249,293]

The NCCN NSCLC Panel recommends lorlatinib (category 2A) as a subsequent therapy option for select patients with *ALK*-positive metastatic NSCLC who have progressed after treatment with ALK inhibitors (see *Lorlatinib* in this Discussion). For patients with *ALK* fusions 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.[158,1065] 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). The panel also 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.

The NCCN NSCLC Panel recommends capmatinib or crizotinib as subsequent therapy options for select patients with metastatic NSCLC and *METex14* skipping mutations who have not previously received either agent (see *Oral TKIs that Inhibit MET Exon 14 Skipping Mutations* in this Discussion in this Discussion). The panel recommends selpercatinib, pralsetinib, cabozantinib, or vandetanib (category 2B for vandetanib) as subsequent therapy options for select patients with *RET* rearrangement positive metastatic NSCLC who have not previously received these agents (see *Oral TKIs that Inhibit RET Rearrangements* in this Discussion).

Most patients with NSCLC do not have *EGFR, ALK, ROS1, METex14* skipping, *RET,* or *BRAF* variants. For patients with all histologic subtypes and PS of 0 to 2 but without these genetic variants who have disease progression during or after initial cytotoxic therapy, recommended subsequent systemic therapy options include PD-1 or PD-L1 inhibitors (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. If ICIs have not previously been given, the NCCN NSCLC Panel recommends (category 1) nivolumab, pembrolizumab, or atezolizumab 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 (see *Pembrolizumab, Atezolizumab*, and *Nivolumab with or Without Ipilimumab* in this Discussion).[309,312,860]

PD-1 or PD-L1 inhibitors are 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).[759] Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.[1057,1058] When compared with docetaxel, pemetrexed has similar median survival but less toxicity.[1059,1066] Pemetrexed is recommended in patients with nonsquamous NSCLC.[888]

Docetaxel is recommended for patients with wild-type *EGFR* tumors based on 2 randomized trials comparing erlotinib versus docetaxel.[1067,1068] In patients with PS of 3 to 4, best supportive care is recommended (see the NCCN Guidelines for NSCLC).[20,651,652] Patients often have a limited response to subsequent chemotherapy other than ICIs, although chemotherapy may serve a useful palliative role.[1069]

Subsequent therapy is recommended for certain patients after second disease progression if the following agents have not already been given: 1) nivolumab, pembrolizumab, or atezolizumab if none has 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).[1052,1068,1070,1071] These patients include those with advanced NSCLC, a PS of 0 to 2, and PD-L1 less than 1%.

The NCCN NSCLC Panel previously 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.[890] Data showed that overall survival and PFS were not improved in patients receiving erlotinib when compared with placebo. 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.[795] Overall survival was 7.9 months (95% CI, 7.2–8.7) for afatinib versus 6.8 months (95% CI, 5.9–7.8) for erlotinib (HR, 0.81; 95% CI, 0.69–0.95; *P* = .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.[312] 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 patients with squamous cell NSCLC based on a phase 3 randomized trial showing low response rates; they are less efficacious and safe compared to other available options.[795]

Doublet chemotherapy options used for initial cytotoxic therapy are recommended for patients with metastatic NSCLC (eg, carboplatin/paclitaxel) and genetic variants who progress with symptomatic systemic multiple lesions after first-line targeted therapy.[720] The IMPRESS trial indicated that chemotherapy should be used alone and not be combined with EGFR inhibitors, such as gefitinib, in patients who have progressed on gefitinib.[1072] 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.[200,1017,1049,1050] Osimertinib is recommended for patients with T790M whose disease becomes resistant to erlotinib, afatinib, or gefitinib.[243] Afatinib/cetuximab may be considered for second progression for patients with sensitizing *EGFR* mutations who have progressed after erlotinib, gefitinib, dacomitinib, or afatinib and after doublet chemotherapy.[1063] 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.[156,822,824] Flare phenomenon may occur in some patients who discontinue EGFR or ALK inhibitors. If disease flare occurs, then EGFR or ALK inhibitors should be restarted.[747-750]

For patients with metastatic NSCLC who have progressed after first-line therapy with single-agent 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 were 7 updates to 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 2020 update (Version 1), the NCCN NSCLC Panel has preference stratified the systemic therapy regimens based on the biomedical literature and experience of the panel members using the following categories: 1) preferred interventions; 2) other recommended interventions; and 3) interventions that are useful in certain circumstances. The NCCN NSCLC Panel has also preference stratified the new regimens that were added with each of the version updates for 2020 (Versions 2-6). These new preference categories are intended to emphasize the preferred regimens in clinical practice and are not intended to replace the NCCN Categories of Evidence and Consensus, such as category 1 or category 2A.

For the 2020 update (Version 1), the NCCN NSCLC Panel deleted “or unknown” regarding test results for actionable molecular or immune biomarkers, because the panel feels that clinicians should obtain biomarker test results for eligible patients with metastatic NSCLC before administering first-line therapy, if clinically feasible.[22] Patients with metastatic NSCLC and PD-L1 expression levels of 1% or more—but who also have a targetable driver oncogene molecular variant (eg, *EGFR, ALK*)—should receive first-line targeted therapy for that oncogene and not first-line immunotherapy regimens, because targeted therapies yield higher response rates (eg, osimertinib, 80%) than immunotherapy regimens (poor response rates) in the first-line setting, targeted therapy is better tolerated, and these patients are unlikely to respond to ICIs.[249,321-323,751] For the 2020 update (Version 1, Version 4), the NCCN NSCLC Panel added *ROS1* fusions, *RET* rearrangements, *METex14* skipping mutations, and *BRAF* mutations to the list of actionable biomarkers that need to be negative before administering immunotherapy regimens; the complete list is as follows: *EGFR, ALK, ROS1*, *METex14* skipping*, RET*, and *BRAF* variants.[183]

For the 2020 update (Version 2), the NCCN NSCLC Panel recommends the following systemic therapy regimens as options for certain patients with metastatic NSCLC, regardless of PD-L1 levels: 1) erlotinib plus either ramucirumab (category 2A) or bevacizumab (category 2B) for *EGFR* mutation–positive metastatic disease; 2) atezolizumab plus carboplatin plus albumin-bound paclitaxel (category 2A) for metastatic nonsquamous NSCLC with negative test results for actionable genetic variants; and 3) nivolumab plus ipilimumab (category 2A) for metastatic nonsquamous and squamous cell NSCLC with negative test results for actionable genetic variants.

For the 2020 update (Version 4), the NCCN NSCLC Panel recommends capmatinib as a first-line therapy or subsequent therapy option (category 2A; preferred) for eligible patients with metastatic NSCLC who are positive for *METex14* skipping mutations based on preliminary clinical trial data and on the FDA approval for capmatinib.[294] Crizotinib is also recommended as a first-line therapy or subsequent therapy option (category 2A; useful in certain circumstances) for certain patients with metastatic NSCLC who are positive for *METex14* skipping mutations.[295] Capmatinib or crizotinib may be used as subsequent therapy if they were not previously given as first-line therapy for *METex14* skipping mutation–positive metastatic NSCLC. The NCCN NSCLC Panel also preference stratified regimens that are recommended for *METex14* skipping mutations and voted that capmatinib is a preferred first-line therapy or subsequent therapy option for *METex14* skipping mutation–positive metastatic NSCLC based on clinical trial data.[294] The panel voted that crizotinib is useful in certain circumstances as either a first-line therapy or subsequent therapy option for *METex14* skipping mutation–positive metastatic NSCLC.[295] For the Version 4 update, the NCCN NSCLC Panel recommends testing for *METex14* skipping mutations (category 2A) in certain patients with metastatic NSCLC based on data showing the efficacy of capmatinib and crizotinib for patients with *METex14* skipping mutation–positive metastatic NSCLC and on the FDA approval for capmatinib.[294,295]

For the 2020 updates (Versions 4 and 7), the NCCN NSCLC Panel recommends selpercatinib or pralsetinib as a first-line therapy or subsequent therapy options (category 2A; preferred) for eligible patients with metastatic NSCLC who are positive for *RET* rearrangements based on preliminary clinical trial data and on the FDA approvals for both agents.[302,303] The NCCN NSCLC Panel recommends cabozantinib as a first-line therapy or subsequent therapy option (category 2A; useful in certain circumstances) for *RET* rearrangement–positive metastatic NSCLC.[152,304] The NCCN NSCLC Panel also recommends vandetanib as a first-line therapy or subsequent therapy option (category 2B; as useful in certain circumstances) for *RET* rearrangement–positive metastatic NSCLC.[746] Selpercatinib, pralsetinib, cabozantinib, or vandetanib may be used as subsequent therapy if they were not previously given as first-line therapy for *RET* rearrangement–positive metastatic NSCLC. The NCCN NSCLC Panel also preference stratified the regimens that are recommended for *RET* rearrangements and voted that selpercatinib and pralsetinib are preferred first-line therapy or subsequent therapy options for *RET* rearrangement–positive metastatic NSCLC based on clinical trial data.[302,303,833] The panel decided that cabozantinib (category 2A) and vandetanib (category 2B) are both useful in certain circumstances as either first-line therapy or subsequent therapy options for *RET* rearrangements.[152,304,835] For the Version 4 and 7 updates, the NCCN NSCLC Panel recommends testing for *RET* rearrangements (category 2A) in certain patients with metastatic NSCLC based on data showing the efficacy of selpercatinib, pralsetinib, cabozantinib, and vandetanib for patients with *RET* rearrangement–positive metastatic NSCLC and on the FDA approvals for selpercatinib an pralsetinib.[302,303]

For the 2020 update (Version 5), the NCCN NSCLC Panel recommends atezolizumab monotherapy as a first-line therapy option (category 2A; preferred) for eligible patients with metastatic NSCLC based on preliminary clinical trial data and on the FDA approval.[858,859] Atezolizumab monotherapy is recommended as a first-line therapy option (category 2A; preferred) for patients with metastatic NSCLC, PD-L1 levels of 50% or more, and negative test results for *EGFR, ALK, ROS1, METex14* skipping, *RET,* or *BRAF* variants, regardless of histology; maintenance therapy with atezolizumab is also recommended in this setting.

For the 2020 update (Version 6), the NCCN NSCLC Panel recommends nivolumab/ipilimumab/chemotherapy as a first-line therapy option (category 2A; other recommended) for eligible patients with metastatic NSCLC based on preliminary clinical trial data and the FDA approval.[863] For metastatic nonsquamous NSCLC, the recommended chemotherapy is pemetrexed with either cisplatin or carboplatin; for metastatic squamous NSCLC, the recommended chemotherapy is paclitaxel with carboplatin. Nivolumab plus ipilimumab plus chemotherapy is recommended for patients with metastatic NSCLC, regardless of PD-L1 levels; negative test results for *EGFR, ALK, ROS1, METex14* skipping, *RET,* or *BRAF* variants; and no contraindications to PD-1/PD-L1 inhibitors.

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