National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

NCCN Evidence Blocks™

Version 8.2025 — August 15, 2025

NCCN.org

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NCCN Guidelines Version 8.2025
Non-Small Cell Lung Cancer
NCCN Evidence Blocks™

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‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocacy
Ξ Pulmonary medicine
§ Radiation oncology/ Radiotherapy
¶ Surgery/Surgical oncology
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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.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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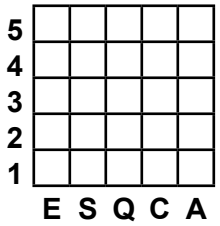
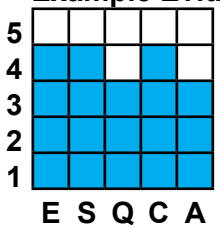
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

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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.**
- **The number of lung cancers in individuals who do not smoke is increasing worldwide. More research is necessary to identify relevant risk factors—such as environmental exposures (eg, indoor and outdoor air pollution, radon, asbestos), chronic lung diseases, and family history/genetic predisposition—to augment lung cancer screening in the future.**
- **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 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 person who smokes. 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 to identify, counsel, and treat patients with nicotine habituation.**
- **Patients who smoke or who formerly smoked 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 patients at high risk for lung cancer who smoke or formerly smoked (see the NCCN Guidelines for Lung Cancer Screening).**
- **See the NCCN Guidelines for Smoking Cessation.**

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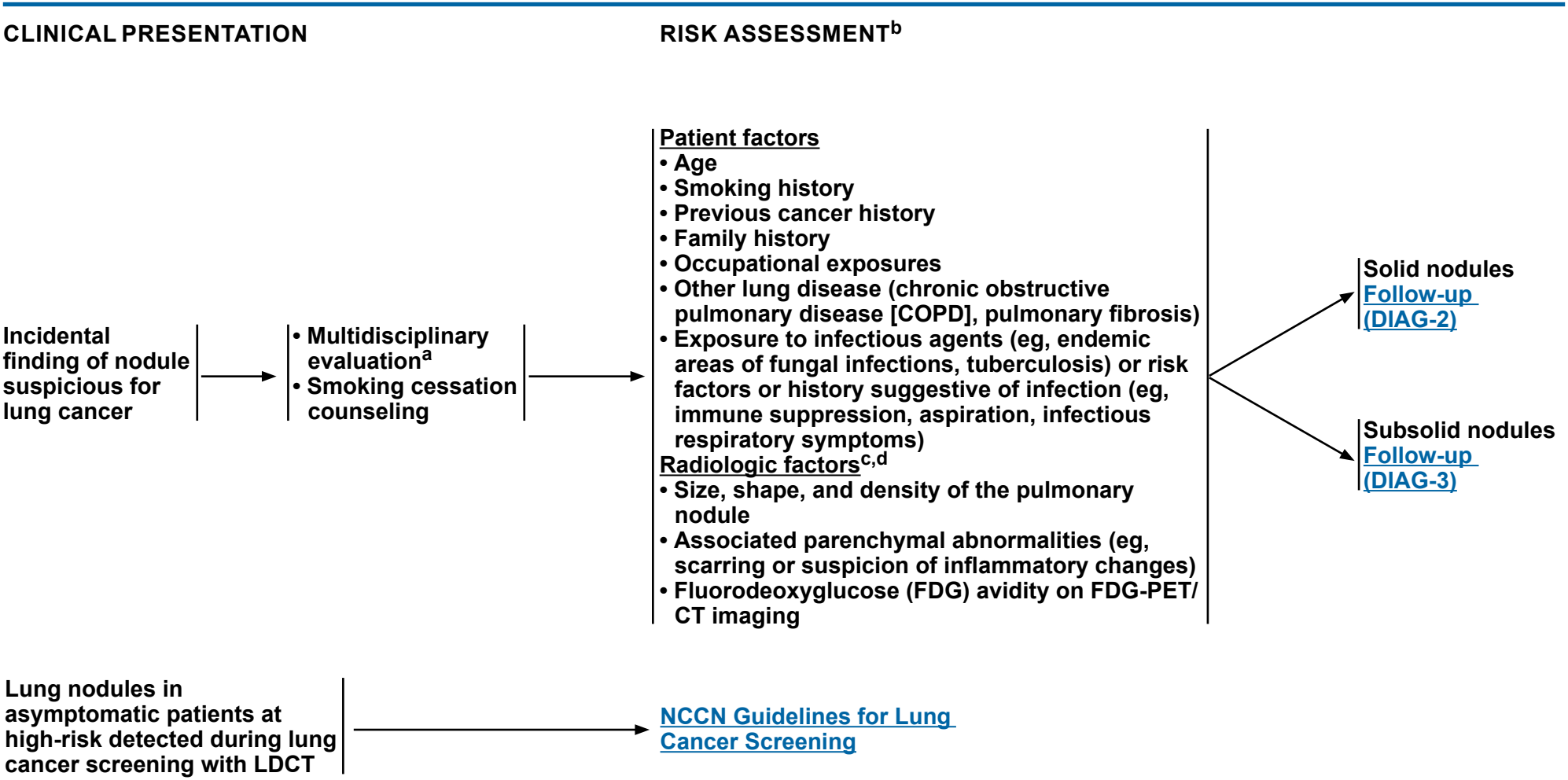

[a] Multidisciplinary evaluation including thoracic surgeons, thoracic radiologists, and pulmonologists to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy.
[b] Risk calculators can be used to quantify individual patient and radiologic factors but do not 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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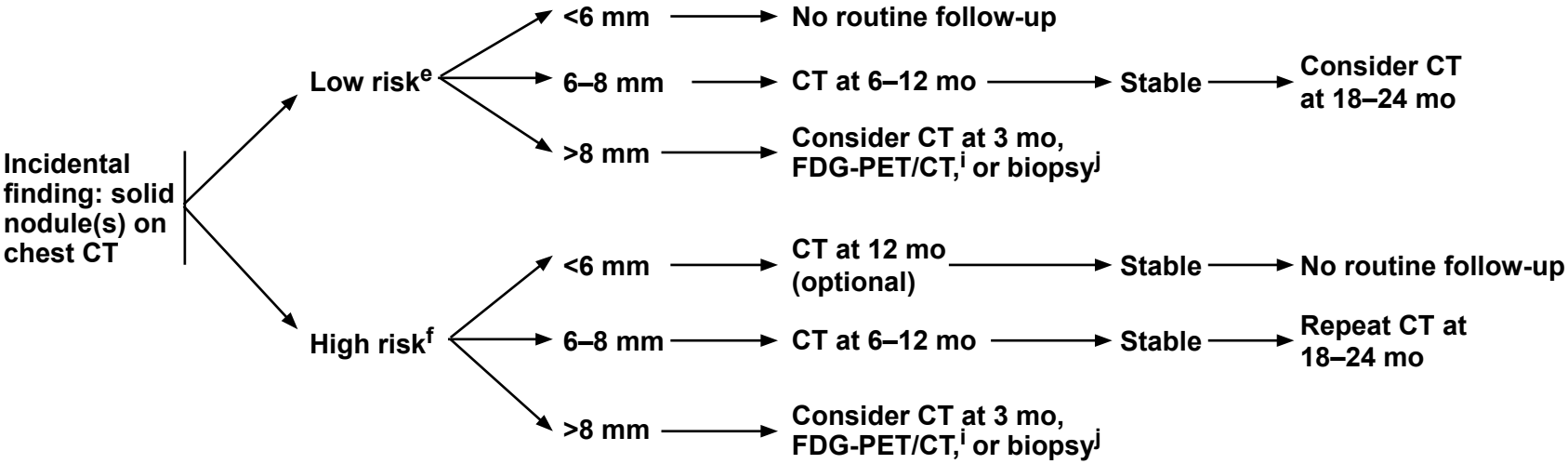
FINDINGS **FOLLOW-UP[c,d,g,h]**



[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 or 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] FDG-PET/CT performed skull base to mid-thigh. A positive FDG-PET/CT result is defined as a standardized uptake value (SUV) in the lung nodule greater than the baseline mediastinal blood pool. A false-positive FDG-PET/CT 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 FDG-PET/CT 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 [AIS; previously known as bronchoalveolar carcinoma], carcinoid tumor). If a false-negative FDG-PET/CT is due to low tumor avidity and/or low cellularity is suspected, follow-up CT or biopsy are reasonable options.
[j] Prior to treatment, multidisciplinary evaluation that includes treating physicians and specialists in obtaining tissue diagnosis (thoracic surgery, interventional pulmonology, and interventional radiology) is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult, that a clinical diagnosis of lung cancer is appropriate, and that treatment is warranted.

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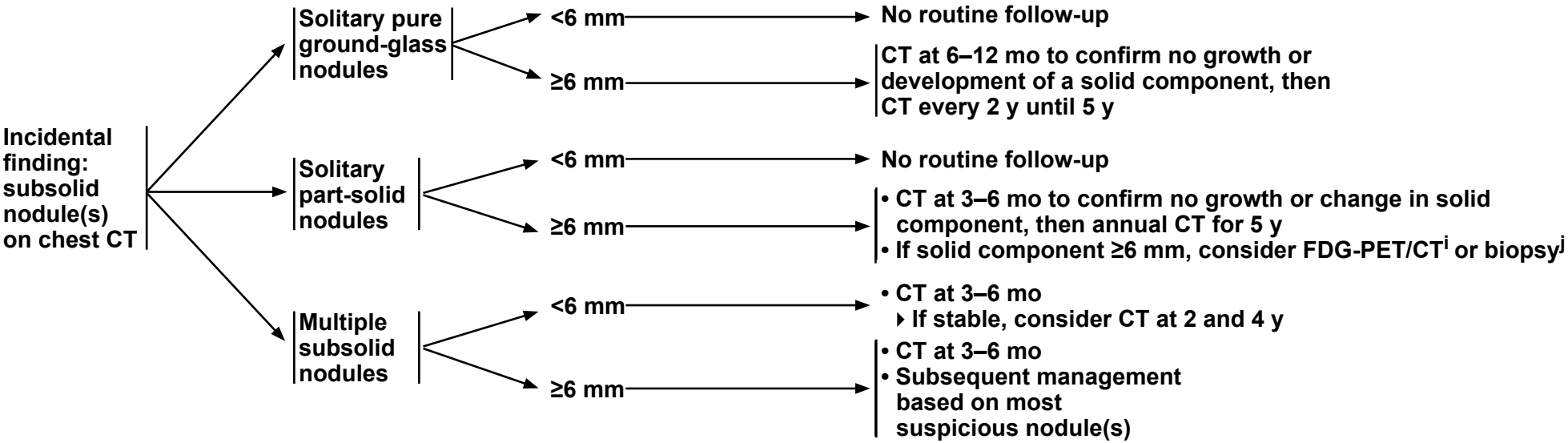

[c] Principles of Diagnostic Evaluation (DIAG-A 1 of 3).
[d] The most important radiologic factor is change or stability compared with a previous imaging study.
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[i] FDG-PET/CT performed skull base to mid-thigh. A positive FDG-PET/CT result is defined as an SUV in the lung nodule greater than the baseline mediastinal blood pool. A false-positive FDG-PET/CT 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 FDG-PET/CT scan can be caused by a small nodule, low cellular density (nonsolid nodule or GGO), or low tumor avidity for FDG (eg, AIS [previously known as bronchoalveolar carcinoma], carcinoid tumor). If a false-negative FDG-PET/CT is due to low tumor avidity and/or low cellularity is suspected, follow-up CT or biopsy are reasonable options.
[j] Prior to treatment, multidisciplinary evaluation that includes treating physicians and specialists in obtaining tissue diagnosis (thoracic surgery, interventional pulmonology, and interventional radiology) is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult, that a clinical diagnosis of lung cancer is appropriate, and that treatment is warranted.

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PRINCIPLES OF DIAGNOSTIC EVALUATION

- **The decision to pursue preoperative biopsy of a potential stage I lung cancer should be informed by the pre-test probability of malignancy.**
  - **Factors that might be considered in pre-test probability assessment include risk factors, radiologic appearance (including comparison to prior chest imaging if available or FDG-PET/CT if performed), and current or prior residence in regions with prevalent endemic infectious lung disease (ie, fungal, mycobacterial), among other potential factors.**
  - **Patients with very high pre-test probability of stage IA lung cancer do not require a biopsy before surgery. A biopsy adds time, costs, and procedural risk and may not be needed for treatment decisions.**
  - **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.**
  - **Situations in which a preoperative biopsy may be appropriate:**
    - ◊ **A non-lung cancer diagnosis that can be diagnosed by minimally invasive biopsy is at least moderately likely (eg, granulomatous nodule due to endemic fungus).**
    - ◊ **Suspected stage IB or higher lung cancer in patients who may be candidates for systemic therapy prior to surgery.**
    - ◊ **An intraoperative diagnosis appears difficult or very risky.[1]**
    - ◊ **To establish the diagnosis prior to stereotactic ablative radiotherapy (SABR).[2]**

[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 (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595).

[2] Prior to treatment, multidisciplinary evaluation that includes treating physicians and specialists in obtaining tissue diagnosis (thoracic surgery, interventional pulmonology, and interventional radiology) is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult, that a clinical diagnosis of lung cancer is appropriate, and that treatment is warranted.

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PRINCIPLES OF DIAGNOSTIC EVALUATION

- **A preoperative bronchoscopy may also be preferred for tissue diagnosis and/or mediastinal staging (endobronchial ultrasound [EBUS]).**
- **If a bronchoscopy has not been previously performed for diagnosis or staging, bronchoscopy should 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).**
  - **A preoperative bronchoscopy may also be preferred for tissue diagnosis and/or mediastinal staging (EBUS).**
- **Invasive mediastinal staging is recommended before surgical resection for most patients with clinical stage I or II lung cancer (NSCL-2 and NSCL-3). For patients undergoing EBUS/endoscopic ultrasound (EUS) staging, this most commonly should be a separate procedure to allow for pathologic evaluation.**
  - **Patients having mediastinoscopy 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.**
  - **A separate staging procedure adds time, costs, coordination of care, inconvenience, and an additional anesthetic risk.**
  - **Preoperative invasive mediastinal staging may be appropriate for a strong clinical suspicion of N2 or N3 nodal disease or when intraoperative cytology or frozen section analysis is not available.**
- **In patients with suspected non-small cell lung cancer (NSCLC), many techniques are available for tissue diagnosis.**
  - **Diagnostic tools that should be routinely available include:**
    - ◊ **Sputum cytology**
    - ◊ **Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)**
    - ◊ **Image-guided transthoracic needle core biopsy (preferred) or fine-needle aspiration (FNA)**
    - ◊ **Thoracentesis**
    - ◊ **Mediastinoscopy**
    - ◊ **Video-assisted thoracic surgery (VATS) and open surgical biopsy**
    - ◊ **Left anterior mediastinotomy/Chamberlain**
  - **Diagnostic tools that provide important additional strategies for biopsy include:**
    - ◊ **EBUS–guided biopsy**
    - ◊ **EUS–guided biopsy**
    - ◊ **Navigational bronchoscopy**
    - ◊ **Robotic bronchoscopy**

Continued

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PRINCIPLES OF DIAGNOSTIC EVALUATION

- The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.
  - Factors to be considered in choosing the optimal diagnostic step include:
    - ◊ Anticipated diagnostic yield (sensitivity)
    - ◊ Diagnostic accuracy including specificity and particularly the reliability of a negative diagnostic study (ie, true negative)
    - ◊ Adequate volume of tissue specimen for diagnosis and molecular testing
    - ◊ Invasiveness and risk of procedure
    - ◊ Efficiency of evaluation
      - – Access and timeliness of procedure
      - – Concomitant staging is beneficial, because it avoids additional biopsies or procedures. It is preferable to biopsy the pathology that would confer the highest stage (ie, to biopsy a suspected metastasis or mediastinal lymph node rather than the pulmonary lesion). Therefore, FDG-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 FDG-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, thoracic surgeons, and pulmonologists 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. 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 pulmonary nodules may benefit from navigational bronchoscopy (including robotic), 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, 3P, 4R/4L, 7, 10R/10L, 11–13, and other hilar nodal stations if necessary.
      - – An EBUS-TBNA negative for malignancy in a clinically (FDG-PET/CT and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.
      - – EUS–guided biopsy provides additional access to stations 3P, 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 3a, 5, and 6) lymph nodes. 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.
    - ◊ Patients with lung cancer with an associated pleural effusion should undergo thoracentesis and cytology. A negative pleural cytology result does not exclude pleural involvement. Thoracoscopic evaluation of the pleura should be considered before starting curative intent therapy if pleural fluid is a lymphocytic exudate with negative pleural fluid cytology.
    - ◊ 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

INITIAL EVALUATION

NSCLC →
- 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
- Integrate palliative care[c] NCCN Guidelines for Palliative Care
- For tools to aid in the optimal assessment and management of NSCLC in older adults, see the NCCN Guidelines for Older Adult Oncology

CLINICAL STAGE[d]

Stage IA, peripheral[e] (T1abc, N0)	Pretreatment Evaluation (NSCL-2)
Stage IB, peripheral[e] (T2a, N0); Stage I, central[e] (T1abc–T2a, N0); Stage II (T1abc–T2ab, N1; T2b, N0); Stage IIB (T3, N0)[f]; stage IIIA (T3, N1)[f]	Pretreatment Evaluation (NSCL-3)
Stage IIB (T3 invasion, N0); Stage IIIA (T4 invasion, N0–1; T3, N1; T4, N0–1)	Pretreatment Evaluation (NSCL-5)
Stage IIIA (T1–2, N2); stage IIIB (T3, N2)	Pretreatment Evaluation (NSCL-8)
Separate pulmonary nodule(s) (stage IIB, IIIA, IV) Stage IIIA ipsilateral non-primary lobe (T4, N0–1); Stage IV (contralateral lung)	Pretreatment Evaluation (NSCL-8)
Multiple lung cancers	Treatment (NSCL-11)
Stage IIIB (T1–2, N3); stage IIIC (T3, N3)	Pretreatment Evaluation (NSCL-13)
Stage IIIB (T4, N2); stage IIIC (T4, N3)	Pretreatment Evaluation (NSCL-14)
Stage IVA (M1a)[c] (pleural or pericardial effusion)	Pretreatment Evaluation (NSCL-14)
Stage IVA, M1b[c] and stage IVB, M1c[c]	Pretreatment Evaluation (NSCL-15)
Pleural metastases[c] or disseminated metastases[c]	Advanced/ metastatic disease (NSCL-19)

[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] For patients where more than one treatment modality (surgery, radiation therapy [RT], or systemic therapy) is usually considered, a multidisciplinary evaluation should be performed.
[e] Based on the CT of the chest: Peripheral = outer third of lung; Central = inner two thirds of lung.
[f] T3, N0 related to size or satellite nodules.

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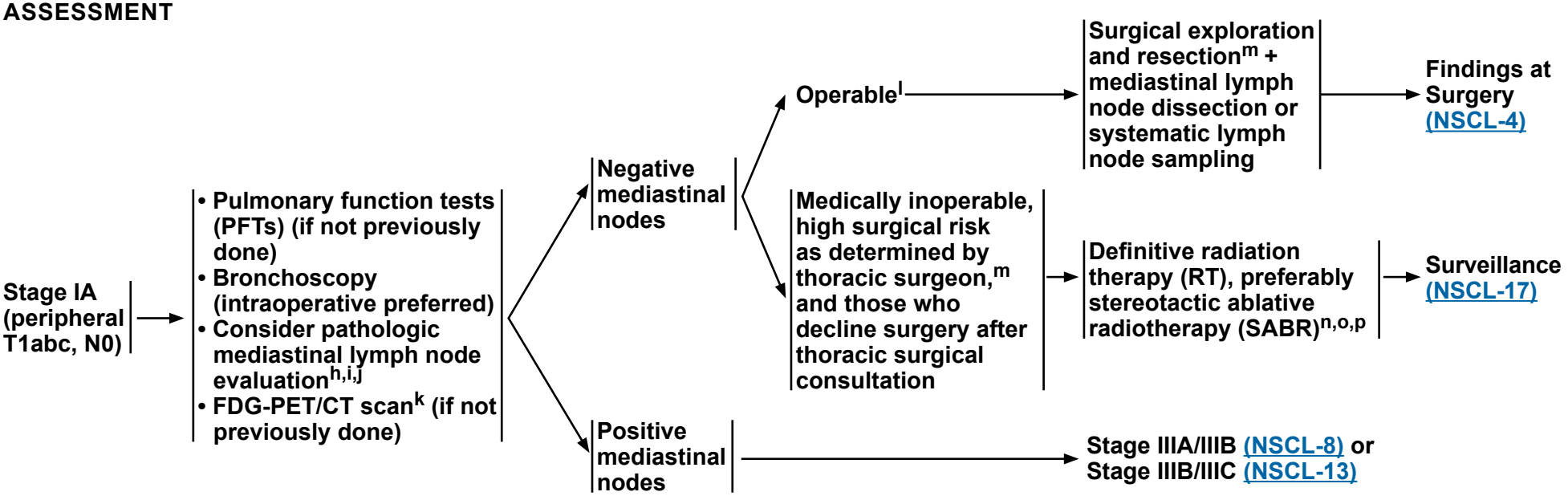

[g] Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.

[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (FDG-PET/CT 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 FDG-PET/CT negative in peripheral tumors (outer third of lung) ≤3 cm. Thus, pretreatment pathologic mediastinal evaluation is optional in these settings. Invasive mediastinal staging is recommended for central tumors.

[j] In patients who are medically inoperable, while mediastinal biopsy is generally preferred, the risks in selected patients may outweigh the benefits.

[k] FDG-PET/CT performed skull base to mid-thigh. Positive FDG-PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If FDG-PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

[l] Surgical resection is considered the first option for operable patients with stage IA lung cancer, but patients may also be informed about SABR as an alternative option through shared decision-making.

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

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

[o] Image-guided thermal ablation (IGTA) therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[p] Prior to treatment, multidisciplinary evaluation that includes treating physicians and specialists in obtaining tissue diagnosis (thoracic surgery, interventional pulmonology, and interventional radiology) is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult, that a clinical diagnosis of lung cancer is appropriate, and that treatment is warranted.

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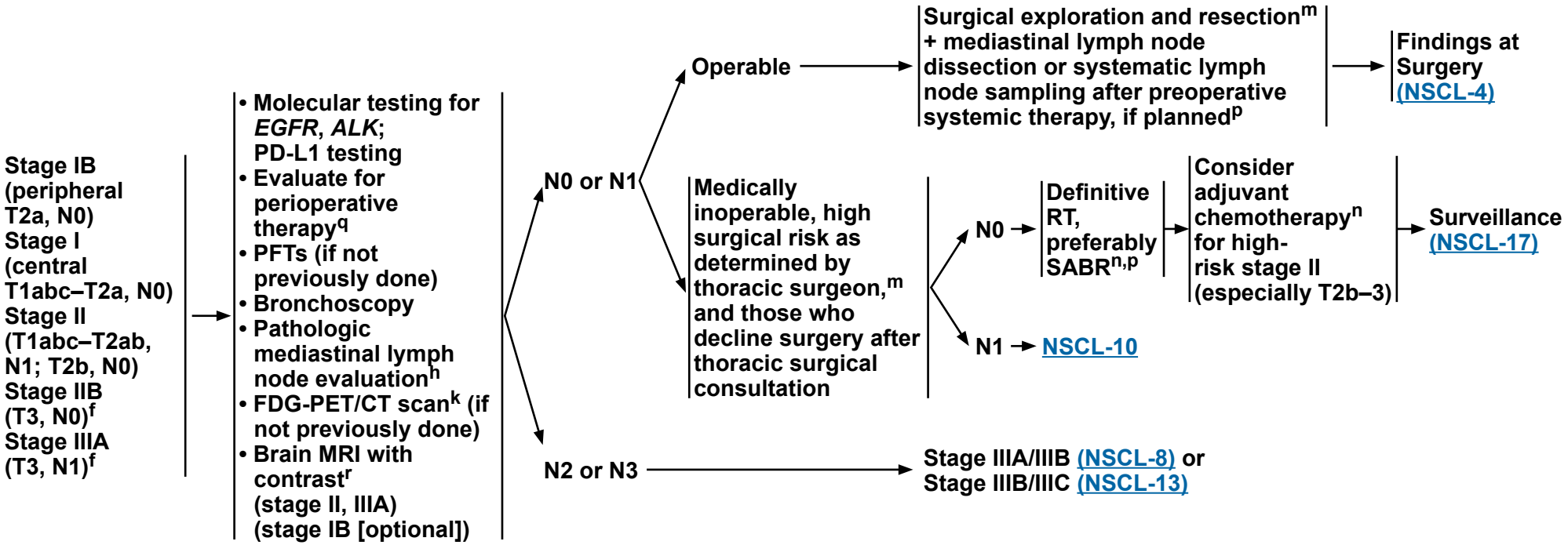

[f] T3, N0 related to size or satellite nodules.
[g] Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.
[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (FDG-PET/CT and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.
[k] FDG-PET/CT performed skull base to mid-thigh. Positive FDG-PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If FDG-PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[m] Principles of Surgical Therapy (NSCL-B).
[n] Principles of Radiation Therapy (NSCL-C).
[p] Prior to treatment, multidisciplinary evaluation that includes treating physicians and specialists in obtaining tissue diagnosis (thoracic surgery, interventional pulmonology, and interventional radiology) is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult, that a clinical diagnosis of lung cancer is appropriate, and that treatment is warranted.
[q] Perioperative Systemic Therapy (NSCL-E).
[r] If MRI is not possible, CT of head with contrast.

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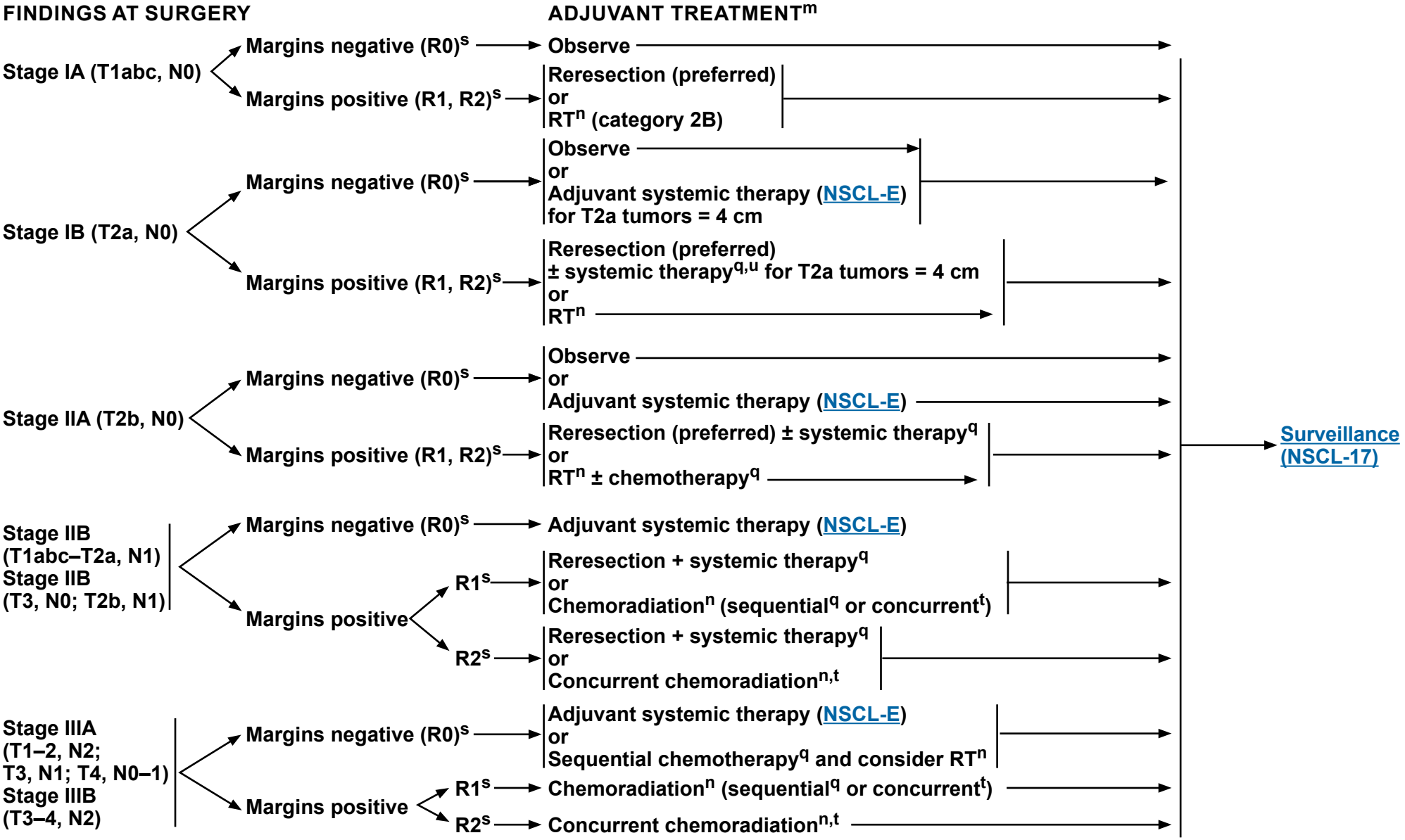

Footnotes on NSCL-4A

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FOOTNOTES FOR NSCL-4

[m] Principles of Surgical Therapy (NSCL-B).
[n] Principles of Radiation Therapy (NSCL-C).
[q] Perioperative Systemic Therapy (NSCL-E).
[s] R0 = complete resection with negative margins, R1 = microscopic positive margins, R2 = gross unresected tumor remaining.
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[u] Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

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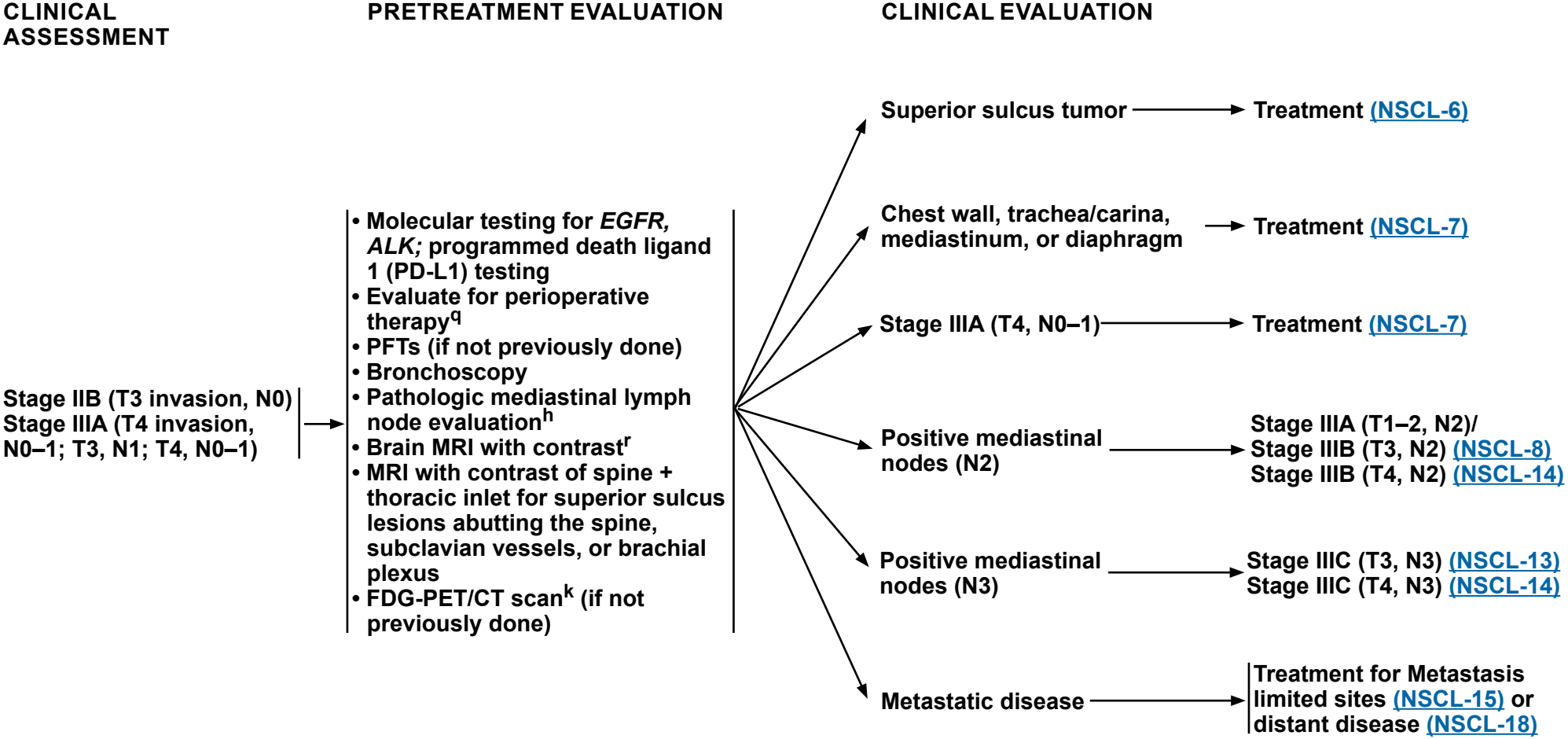

[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (FDG-PET/CT and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.

[k] FDG-PET/CT performed skull base to mid-thigh. Positive FDG-PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If FDG-PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

[q] Perioperative Systemic Therapy (NSCL-E).

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

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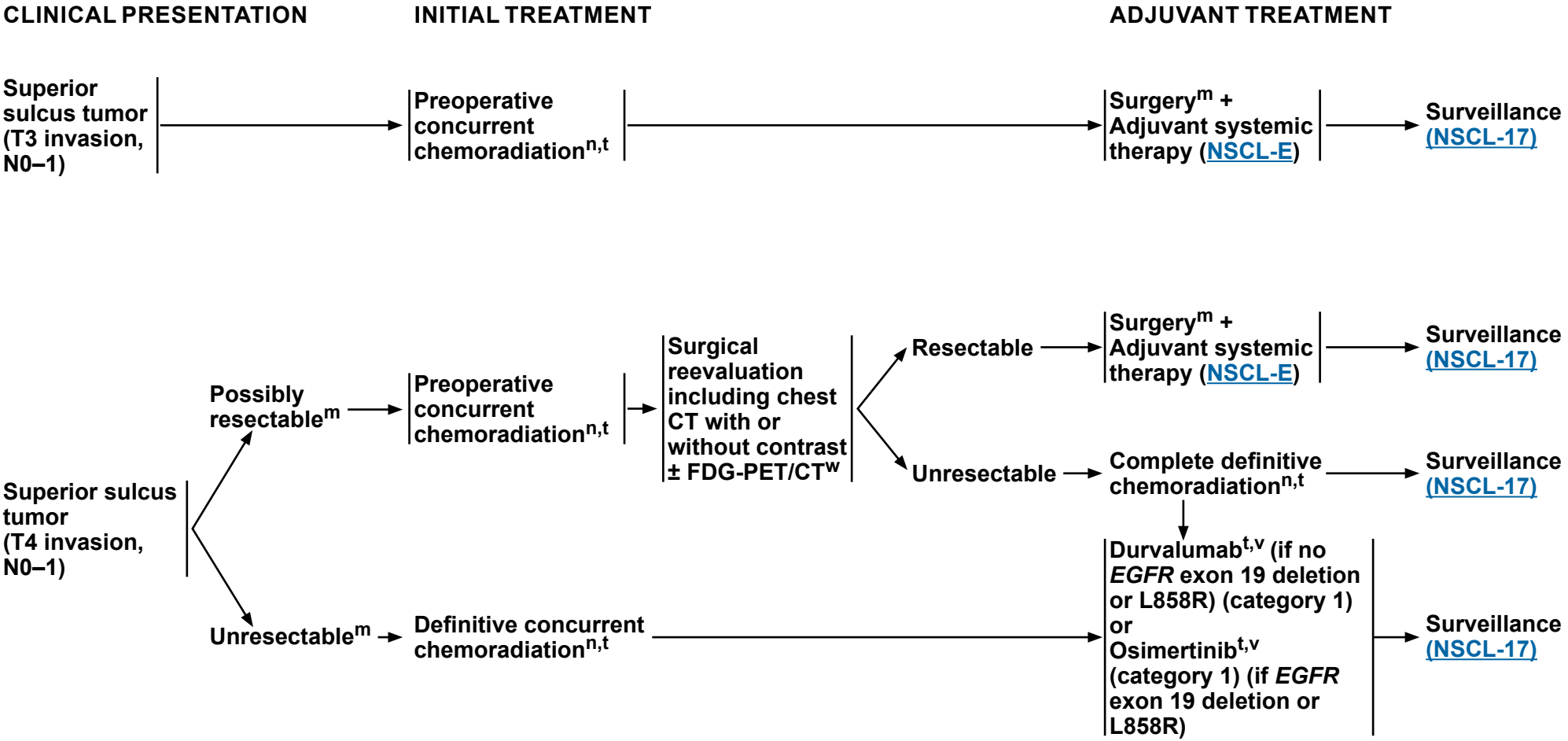

[m] Principles of Surgical Therapy (NSCL-B).
[n] Principles of Radiation Therapy (NSCL-C).
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy or, if *EGFR* exon 19 deletion or L858R, osimertinib is recommended.
[w] MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine, subclavian vessels, or brachial plexus.

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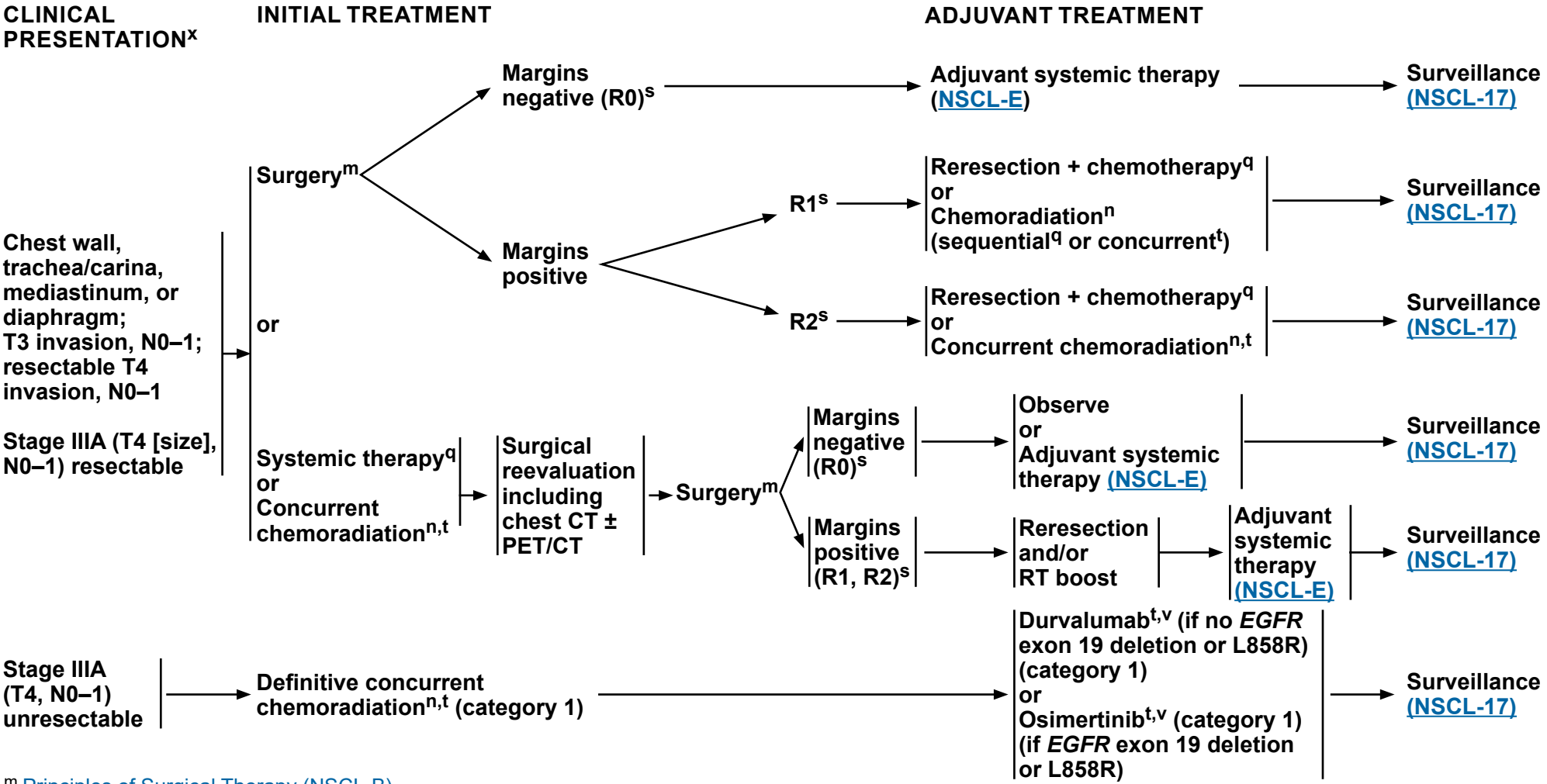

[m] Principles of Surgical Therapy (NSCL-B).
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[q] Perioperative Systemic Therapy (NSCL-E).
[s] R0 = complete resection with negative margins, R1 = microscopic positive margins, R2 = gross unresected tumor remaining.
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy or, if *EGFR* exon 19 deletion or L858R, osimertinib is recommended.
[x] Resectability should be determined by thoracic surgery evaluation prior to initiation of any therapy.

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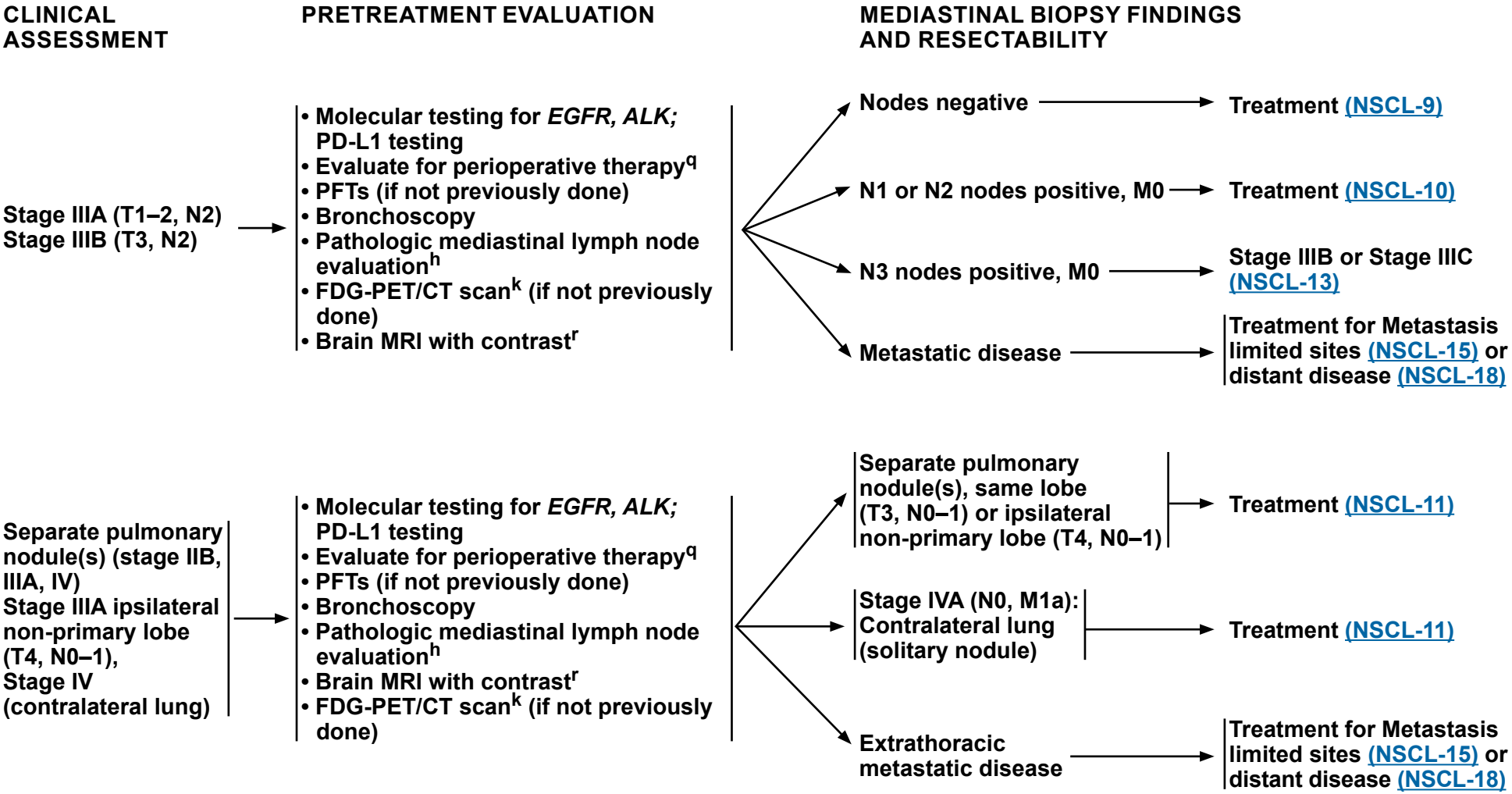

[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (FDG-PET/CT and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.

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[q] Perioperative Systemic Therapy (NSCL-E).

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

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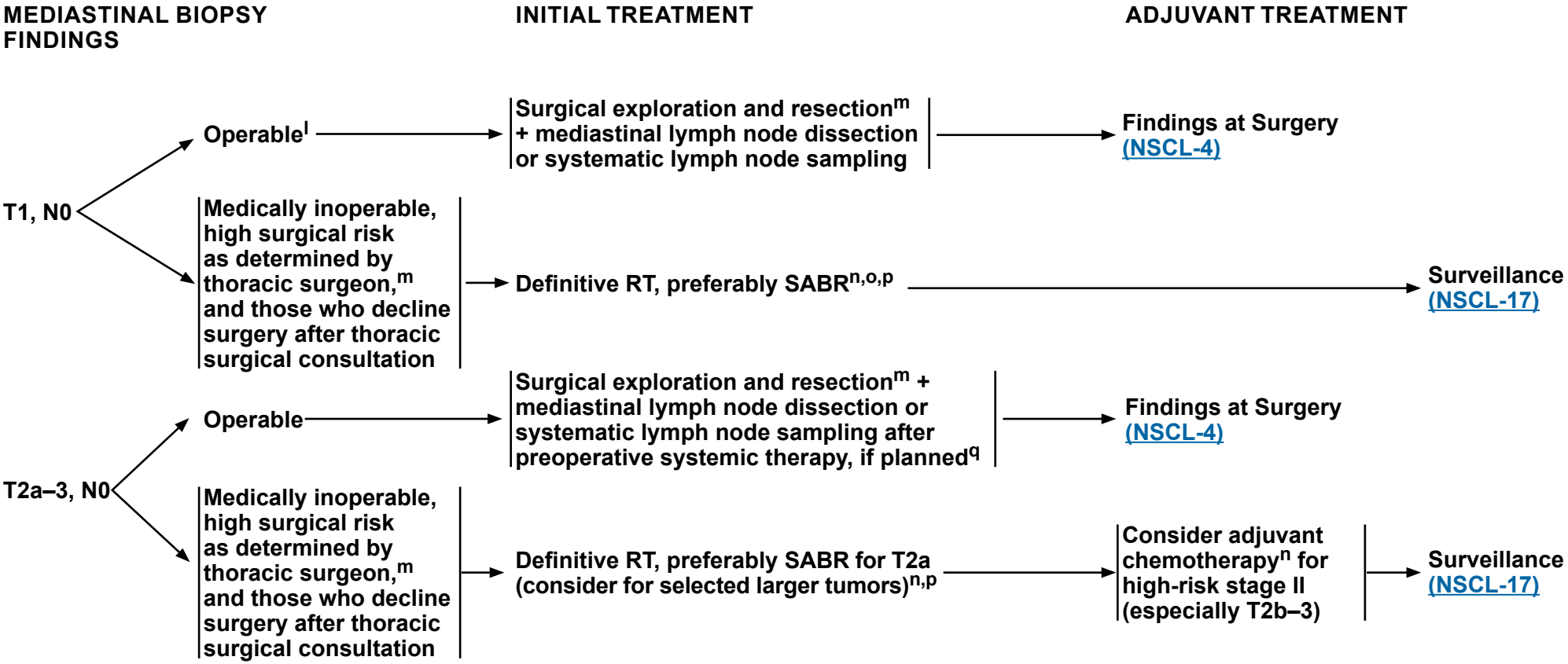

[l] Surgical resection is considered the first option for operable patients with stage IA lung cancer, but patients may also be informed about SABR as an alternative option through shared decision-making.
[m] Principles of Surgical Therapy (NSCL-B).
[n] Principles of Radiation Therapy (NSCL-C).
[o] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[p] Prior to treatment, multidisciplinary evaluation that includes treating physicians and specialists in obtaining tissue diagnosis (thoracic surgery, interventional pulmonology, and interventional radiology) is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult, that a clinical diagnosis of lung cancer is appropriate, and that treatment is warranted.
[q] Perioperative Systemic Therapy (NSCL-E).

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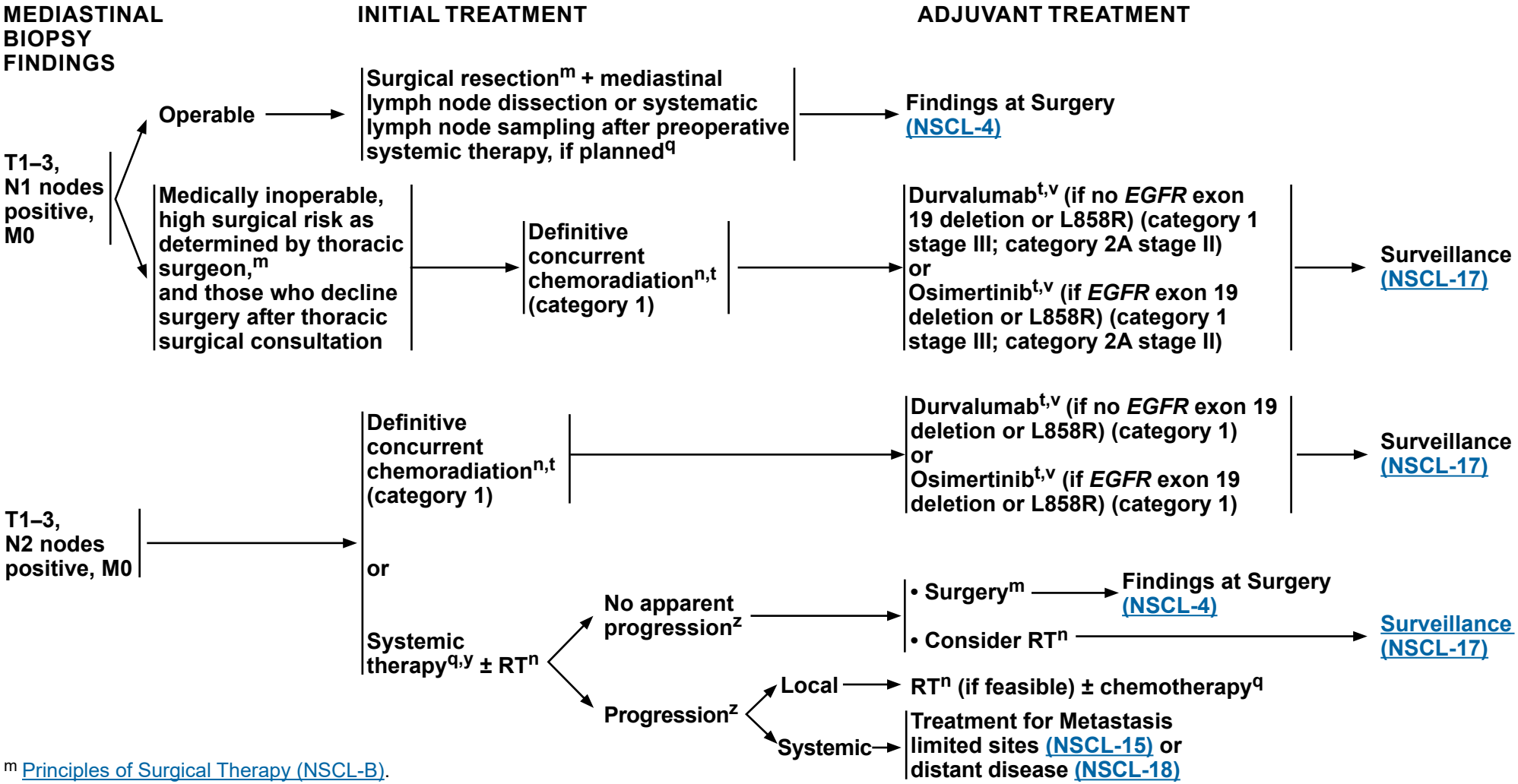

[m] Principles of Surgical Therapy (NSCL-B).
[n] Principles of Radiation Therapy (NSCL-C).
[q] Perioperative Systemic Therapy (NSCL-E).
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy or, if *EGFR* exon 19 deletion or L858R, osimertinib is recommended.
[y] Selected patients with N2 disease (fit, single-station, non-bulky N2, requiring only lobectomy) may be considered for systemic therapy followed by surgery.
[z] Chest CT with contrast and/or FDG-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[m] after preoperative systemic therapy, if planned[q]** → **Findings at Surgery (NSCL-4)**

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

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

- **Disease outside of chest** → **Advanced/metastatic disease (NSCL-19)**
- **No disease outside of chest** → **Pathologic mediastinal lymph node evaluation[h]**
  - **N0–1** → **Initial Treatment (NSCL-12)**
  - **N2–3** → **Advanced/metastatic disease (NSCL-19)**

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

[k] FDG-PET/CT performed skull base to mid-thigh. Positive FDG-PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If FDG-PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

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

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

[q] Perioperative Systemic Therapy (NSCL-E).

[aa] 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-12). 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.

[bb] 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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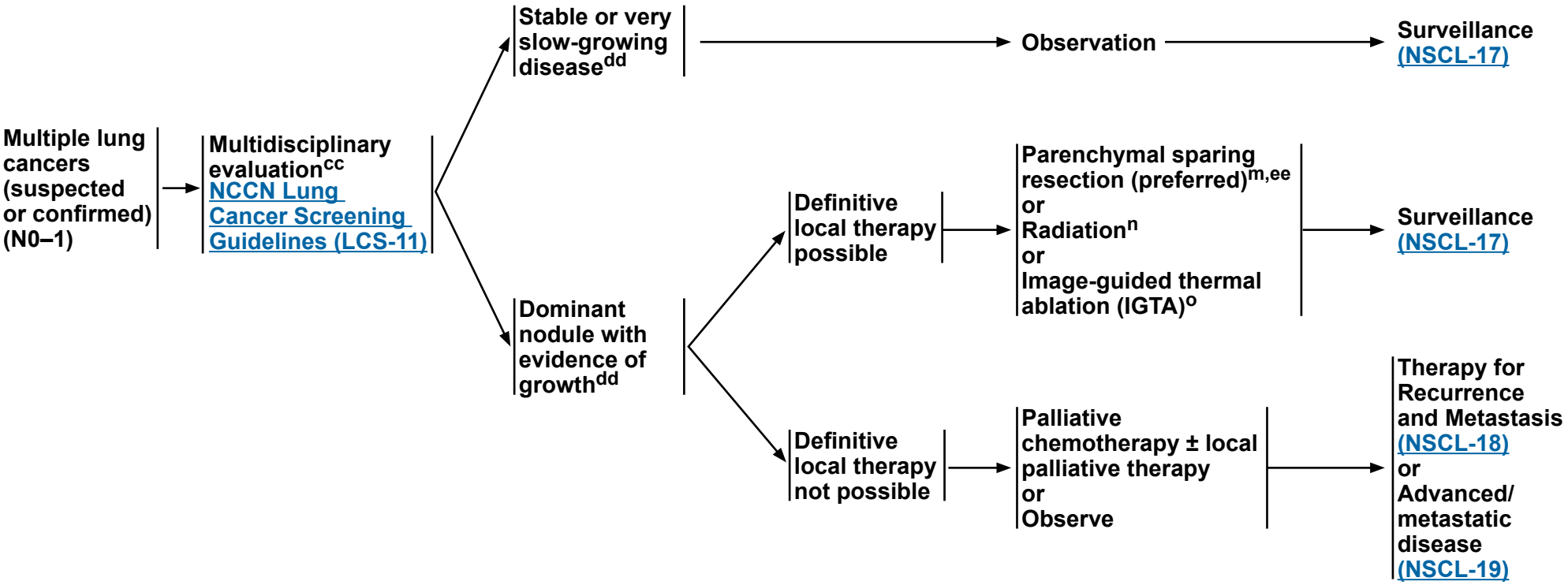
CLINICAL PRESENTATION

INITIAL TREATMENT



[m] Principles of Surgical Therapy (NSCL-B).
[n] Principles of Radiation Therapy (NSCL-C).
[o] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[cc] Multidisciplinary evaluation including thoracic radiology, pulmonary medicine, thoracic surgery, medical oncology, and radiation oncology.
[dd] Lesions at low risk of becoming symptomatic can be observed (eg, small subsolid nodules with slow growth). However, if the lesion(s) show 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 pulmonology and/or interventional radiology as needed).

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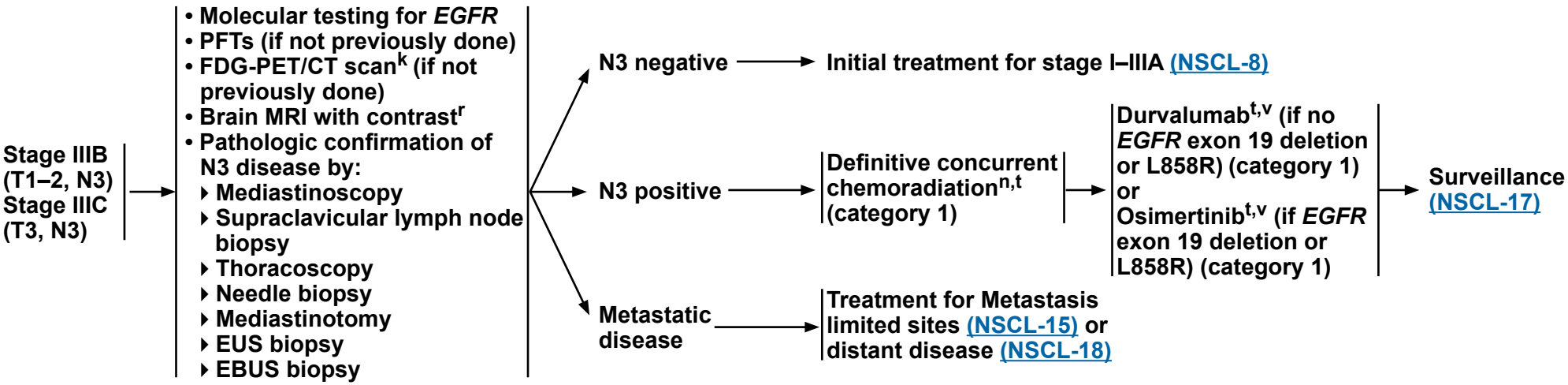

[k] FDG-PET/CT performed skull base to mid-thigh. Positive FDG-PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If FDG-PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[n] Principles of Radiation Therapy (NSCL-C).
[r] If MRI is not possible, CT of head with contrast.
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy or, if *EGFR* exon 19 deletion or L858R, osimertinib is recommended.

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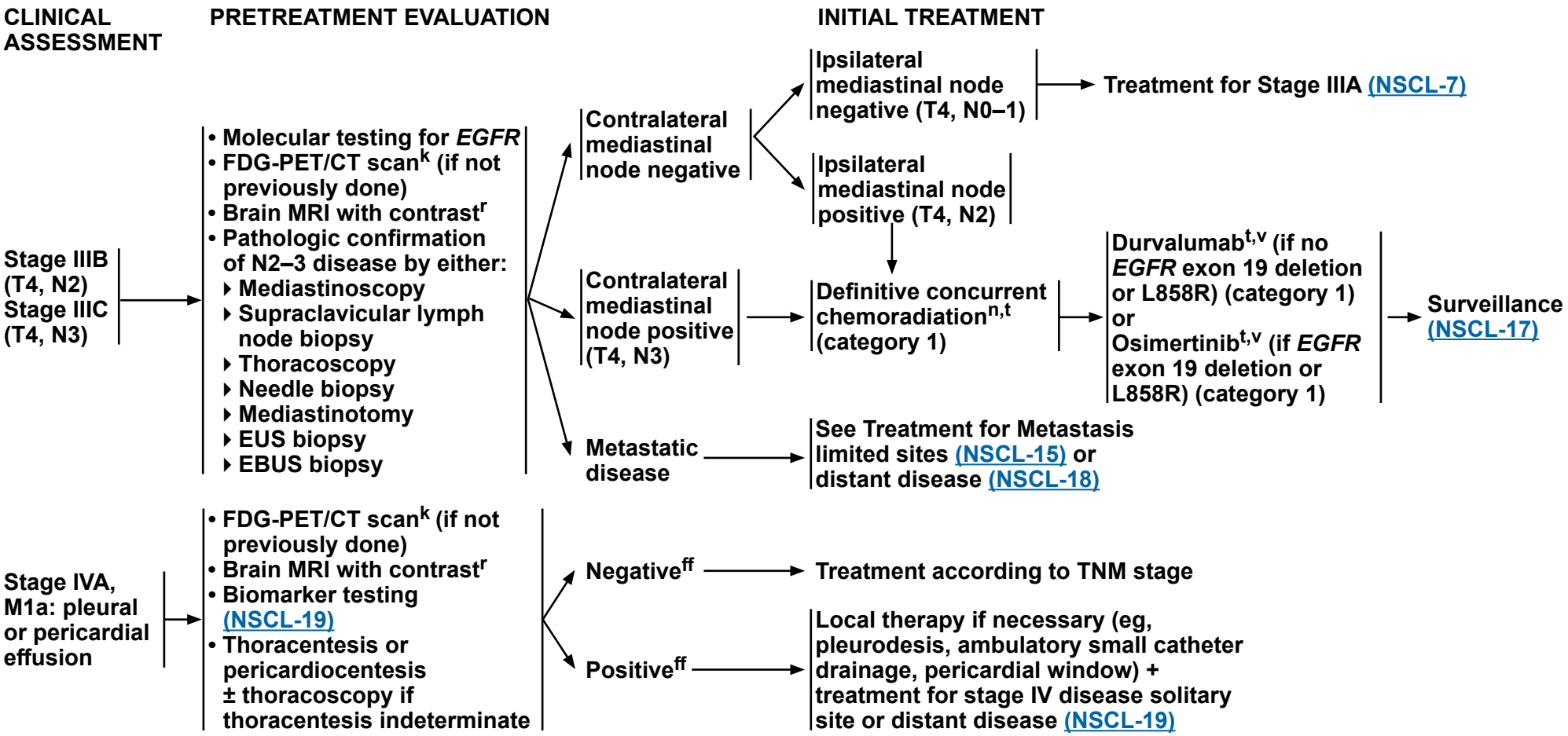

[k] FDG-PET/CT performed skull base to mid-thigh. Positive FDG-PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If FDG-PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

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

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

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

[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy or, if *EGFR* exon 19 deletion or L858R, osimertinib is recommended.

[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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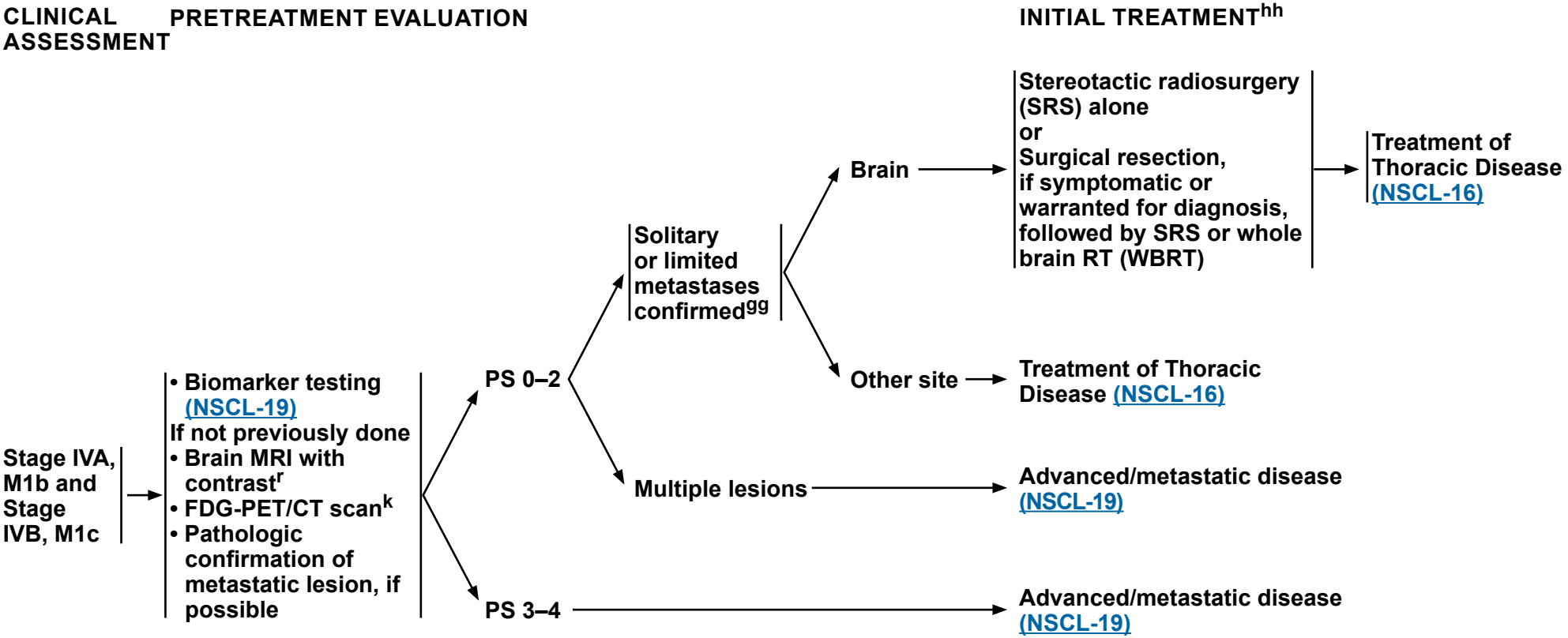

[k] FDG-PET/CT performed skull base to mid-thigh. Positive FDG-PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If FDG-PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[r] If MRI is not possible, CT of head with contrast.
[gg] Including selected patients with stage M1c and limited number and volume of metastatic lesions amenable to definitive local therapy. Clinical trials have included up to 3 to 5 metastatic sites.
[hh] NCCN Guidelines for Central Nervous System Cancers.

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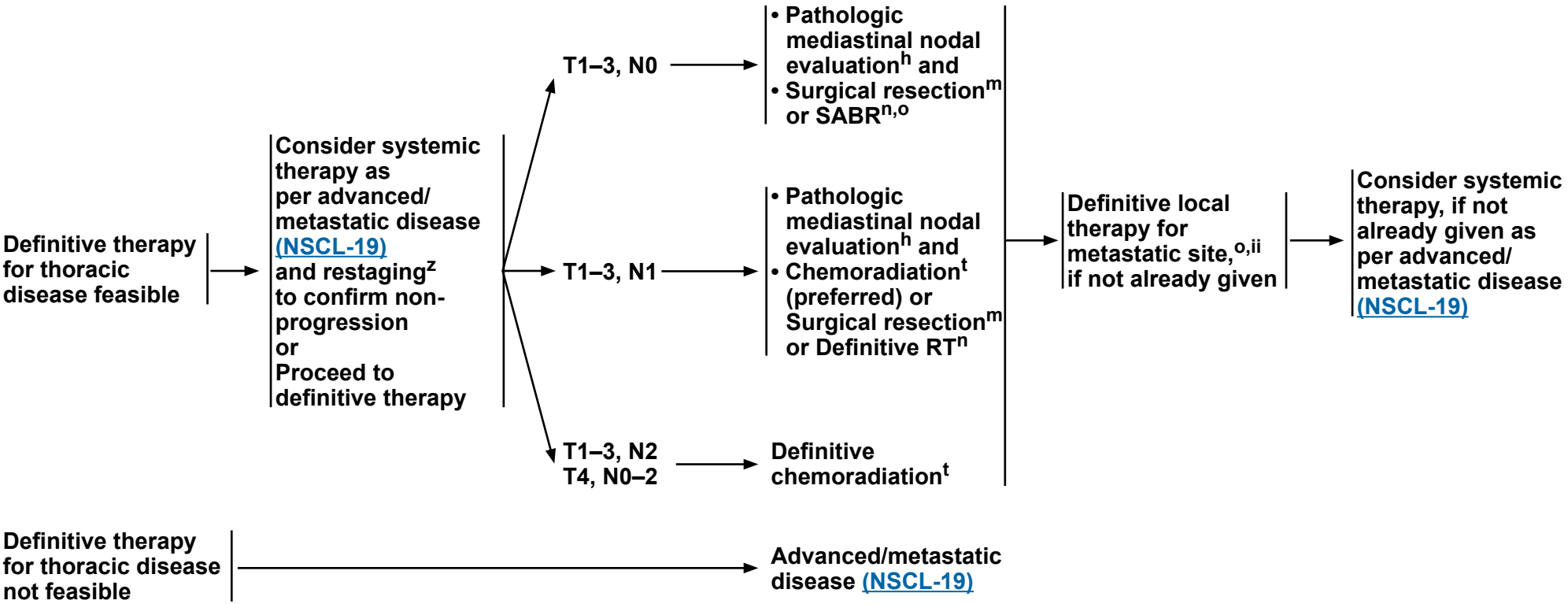
TREATMENT OF THORACIC DISEASE



[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (FDG-PET/CT and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.
[m] Principles of Surgical Therapy (NSCL-B).
[n] Principles of Radiation Therapy (NSCL-C).
[o] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[z] Chest CT with contrast and/or FDG-PET/CT to evaluate progression.
[ii] Typically, RT (including SABR) or surgical resection.

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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[jj] ± 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**
- **FDG-PET/CT[kk] is not routinely indicated**
- **Brain MRI as clinically indicated based on risk assessment**
- **Cancer Survivorship Care (NSCL-G)**

→ **Recurrence** →

- **FDG-PET/CT**
- **Brain MRI with contrast[r]**

→ **Locoregional recurrence** → **Therapy for Recurrence and Metastasis (NSCL-18)**

→ **Distant metastases** → **Therapy for Recurrence and Metastasis (NSCL-18)**

[r] 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 RT, histopathologic confirmation of recurrent disease is needed because areas previously treated with RT 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[m]
  - External-beam RT or brachytherapy[n]
  - Photodynamic therapy
- **Resectable recurrence** →
  - Reresection (preferred)[m]
  - External-beam RT or SABR[n,o]
- **Mediastinal lymph node recurrence**
  - No prior RT → Concurrent chemoradiation[n,t]
  - Prior RT → Advanced/metastatic disease (NSCL-19)
- **Superior vena cava (SVC) obstruction** →
  - Concurrent chemoradiation[n,t] (if not previously given) ± SVC stent
  - External-beam RT[n] ± SVC stent
  - SVC stent
- **Severe hemoptysis** → Any combination of the following:
  - External-beam RT or brachytherapy[n]
  - Laser or photodynamic therapy or embolization
  - Surgery

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

- No evidence of disseminated disease → Observation or Advanced/metastatic disease (NSCL-19) (category 2B)
- Evidence of disseminated disease → Advanced/metastatic disease (NSCL-19)

Distant metastases

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

→ Advanced/metastatic disease (NSCL-19)

- **Limited metastasis** → Stage IVA, M1b and stage IVB, M1c (NSCL-15)
- **Pleural metastases or disseminated metastases** → Advanced/metastatic disease (NSCL-19)

[m] Principles of Surgical Therapy (NSCL-B).
[n] Principles of Radiation Therapy (NSCL-C).
[o] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients.See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[r] If MRI is not possible, CT of head with contrast.
[t] Concurrent Chemoradiation Regimens (NSCL-F).
[hh] NCCN Guidelines for Central Nervous System Cancers.
[ll] An FDA-approved biosimilar is an appropriate substitute.

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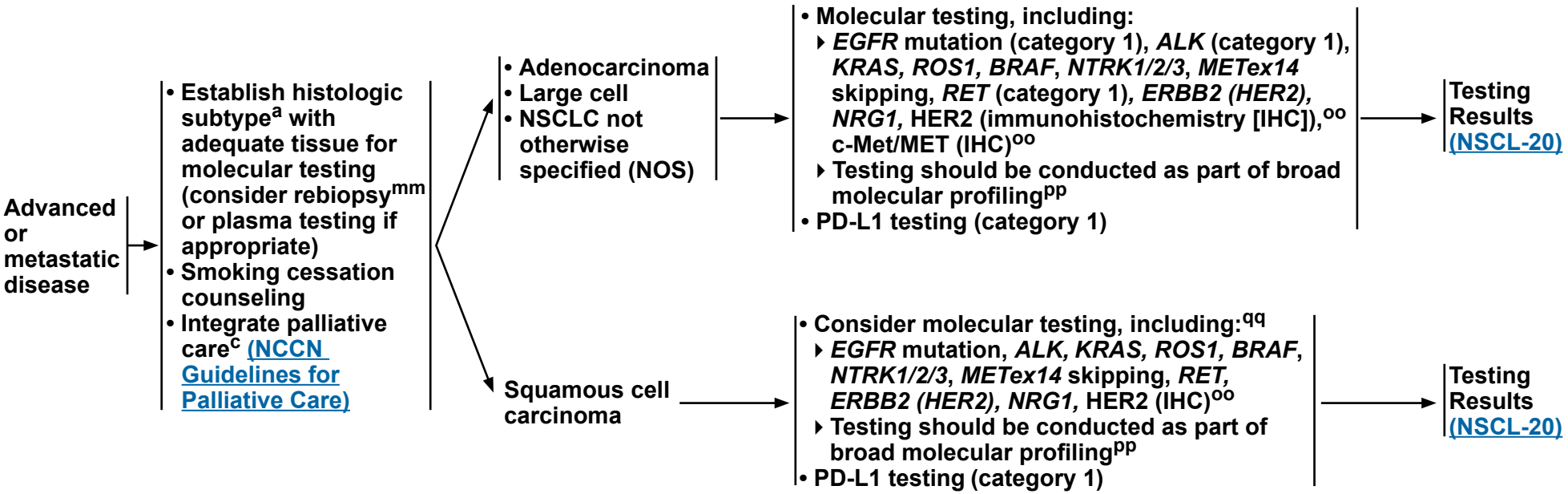

[a] Principles of Pathologic Review (NSCL-A).
[c] Temel JS, et al. N Engl J Med 2010;363:733-742.
[mm] Complete genotyping for *EGFR*, *KRAS, ALK*, *ROS1*, *BRAF*, *NTRK1/2/3, MET, RET, ERBB2 (HER2)*, and *NRG1* via biopsy and/or plasma testing. Combinations of tissue and plasma testing, either concurrently or in sequence are acceptable. Concurrent testing can improve time to test results and should be considered in the appropriate clinical situation. Negative results (meaning absence of definitive driver mutation) by one method suggests the use of a complementary method. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] Testing for HER2 IHC or c-Met/MET IHC is recommended at some point during progression. Timing should be balanced with tissue conservation.
[pp] 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-20 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. See Emerging Biomarkers to Identify Patients for Therapies (NSCL-I).
[qq] 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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TESTING RESULTS[mm,nn]

***EGFR* exon 19 deletion or exon 21 L858R mutation positive**	NSCL-21
***EGFR* S768I, L861Q, and/or G719X mutation positive**	NSCL-24
***EGFR* exon 20 insertion mutation positive**	NSCL-25
***KRAS* G12C mutation positive**	NSCL-26
***ALK* rearrangement positive**	NSCL-27
***ROS1* rearrangement positive**	NSCL-30
***BRAF* V600E mutation positive**	NSCL-32
***NTRK1/2/3* gene fusion positive**	NSCL-33
***METex14* skipping mutation positive**	NSCL-34
***RET* rearrangement positive**	NSCL-35
***ERBB2 (HER2)* mutation positive**	NSCL-36
***NRG1* gene fusion positive**	NSCL-37
PD-L1 ≥1% and negative for actionable molecular biomarkers above	NSCL-38
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-39

See Evidence Blocks on EB-5

[mm] Complete genotyping for *EGFR*, *KRAS, ALK*, *ROS1*, *BRAF*, *NTRK1/2/3, MET, RET, ERBB2 (HER2)*, and *NRG1* via biopsy and/or plasma testing. Combinations of tissue and plasma testing, either concurrently or in sequence are acceptable. Concurrent testing can improve time to test results and should be considered in the appropriate clinical situation. Negative results (meaning absence of definitive driver mutation) by one method suggests the use of a complementary method. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

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

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EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS[nn]

EGFR exon 19 deletion or exon 21 L858R mutations

EGFR mutation discovered prior to first-line systemic therapy

FIRST-LINE THERAPY[rr]

Preferred

Osimertinib[ss] (category 1) → **Progression** → **Subsequent Therapy (NSCL-22)**

Other Recommended

Amivantamab-vmjw + lazertinib (category 1)[tt] → **Progression** → **Subsequent Therapy (NSCL-22)**

or

Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous) (category 1) → **Progression** → **Systemic Therapy, Subsequent (NSCL-K 4 of 5)**

Useful in Certain Circumstances

Afatinib[ss] (category 1)
or Dacomitinib[ss] (category 1)
or Erlotinib[ss] (category 1)
or Erlotinib + bevacizumab[uu,vv]
or Erlotinib + ramucirumab
or Gefitinib[ss] (category 1)

→ **Progression** → **Subsequent Therapy (NSCL-23)**

EGFR mutation discovered during first-line systemic therapy

Add osimertinib to pemetrexed + (cisplatin or carboplatin) (nonsquamous)
or
Interrupt current therapy[ww,xx] and start Osimertinib or Amivantamab-vmjw + lazertinib[tt]
or
Afatinib or Dacomitinib or Erlotinib or Erlotinib + bevacizumab[uu,vv] or Erlotinib + ramucirumab or Gefitinib

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

→ **Progression** → **Subsequent Therapy (NSCL-22)**

→ **Progression** → **Subsequent Therapy (NSCL-23)**

See Evidence Blocks on EB-5

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[ss] For performance status (PS) 0–4.
[tt] Prophylactic anticoagulation is recommended at the time of initiation to prevent venous thromboembolic events.
[uu] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[vv] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[ww] 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. The rate of side effects (pneumonitis) is higher within 3 months. 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; Gettinger S, et al. J Thorac Oncol 2018;13:1363-1372.
[xx] If there is a good response to current therapy, it is reasonable to continue therapy.

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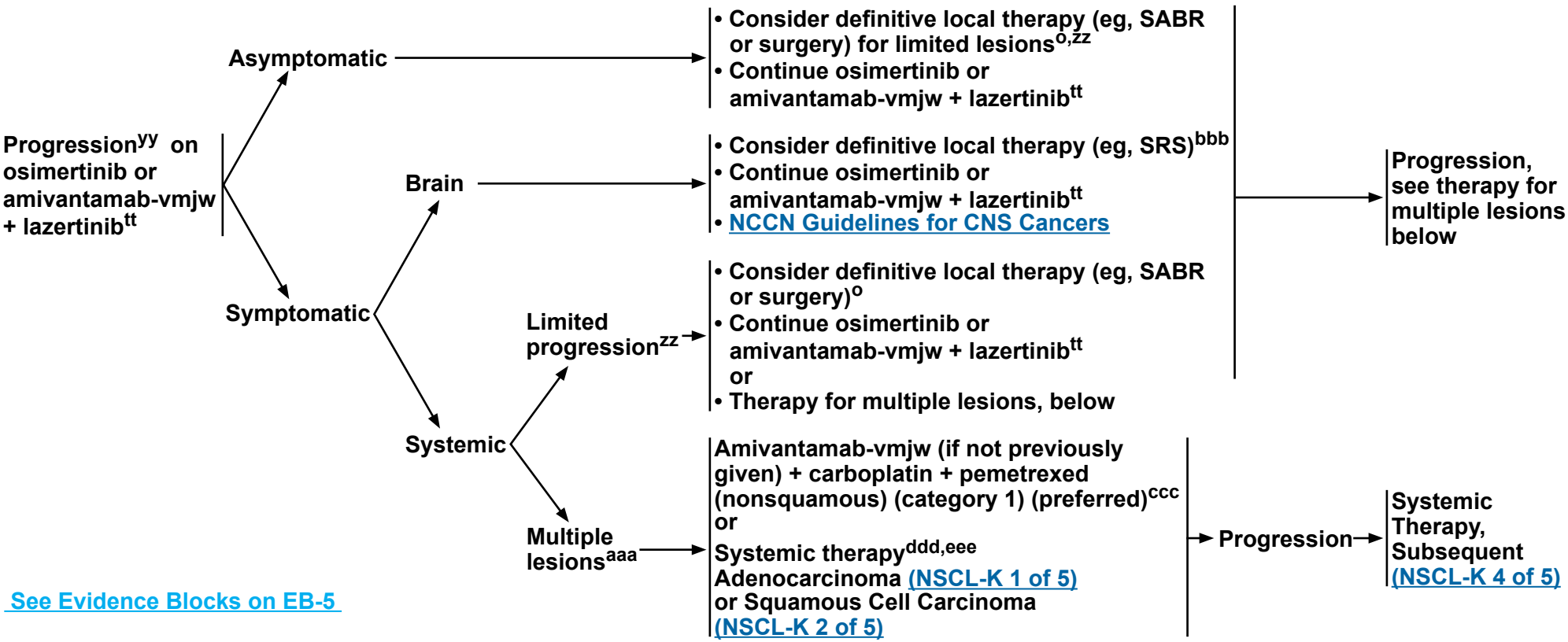

See Evidence Blocks on EB-5

[o] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

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

[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).

[tt] Prophylactic anticoagulation is recommended at the time of initiation to prevent venous thromboembolic events.

[yy] Beware of flare phenomenon in subset of patients who discontinue tyrosine kinase inhibitor (TKI). If disease flare occurs, restart TKI.

[zz] Clinical trials have included up to 3 to 5 progressing sites.

[aaa] Consider a biopsy at time of progression to rule out small cell lung cancer (SCLC) transformation (approximately 6%) and biopsy or plasma testing to evaluate mechanisms of resistance. See Principles of Molecular and Biomarker Analysis (NSCL-H) and NCCN Guidelines for Small Cell Lung Cancer.

[bbb] Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on factors including site, location, and edema.

[ccc] Not an option for *EGFR* S768I, L861Q, and/or G719X mutations.

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

[eee] The data in the second-line setting suggest that programmed cell death protein 1 (PD-1)/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR* exon 19 deletion or exon 21 L858R, *ALK*+ NSCLC.

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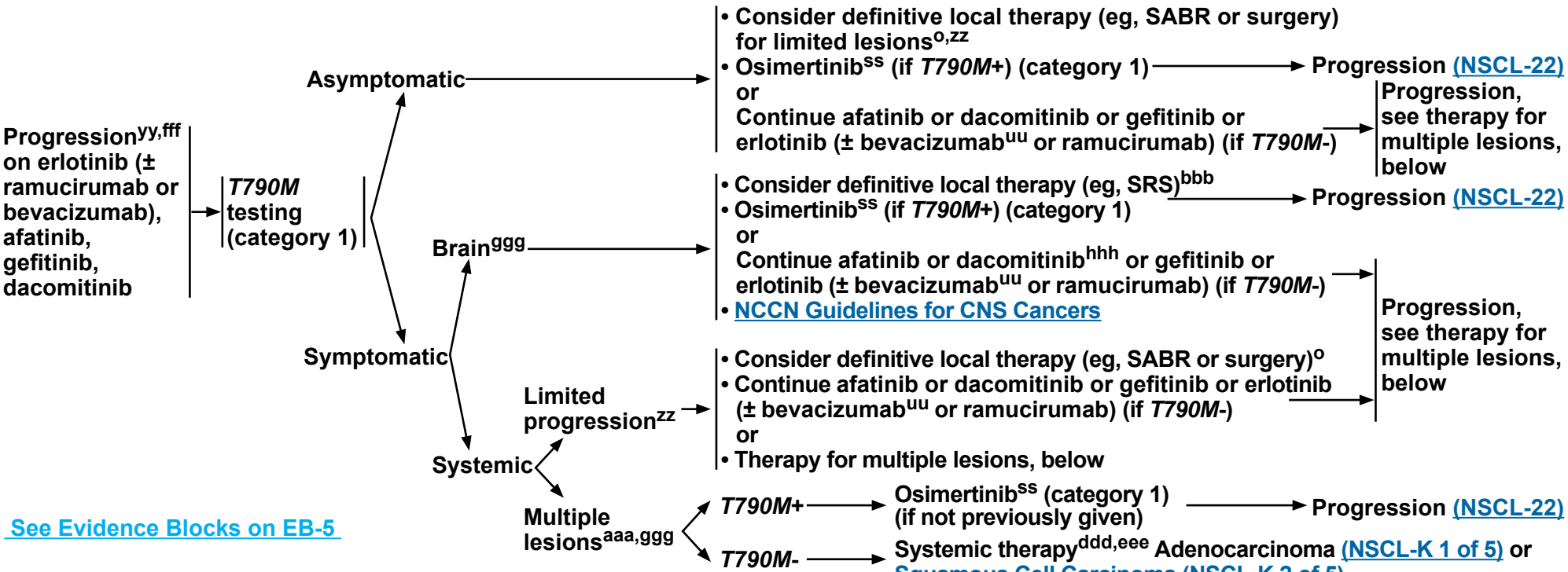
EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS[nn]



See Evidence Blocks on EB-5

[o] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

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

[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).

[ss] For PS 0–4.

[uu] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.

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

[zz] Clinical trials have included up to 3 to 5 progressing sites.

[aaa] Consider a biopsy at time of progression to rule out SCLC transformation (approximately 6%) and biopsy or plasma testing to evaluate mechanisms of resistance. See Principles of Molecular and Biomarker Analysis (NSCL-H) and NCCN Guidelines for Small Cell Lung Cancer.

[bbb] Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on factors including site, location, and edema.

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

[eee] 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 exon 21 L858R, *ALK*+ NSCLC.

[fff] 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.

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

[hhh] 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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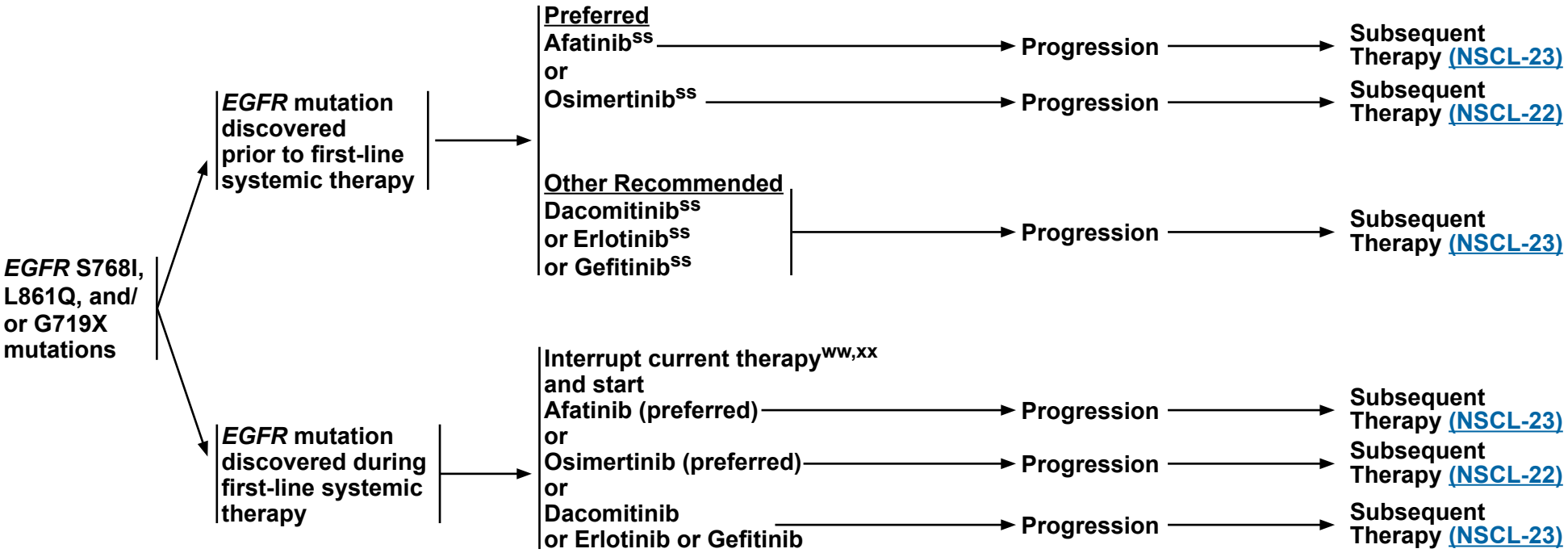
EGFR S768I, L861Q, and/or G719X MUTATIONS[nn]

FIRST-LINE THERAPY[rr]



See Evidence Blocks on EB-5

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[ss] For PS 0–4.
[ww] 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. The rate of side effects (pneumonitis) is higher within 3 months. 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; Gettinger S, et al. J Thorac Oncol 2018;13:1363-1372.
[xx] If there is a good response to current therapy, it is reasonable to continue therapy.

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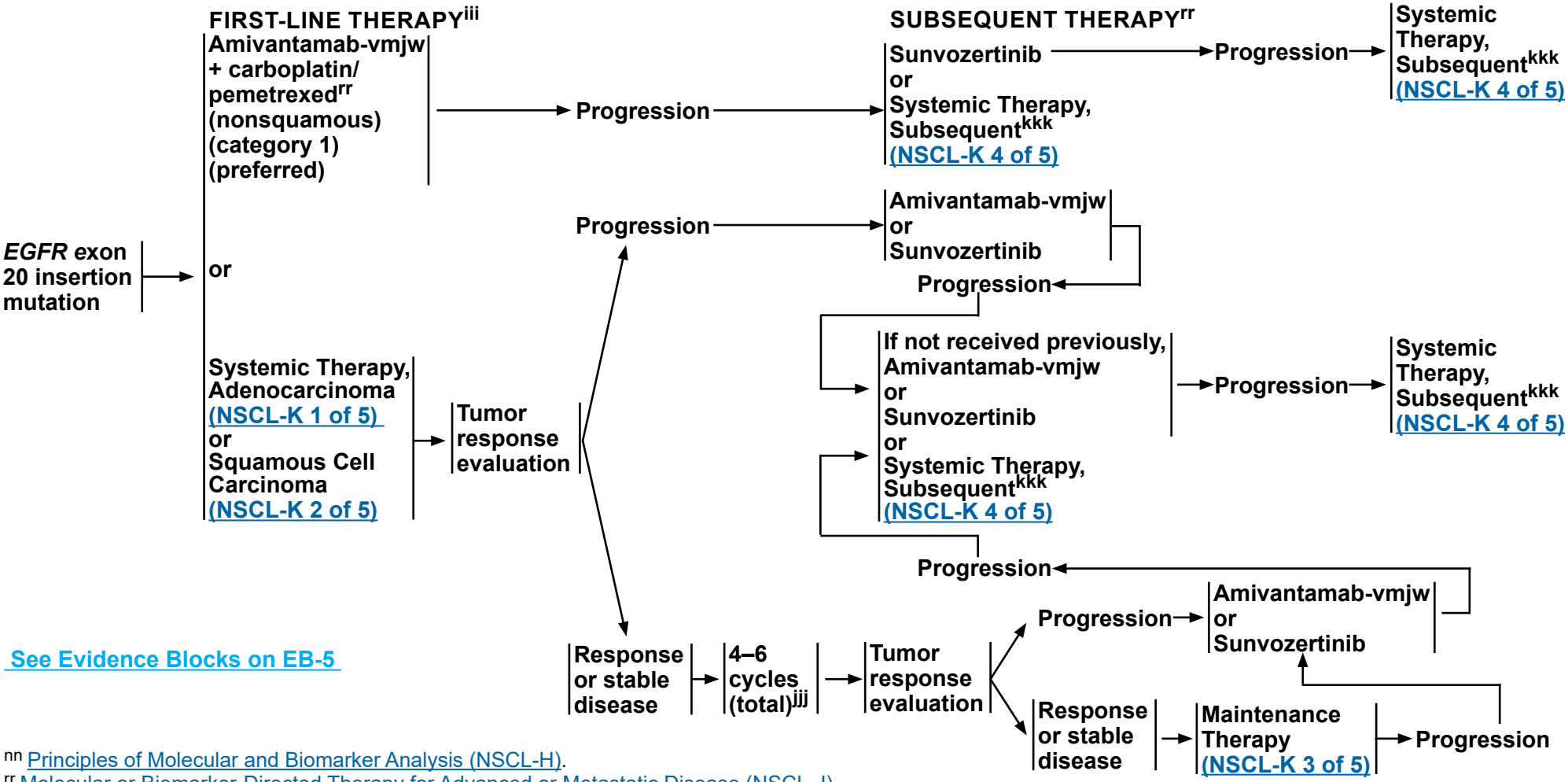
EGFR EXON 20 INSERTION MUTATION[nn]



[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[iii] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease (eg, chest, abdomen, pelvis) with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[jjj] 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.
[kkk] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease (eg, chest, abdomen, pelvis) with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

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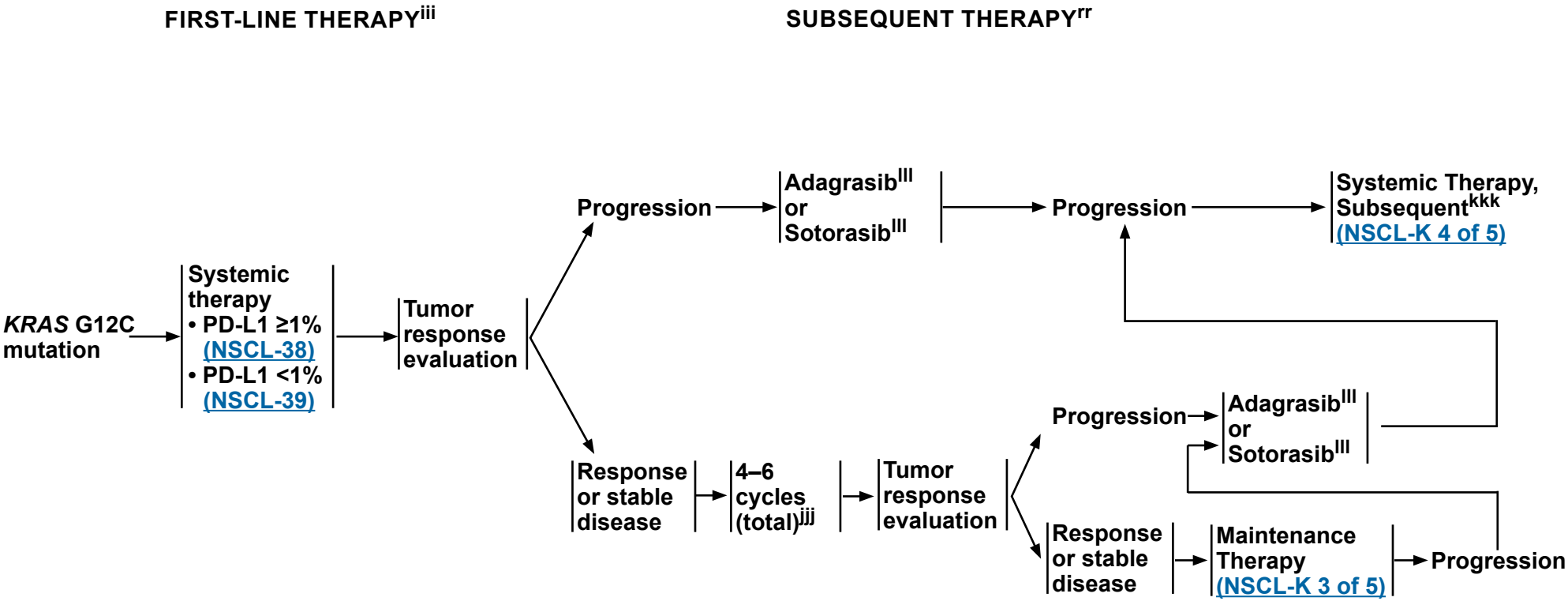
KRAS G12C MUTATION[nn]



See Evidence Blocks on EB-5

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[iii] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease (eg, chest, abdomen, pelvis) with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[jjj] 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.
[kkk] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease (eg, chest, abdomen, pelvis) with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
[lll] Sotorasib or adagrasib may be used after at least one line of therapy (or second-line and beyond), if no previous *KRAS* G12C-targeted therapy.

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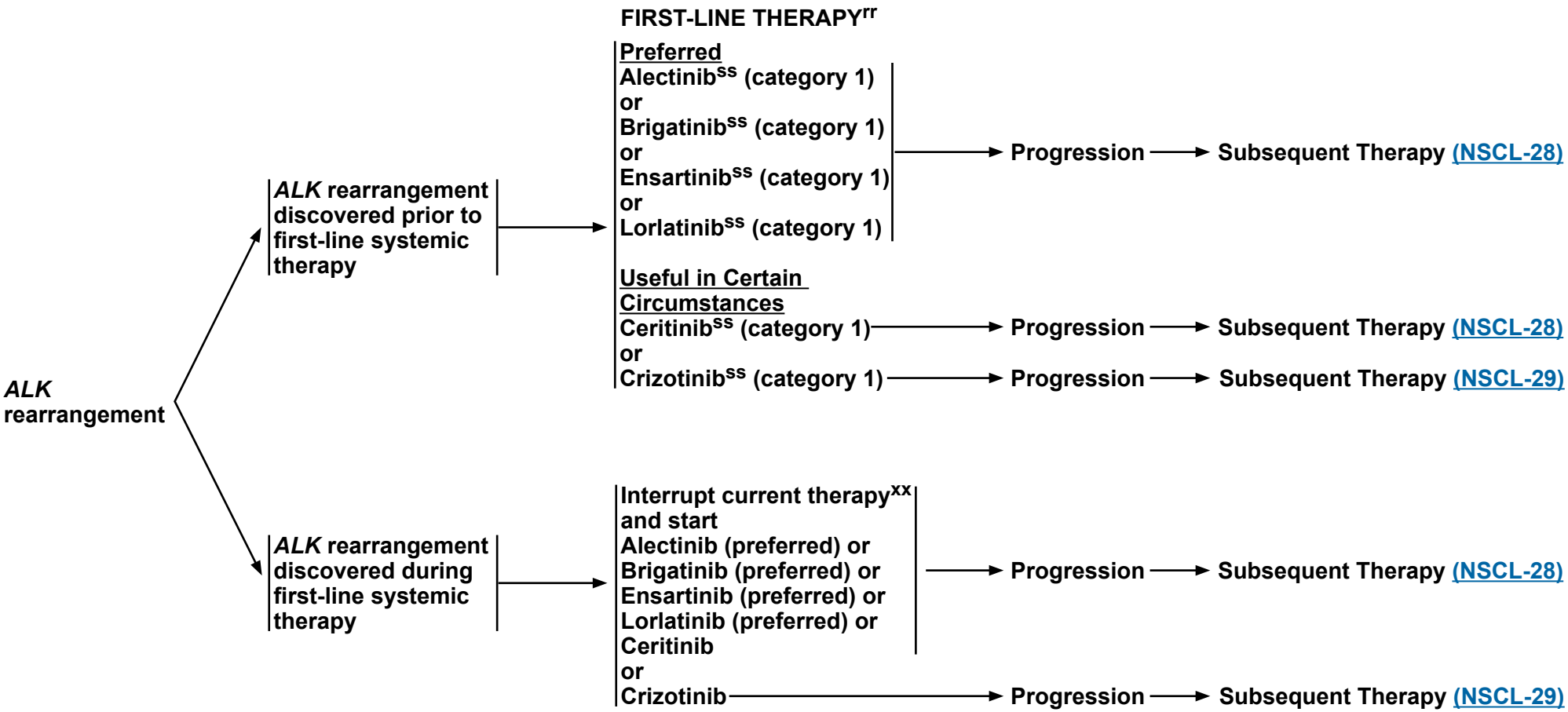
ALK REARRANGEMENT[nn]



See Evidence Blocks on EB-5

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[ss] For PS 0–4.
[xx] If there is a good response to current therapy, it is reasonable to continue therapy.

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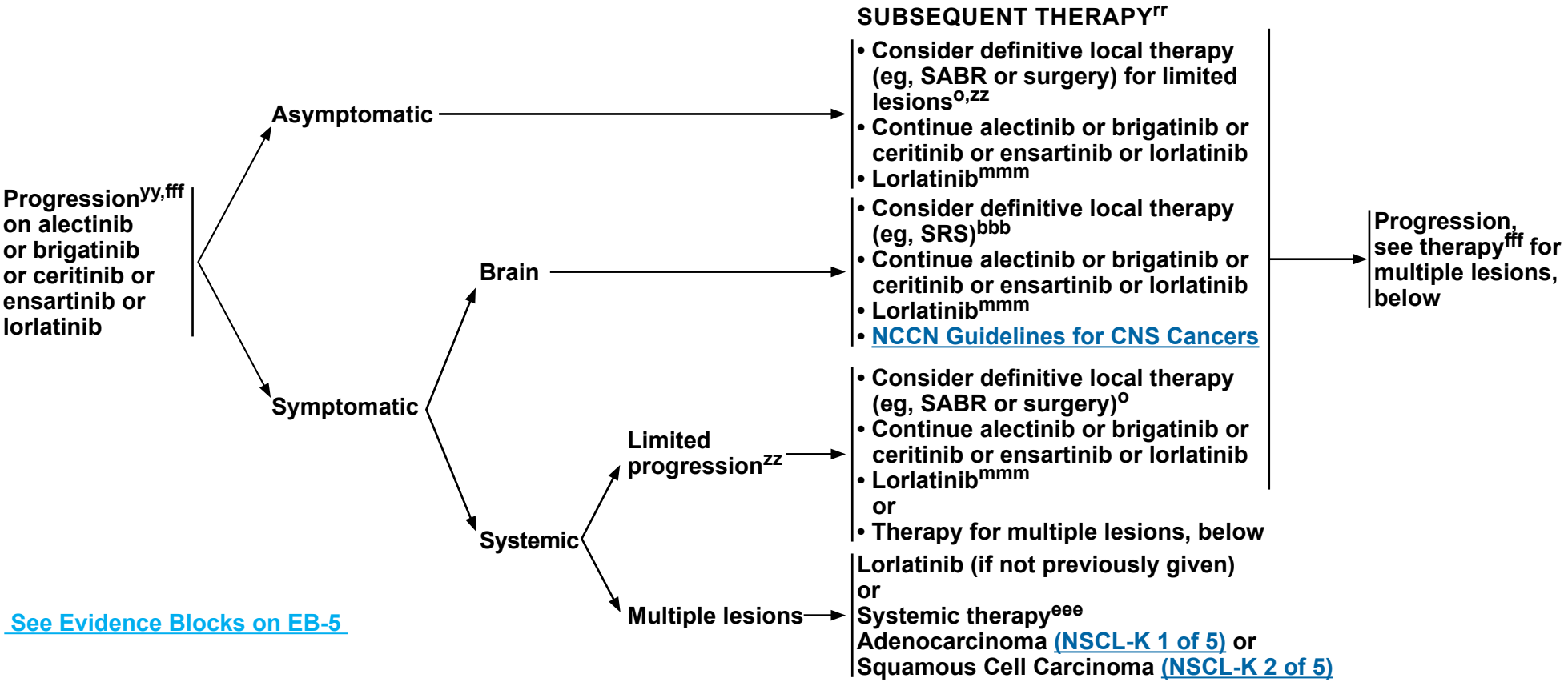
ALK REARRANGEMENT[nn]



See Evidence Blocks on EB-5

[o] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[yy] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[zz] Clinical trials have included up to 3 to 5 progressing sites.
[bbb] Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on factors including site, location, and edema.
[eee] 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 exon 21 L858R, *ALK*+ NSCLC.
[fff] 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.
[mmm] Lorlatinib is an option for resistant mutations, such as *ALK* G1202R and L1196M (except compound L1196M/G1202R).

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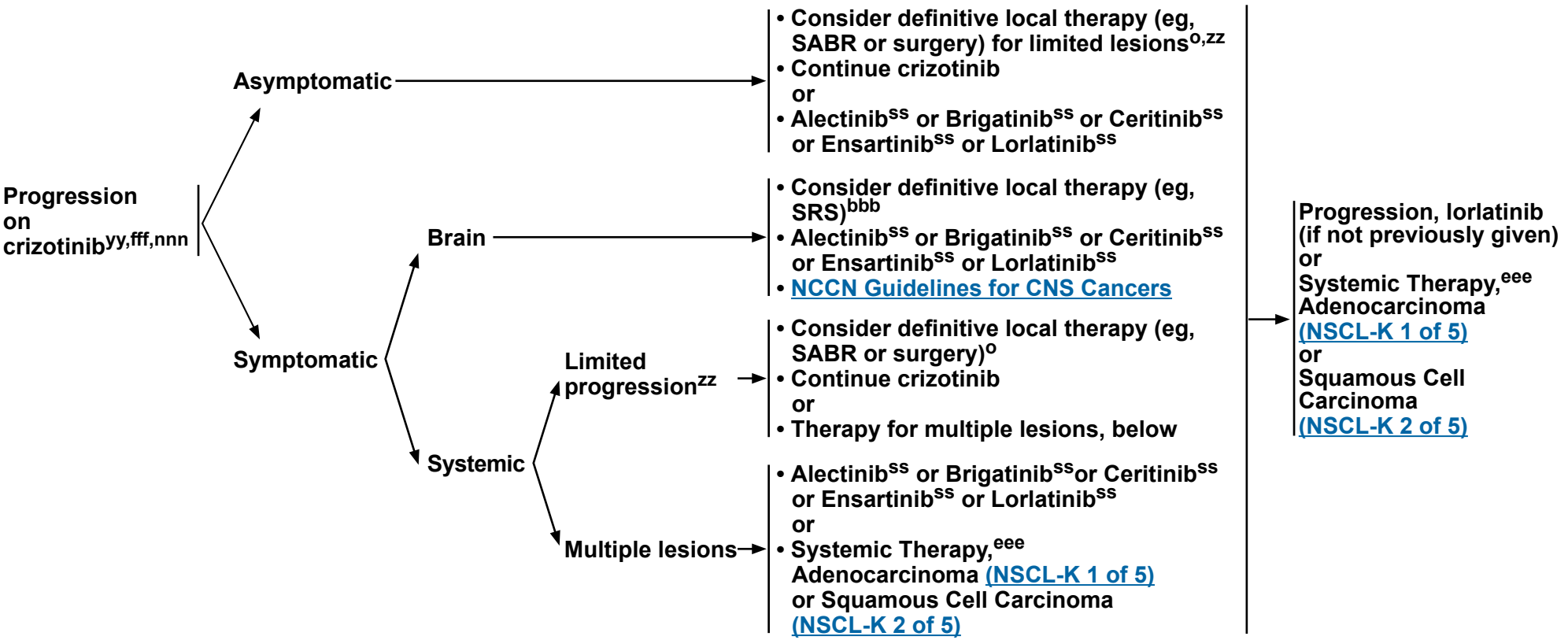

[o] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

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

[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).

[ss] For PS 0–4.

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

[zz] Clinical trials have included up to 3 to 5 progressing sites.

[bbb] Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on factors including site, location, and edema.

[eee] 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 exon 21 L858R, *ALK*+ NSCLC.

[fff] 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.

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

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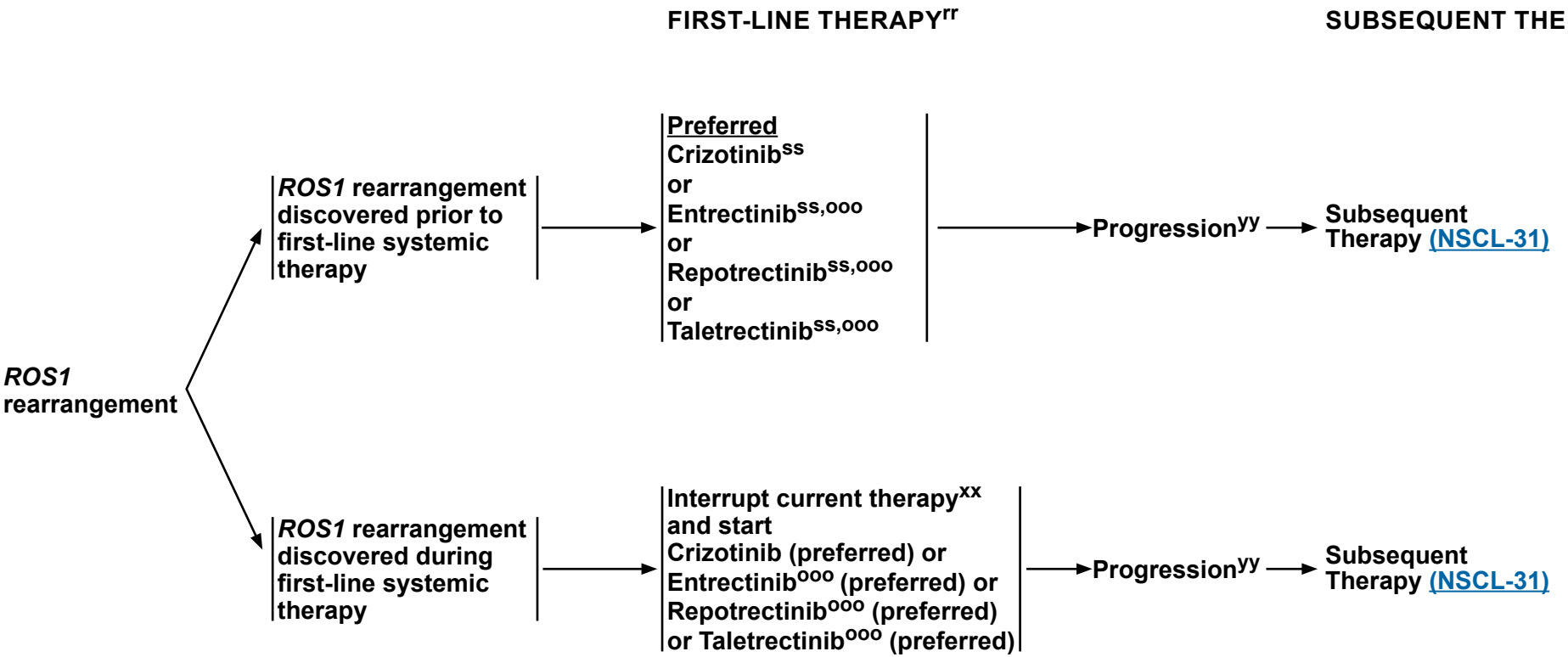
ROS1 REARRANGEMENT[nn]



See Evidence Blocks on EB-5

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[ss] For PS 0–4.
[xx] If there is a good response to current therapy, it is reasonable to continue therapy.
[yy] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[ooo] Entrectinib, repotrectinib, or taletrectinib may be better for patients with brain metastases.

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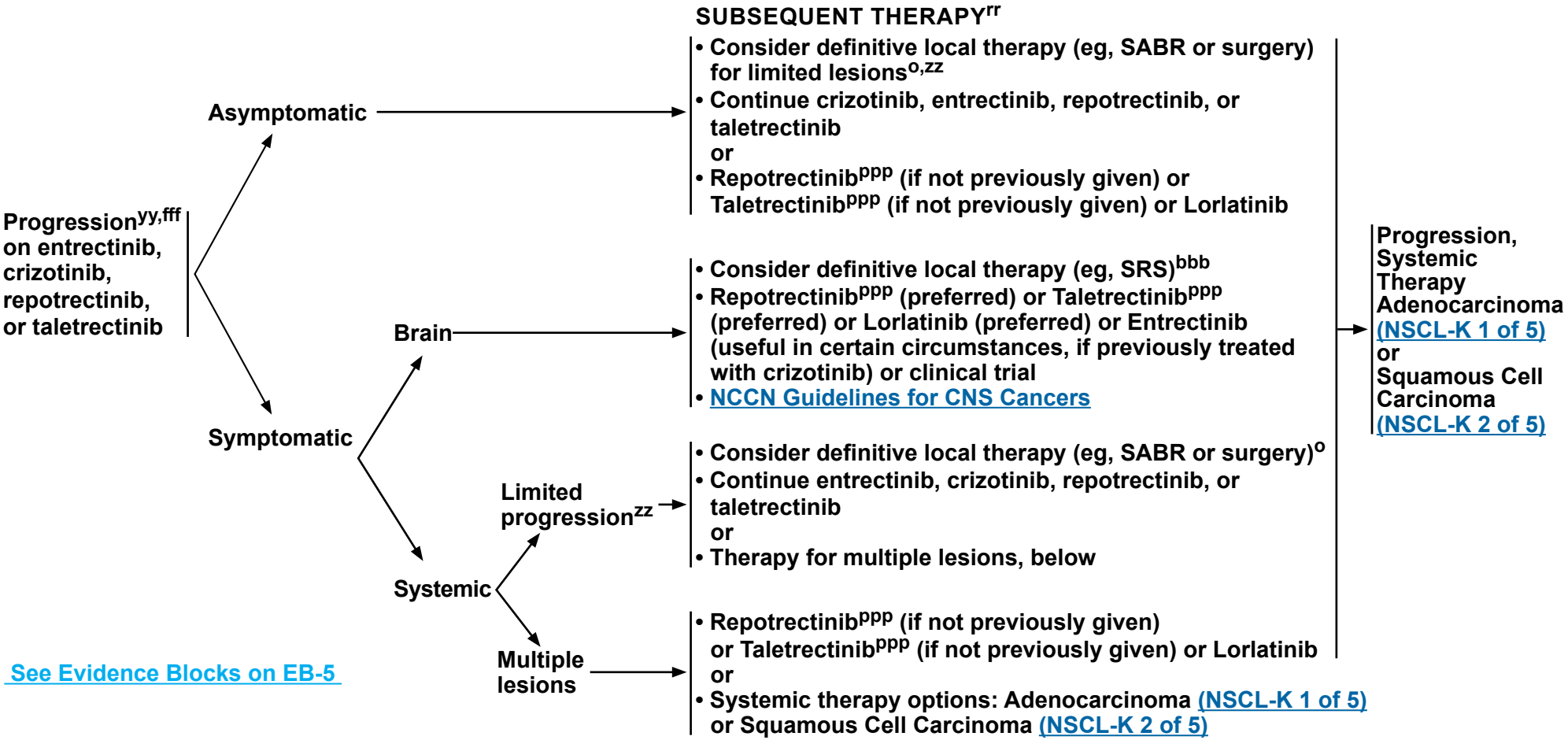
ROS1 REARRANGEMENT[nn]



See Evidence Blocks on EB-5

[o] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[yy] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[zz] Clinical trials have included up to 3 to 5 progressing sites.
[bbb] Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on factors including site, location, and edema.
[fff] 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.
[ppp] Repotrectinib or taletrectinib is an option for resistant mutations, such as *ROS1* G2032R.

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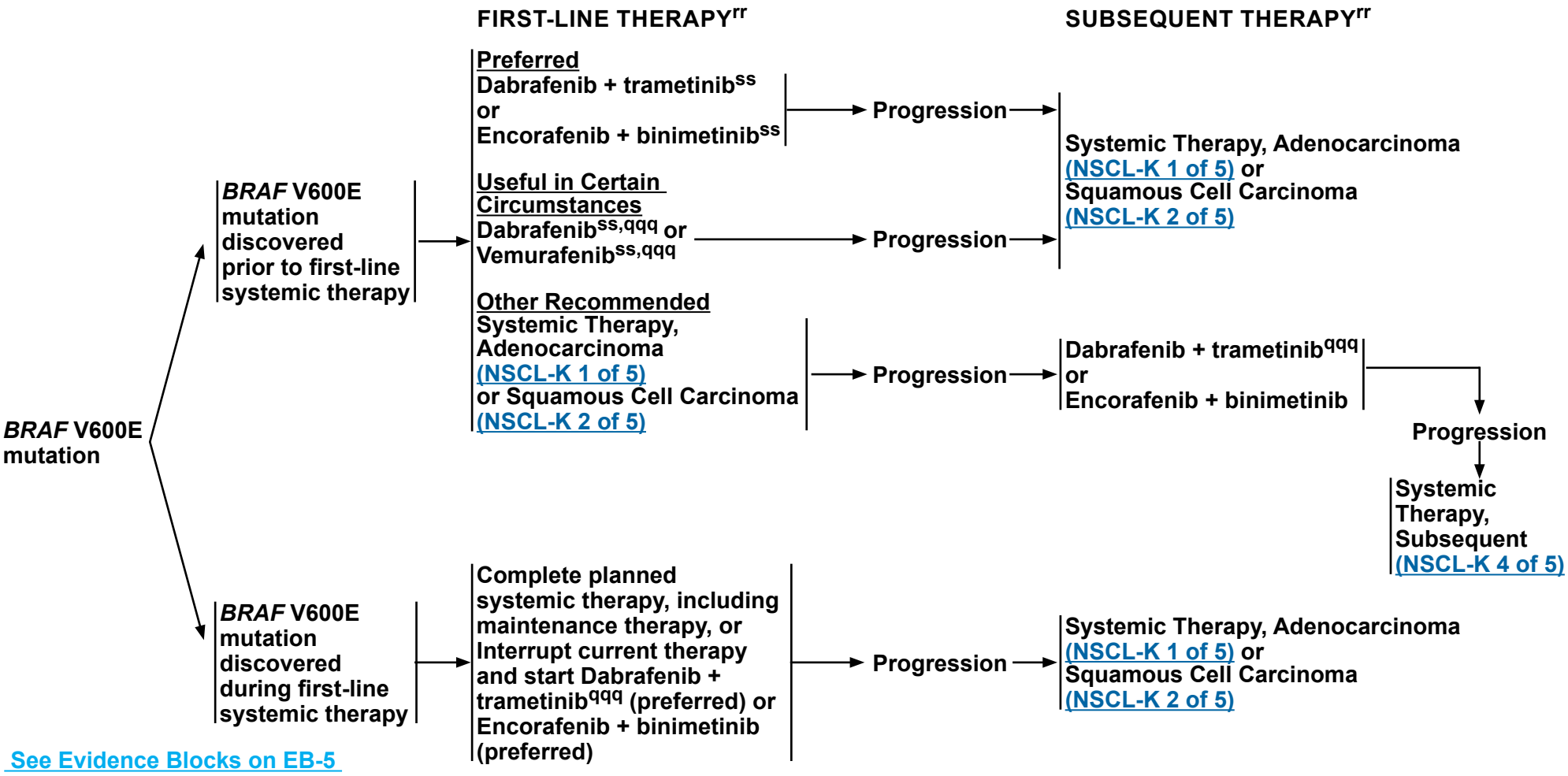
BRAF V600E MUTATION[nn]



See Evidence Blocks on EB-5

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[ss] For PS 0–4.
[qqq] Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated.

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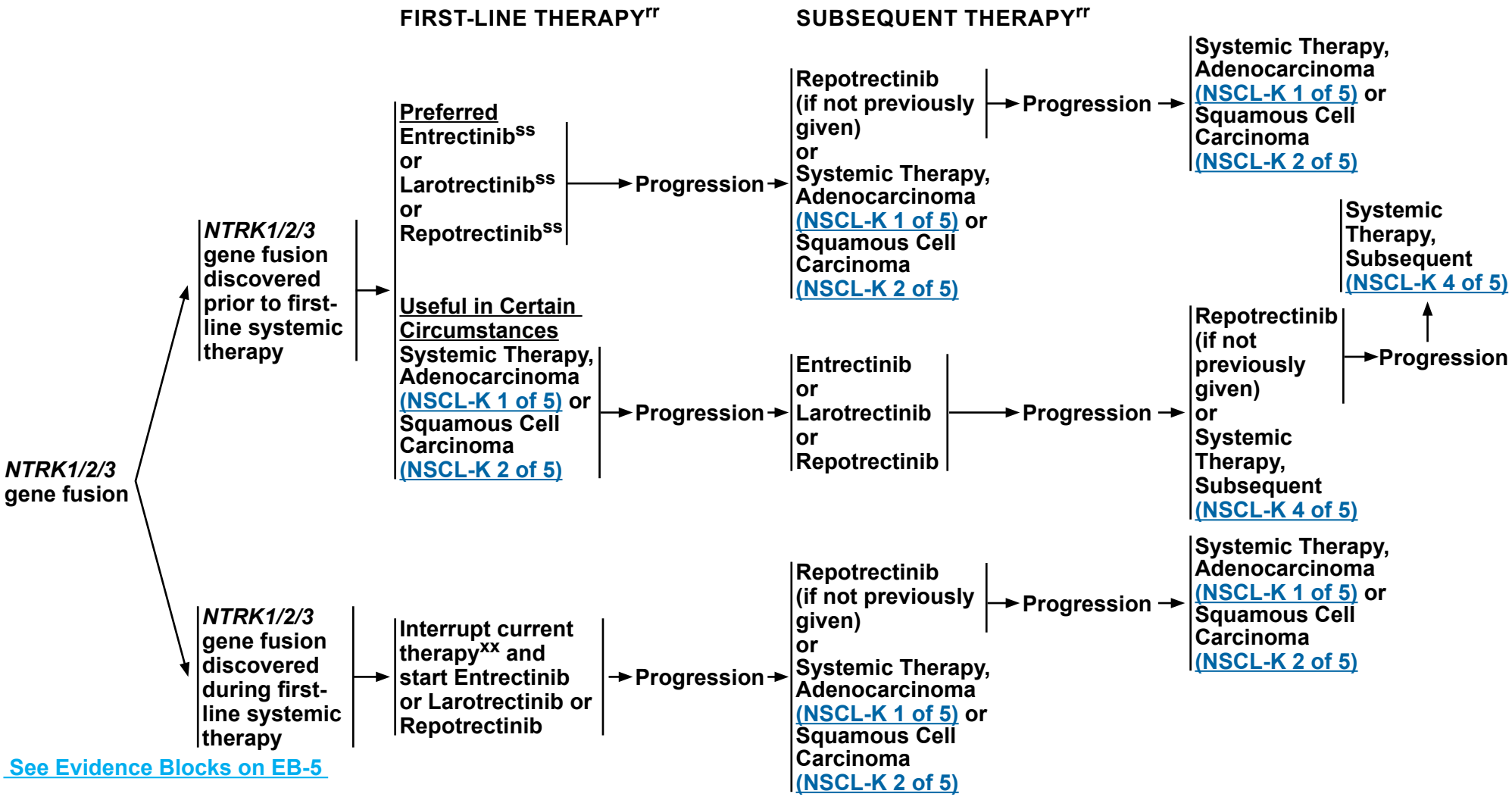
NTRK GENE FUSION[nn]



See Evidence Blocks on EB-5

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[ss] For PS 0–4.
[xx] If there is a good response to current therapy, it is reasonable to continue therapy.

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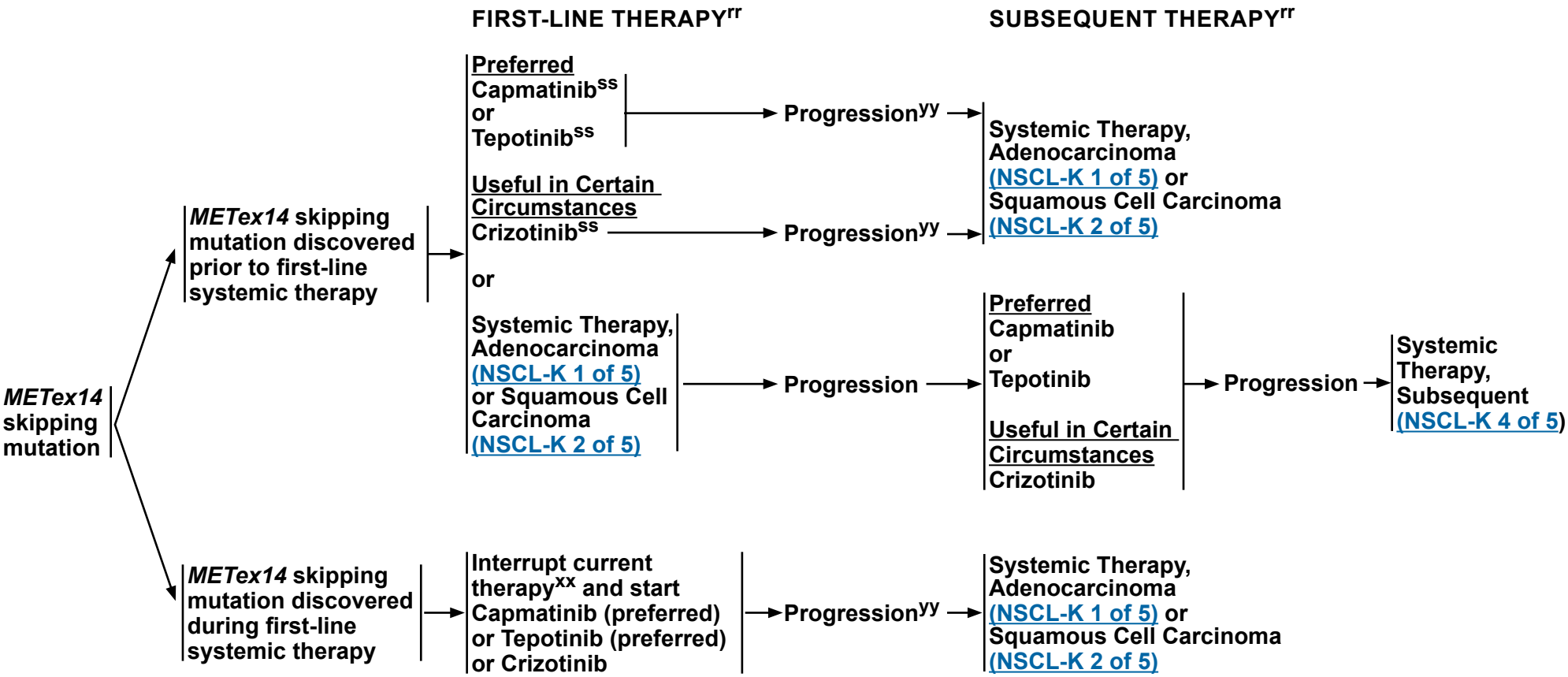
METex14 SKIPPING MUTATION[nn]



See Evidence Blocks on EB-5

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
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[ss] For PS 0–4.
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[yy] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

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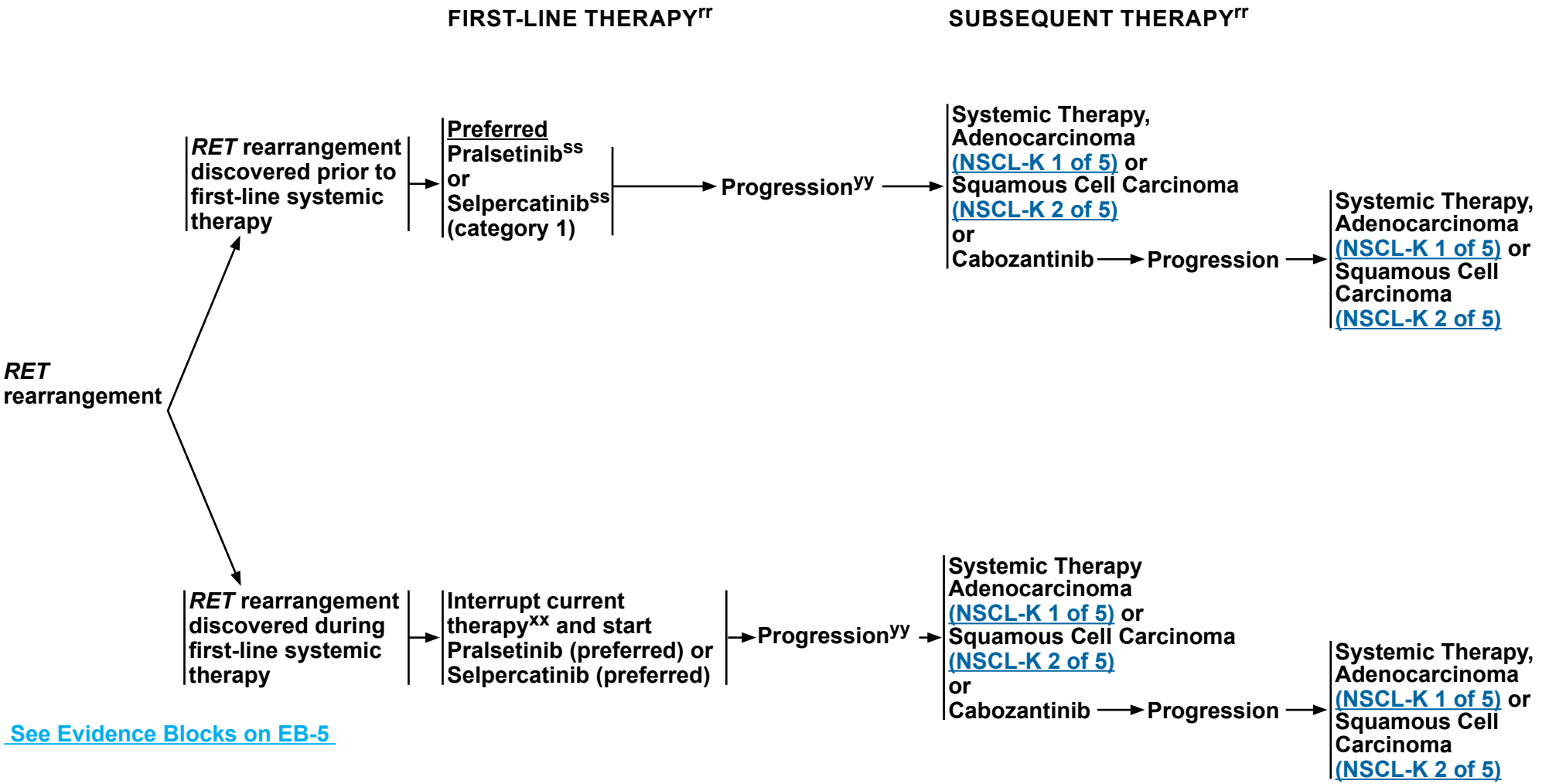
RET REARRANGEMENT[nn]



See Evidence Blocks on EB-5

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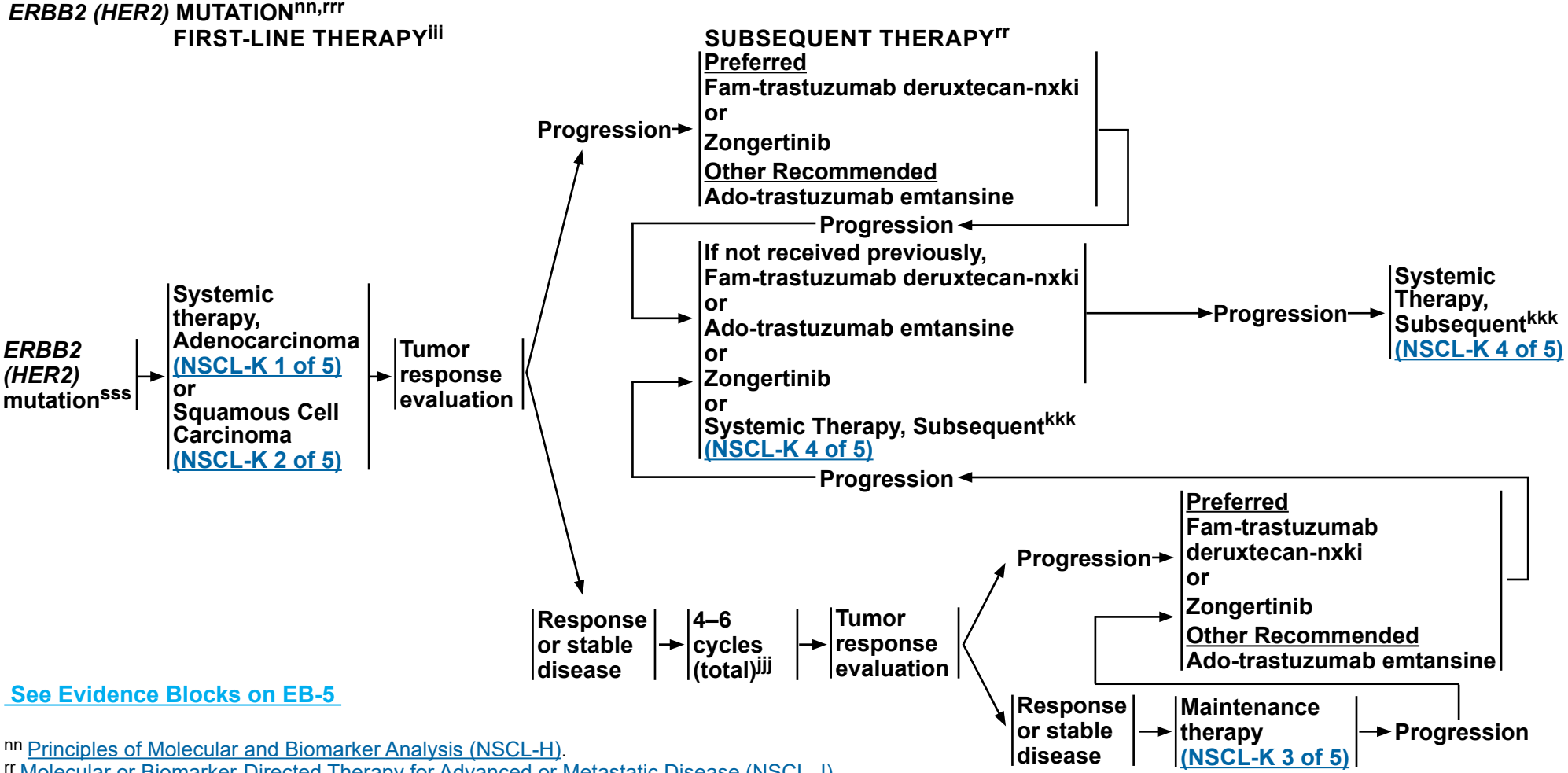

See Evidence Blocks on EB-5

nn Principles of Molecular and Biomarker Analysis (NSCL-H).
rr Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
iii Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease (eg, chest, abdomen, pelvis) with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
jjj 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.
kkk Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease (eg, chest, abdomen, pelvis) with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
rrr For HER2 protein overexpression (IHC3+) treatment options, see NSCL-K 4 of 5.
sss For oncogenic or likely oncogenic *ERBB2 (HER2)* mutations, refer to definitions at oncokb.org.

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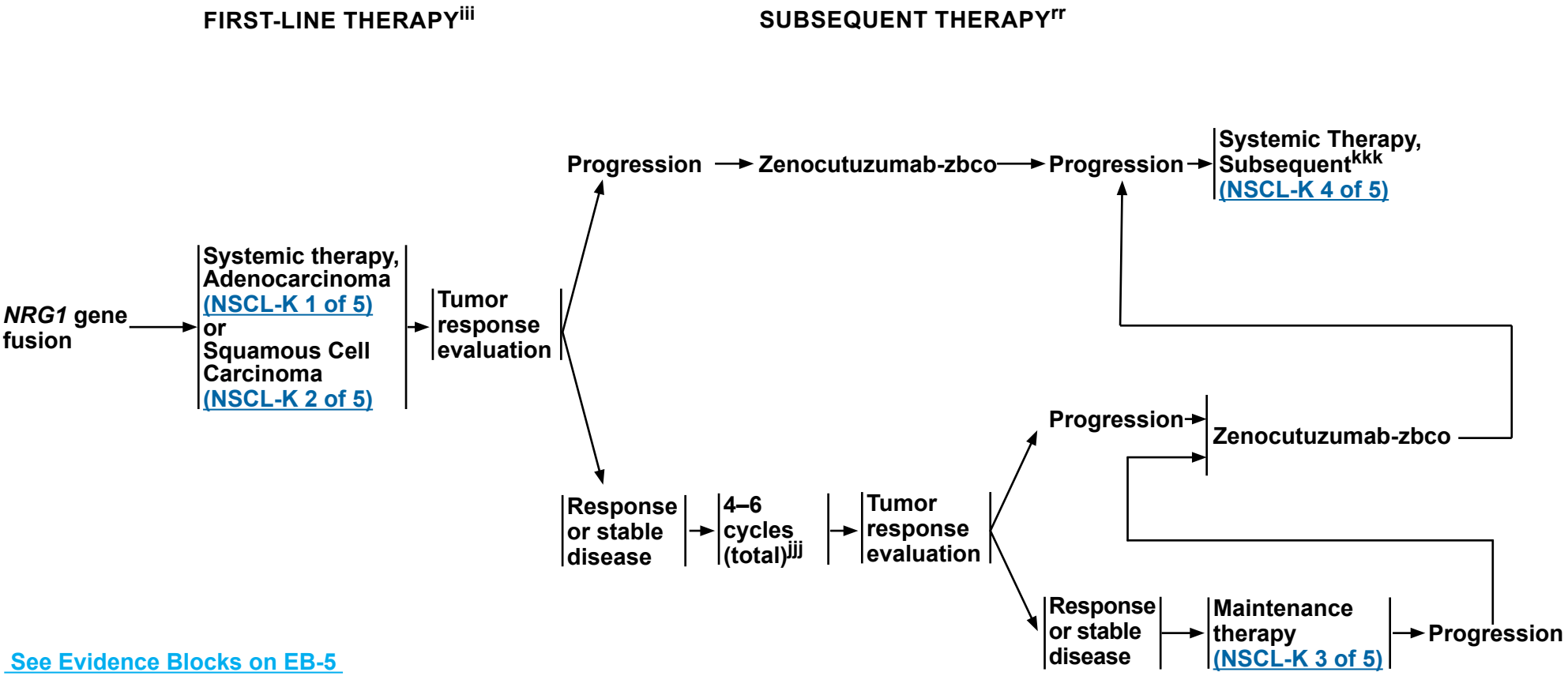
NRG1 GENE FUSION[nn]



See Evidence Blocks on EB-5

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
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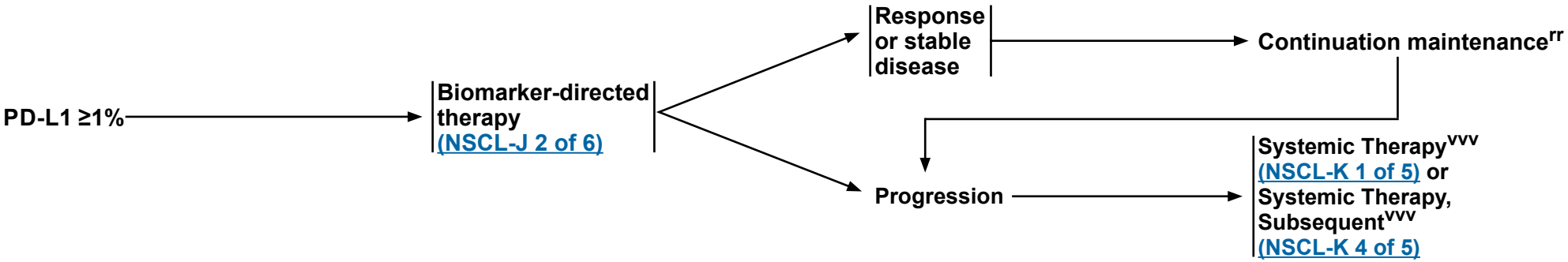
PD-L1 POSITIVE (≥1%)[nn,ttt]

FIRST-LINE THERAPY[rr,uuu]



[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).
[rr] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[ttt] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR* exon 19 deletion or L858R; *ALK, RET,* or *ROS1* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors. If there are contraindications, refer to NSCL-K 1 of 5 (adenocarcinoma) or NSCL-K 2 of 5 (squamous cell carcinoma).
[uuu] 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.
[vvv] 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."

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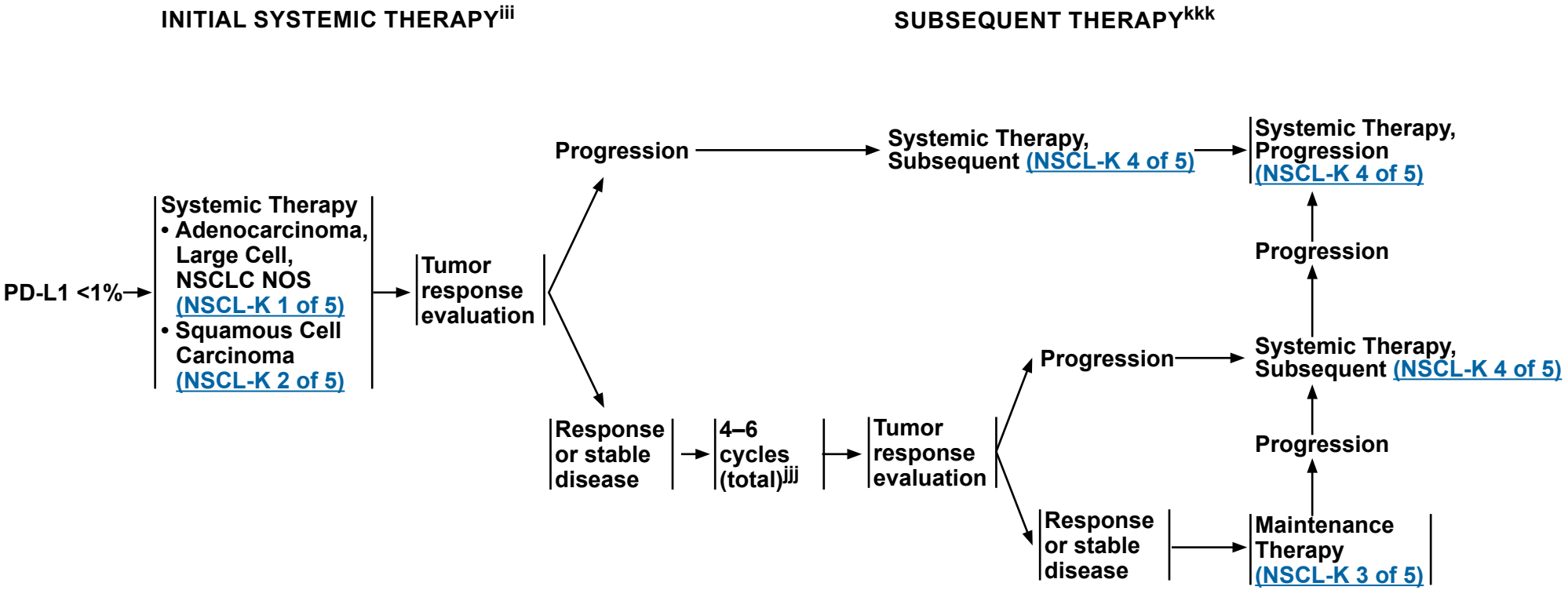
PD-L1 <1%



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

[jjj] 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.

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

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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 2021 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 IHC 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.**

[1] Non-small cell carcinomas (NSCC, without the L for lung) that show no clear adenocarcinoma or squamous cell carcinoma morphology or IHC 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 IHC 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 with IHC stains that exclude adenocarcinoma (thyroid transcription factor-1 [TTF-1], napsin A) and squamous cell (p40, p63) carcinoma. This diagnosis 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 (TTF-1, 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 TTF-1 are preferably classified as adenocarcinoma. A simple panel of TTF-1 and p40 may be sufficient to classify most NSCC-NOS cases.**
- **Testing for nuclear protein in testis (NUT) expression by IHC should be considered in all poorly differentiated carcinomas that lack glandular differentiation or specific etiology, particularly in patients who do not smoke 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 IHC stains is recommended to assess for metastatic carcinoma to the lung.**
  - **TTF-1 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. TTF-1 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 TTF-1 except in metastatic thyroid malignancies, in which case thyroglobulin and PAX8 are also positive. Rare cases of TTF-1 positivity in tumors of other organs (gynecologic tract, pancreatobiliary) have been noted, and may be dependent on the specific TTF-1 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 TTF-1.**
  - **The panel of TTF-1 (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.**

Continued

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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 >10% of the tumor cells.**
- **Pleural mesothelioma versus pulmonary adenocarcinoma**
  - **The distinction between pulmonary adenocarcinoma and pleural 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 pleural mesothelioma include WT-1, calretinin, CK5/6, and D2-40 (usually negative in adenocarcinoma).**
  - **Immunostains sensitive and specific for adenocarcinoma include pCEA, Claudin-4, TTF-1, and napsin A (negative in pleural mesothelioma). Other potentially useful markers that can be considered include B72.3, Ber-EP4, MOC-31, 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 pleural mesothelioma and metastatic carcinoma, and will also help determine the tumor origin. Examples include markers for lung adenocarcinoma (TTF-1 and napsin A), breast carcinoma (ERα, PR, GCDFP-15, 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 pleural 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 FDG-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 patients at high risk or who are borderline operable, 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 patients with lung cancer (eg, multidisciplinary clinic and/or tumor board).**
- **Patients who actively smoke should be provided counseling and smoking cessation support (NCCN Guidelines for Smoking Cessation). While patients who actively smoke 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 (NSCL-B 2 of 6)
Margins and Nodal Assessment (NSCL-B 3 of 6)

The Role of Surgery in Patients with N2 NSCLC (NSCL-B 3 of 6 through NSCL-B 5 of 6)

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PRINCIPLES OF SURGICAL THERAPY

Resection

- **Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.**
- **Sublobar resection - Segmentectomy and wedge resection should be strongly considered for peripheral T1ab, N0 tumors.[1,2]**
- **Sublobar 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 with poor pulmonary reserve or other major comorbidity that contraindicates lobectomy.**
- **Minimally invasive surgery (VATS or 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. Robotic surgery should only be initiated by surgeons who have completed and maintained proficiency in the technique.**
- **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.[3]**
- **Studies of robotic-assisted pulmonary resection show non-inferiority to traditional VATS approaches when performed by experienced robotic surgeons.[4,5]**
- **Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and margin-negative resection is achieved.**
- **T3 (invasion) and T4 local invasion 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.**

Evaluation (NSCL-B 1 of 6)
Margins and Nodal Assessment (NSCL-B 3 of 6)

The Role of Surgery in Patients with N2 NSCLC (NSCL-B 3 of 6 through NSCL-B 5 of 6)

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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 one N1 and three N2 stations sampled or complete lymph node dissection. Preoperative sampling with EBUS or mediastinoscopy should be part of N2 assessment to achieve 3 N2 nodal stations.
- Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for 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 clinical stage IB or greater, or high-risk factors, should be referred to medical oncology for evaluation.
- Consider referral to a radiation oncologist for N2 disease.

The Role of Surgery in Patients with N2 NSCLC

The role of surgery in patients with pathologically documented N2 disease remains controversial.[6] Two randomized trials evaluated the role of surgery in this population, but neither showed an overall survival benefit with the use of surgery.[7,8] 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, NSCL-3, NSCL-5, NSCL-8, NSCL-11, NSCL-13, and NSCL-14)
- 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 their practice dedicated to thoracic oncology.[9]
- 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 N2 NSCLC is continued on NSCL-B 4 of 6 through NSCL-B 5 of 6

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PRINCIPLES OF SURGICAL THERAPY

The Role of Surgery in Patients with 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.[10]**
- **Patients with a single lymph node <3 cm can be considered for a multimodality approach that includes surgical resection.[6,11,12]**
- **Restaging after induction therapy is difficult to interpret, but CT ± FDG-PET/CT should be performed to exclude disease progression or interval development of metastatic disease.**
- **Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.[12,13]**
- **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.[10,14] Neoadjuvant chemoradiotherapy is associated with higher rates of pathologic complete response and negative mediastinal lymph nodes.[15] 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 >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.[16,17] 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.[7] 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.[18-21] 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.[22]**

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PRINCIPLES OF SURGICAL THERAPY

The Role of Surgery in Patients with N2 NSCLC

A questionnaire was submitted to the NCCN Member Institutions in 2024 regarding their approach to patients with N2 disease. Their responses indicate the patterns of practice when approaching this difficult clinical problem.

- **All NCCN Member Institutions treat select N2 patients with multimodality therapy that includes surgery.**
- **All NCCN Member Institutions consider surgery for single-station non-bulky N2 disease.**
  - **100% consider surgery after neoadjuvant therapy**
  - **33% consider upfront surgery for single-station non-bulky N2 disease**
  - **None consider upfront surgery for multi-station or bulky (≥3 cm) N2 disease**
- **After neoadjuvant therapy, 100% consider surgery for single-station non-bulky N2 disease**
  - **76% consider surgery for single-station bulky (≥3 cm) disease**
  - **67% consider surgery for multi-station non-bulky disease**
  - **27% consider surgery for multi-station bulky (≥3 cm) disease**
- **All NCCN Member Institutions prefer neoadjuvant chemotherapy ± immunotherapy most of the time.**
  - **None use chemoradiotherapy most of the time.**
- **85% require at least stable disease on imaging after induction neoadjuvant therapy for consideration of surgery.**
  - **None require imaging complete response in mediastinal lymph nodes.**
  - **94% do not require pathologic complete response in mediastinal lymph nodes.**
  - **82% do not use pathologic evaluation of mediastinal lymph nodes to make a final decision regarding surgery.**
- **76% would consider pneumonectomy after neoadjuvant chemotherapy.**
- **54% would consider adjuvant RT for positive residual N2 disease, but only 9% would consider RT for N2 pathologic complete response.**
- **For a resected stage III tumor, adjuvant immunotherapy is given for 30% of patients and considered for another 24% of patients if PD-L1 negative.**
  - **Given for 81% and considered for another 13% if PD-L1 ≥1%–49%**
  - **Given for 91% and considered for another 9% if PD-L1 ≥50%**
- **If neoadjuvant chemo-immunotherapy is given and there is a pathologic complete response, adjuvant therapy is recommended about a quarter of the time (24%) and considered another 27% of the time.**

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PRINCIPLES OF RADIATION THERAPY

I. General Principles

- Determination of the appropriateness of 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-conformal RT (CRT).[1]
- More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT, FDG-PET/CT and/or MRI simulation, intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), image-guided RT (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 chemotherapy/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. In retrospective studies, intensity-modulated proton therapy (IMPT) has also been shown to reduce the toxicities as compared with 3D-based passive scattering proton therapy in stage III NSCLC.[3]
- Highly conformal RT, such as IMRT or proton therapy, should be used in the setting of prior RT, potentially with hyperfractionation, to reduce risk of toxicity.
- 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 vascular endothelial growth factor (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.

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PRINCIPLES OF RADIATION THERAPY

II. Radiation Therapy Simulation, Planning, and Delivery (continued)

- **FDG-PET/CT significantly improves targeting accuracy,[6] especially for patients with significant atelectasis and when IV CT contrast is contraindicated. A randomized trial of FDG-PET/CT versus CT-only RT planning demonstrated improved preemption of futile radical RT, decreased recurrences, and a trend toward improved overall survival with FDG-PET/CT RT planning.[7] Given the potential for rapid progression of NSCLC,[8,9] FDG-PET/CT should be obtained preferably within 4 weeks before treatment. It is ideal to obtain FDG-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.**
- **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 cone-beam CT [CBCT], CT on rails, or MRI)—is recommended when using SABR, 3D-CRT/IMRT, and proton therapy with steep dose gradients around the target, when organs at risk (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 1–4 on NSCL-C 6 of 10 and NSCL-C 7 of 10)

- **ICRU Reports 62 and 83 detail the current definitions of target volumes for 3D-RT and IMRT. Gross tumor volume (GTV) comprises the known extent of disease (primary and nodal) on imaging and pathologic assessment, clinical target volume (CTV) includes regions of presumed microscopic extent or dissemination, and planning target volume (PTV) comprises the internal target volume (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 1 through 4. 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.**

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PRINCIPLES OF RADIATION THERAPY

IV. General Treatment Information

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

- SABR (also known as stereotactic body RT [SBRT])[19] has achieved good primary tumor control rates and overall survival, as well as higher than conventionally fractionated radiotherapy. Although SABR is not proven equivalent to lobectomy, some prospective series have demonstrated similar overall and cancer-specific survival with reduced acute toxicity.[20-31]
- 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 or cardiac function]).
- More modestly hypofractionated or dose-intensified conventionally fractionated highly conformal radiation (IMRT with IGRT preferred) are less preferred alternatives and may be considered if referral for SABR is not feasible.[32-34]
- In patients treated with surgery, postoperative radiotherapy (PORT) is not recommended unless there are positive margins (see *Locally Advanced NSCLC* in this section for patients upstaged to N2).
- Close follow-up and therapy for isolated local and/or locoregional recurrence after SABR have been shown to improve overall survival in a large retrospective study.[35]

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 biologically effective dose (BED) ≥100 Gy are associated with significantly better local control and survival than less intensive regimens.[36,37] 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.[36,38] 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 or, in some definitions, other critical mediastinal structures as well), 4 to 10 fraction risk-adapted SABR regimens appear to be effective and safe,[39-42] while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.[43] 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.[44]
- 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.[44,45]
- Retrospective data suggest that chemotherapy in addition to SABR provides a survival advantage for patients with large tumors (≥5 cm).[46] Adjuvant chemotherapy may be considered for large tumors in selected patients for whom it is safe.
- 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.[10,47,48] All of these must be considered when interpreting or emulating regimens from prior studies.

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Locally Advanced NSCLC (stage II–III)

- Concurrent chemotherapy/RT is recommended for patients with inoperable stage II (node-positive) and stage III NSCLC.[49-52]
- 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 patients who are frail and unable to tolerate concurrent therapy.[53,54] Accelerated RT regimens may be beneficial, particularly if concurrent chemotherapy would not be tolerated (ie, in a sequential or RT-only approach).[55,56]
- Preoperative systemic therapy and postoperative RT is an option for patients with resectable N2 NSCLC (minimal N2 and treatable with lobectomy).[57,58]
- Preoperative concurrent chemotherapy/RT is an alternative option for patients with resectable N2 NSCLC and is recommended for resectable superior sulcus tumors.[59,60] 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.
- The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and is controversial.[61,62]
- 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 with completely resected disease, two randomized studies did not show an overall survival benefit of PORT, although locoregional control was significantly improved.[63,64] PORT (generally following postoperative chemotherapy) may be considered for selected patients with high-risk N2 disease, such as extracapsular extension, multi-station involvement, inadequate lymph node dissection/sampling, and/or refusal or intolerance of adjuvant systemic therapy. To minimize potential lung and heart toxicities, highly conformal RT techniques such as IMRT or proton therapy are preferred.[65-68]
- In patients with completely resected pN1 receiving adjuvant systemic therapy, PORT is not recommended. PORT may be considered for these patients if they are unable to receive adjuvant systemic therapy.[62]

Conventionally Fractionated RT for Locally Advanced NSCLC

- Involved field irradiation (IFI) omitting elective nodal irradiation (ENI) allows tumor dose escalation and is associated with a low risk of isolated nodal relapse, particularly in a patient staged with FDG-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 chemotherapy/RT,[79] or concurrent chemotherapy/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]

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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 chemotherapy/RT 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.[95-97] Lung dose constraints should be more conservative, because tolerance appears to be reduced after surgery. The LungART and PORT-C trials provide useful guidelines for PORT technique.[98] Highly conformal techniques to minimize lung and heart dose are preferred.**

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 (PS) who have also received radical therapy to the intrathoracic disease.[99] 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.[100,101] In two randomized phase II trials, significantly improved progression-free survival and overall survival in one trial[102,103] were found for local consolidative therapy (RT or surgery) to oligometastatic lesions versus maintenance systemic therapy or observation for patients whose disease was not progressing on systemic therapy.[102-104]**
- **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 RT to a certain immune checkpoint inhibitor (anti-PD-1) significantly increased responses and clinical outcomes in patients with metastatic NSCLC.[105] Larger phase III randomized studies are ongoing.**

Palliative RT for Advanced/Metastatic NSCLC

- **The dose and fractionation of palliative RT should be individualized based on goals of care, symptoms, PS, and logistical considerations. Shorter courses of RT are preferred for patients with poor PS and/or shorter life expectancy because they provide similar pain relief as longer courses, although there is a higher potential need for retreatment.[106-109] 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 PS.[110,111] 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 (SRT) 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.[112] SABR/SRS has been found in randomized clinical trials to produce better pain and tumor control of spine and non-spine bone metastases than conventionally fractionated palliative RT, and is appropriate especially for patients with longer expected survival.[113]**

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Please note: Tables 1–4 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

Table 1. 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 tumors
50–60 Gy	5	Peripheral tumors
60–70 Gy	8–10	Central tumors

Table 2. 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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Please note: Tables 1–4 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

Table 3. 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 4. 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	V40 ≤20%; 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 OAR 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: patients ≥70 years, taxane chemotherapy, and poor PFTs (such as FEV1 or DLCO <50% normal). Use more conservative limits with a diagnosis or radiologic evidence of idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) (the tolerance of these patients is lower though not well characterized).

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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 forced expiratory volume in the first second (FEV1) and diffusing capacity of the lung for carbon monoxide (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 patients who are high risk or borderline operable, 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%, age ≥75 years, pulmonary hypertension, left ventricular ejection fraction (LVEF) ≤40%, resting or exercise PaO_2 <55 mmHg, and pCO_2 >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 IA 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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PERIOPERATIVE SYSTEMIC THERAPY

- Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors
- Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors
- Adjuvant Chemotherapy
- Systemic Therapy Following Surgical Resection

See Evidence Blocks on EB-1 and EB-2

Neoadjuvant Systemic Therapy[a]

- **Patients with tumors ≥4 cm or node positive should be evaluated for preoperative therapy, with strong consideration for an immune checkpoint inhibitor + chemotherapy. Otherwise refer to the Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors.**
- **Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3–4, N2]). PD-L1 status can be incorporated with other clinical and molecular factors to determine patients who may benefit from induction chemotherapy and immune checkpoint inhibitor. See Principles of Molecular and Biomarker Analysis (NSCL-H).**
- **After surgical evaluation, patients ineligible for immunotherapy and likely to receive adjuvant chemotherapy may be treated with neoadjuvant systemic therapy as an alternative.**

[a] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR* exon 19 deletion or exon 21 L858R; *ALK*, *RET, or ROS1* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

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PERIOPERATIVE SYSTEMIC THERAPY

Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors[a]

- **Nivolumab 360 mg and platinum-based doublet chemotherapy every 3 weeks for up to 4 cycles[1,2] with the option of continuing single-agent nivolumab as adjuvant treatment after surgery (for patients with no known *EGFR* mutations or *ALK* rearrangements) (category 1);[2]** Systemic Therapy Following Surgical Resection
- **Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.**
  - **Platinum-doublet chemotherapy options include:**
    - ◊ **Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)**
    - ◊ **Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)**
    - ◊ **Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)**
    - ◊ **Cisplatin 75 mg/m² day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)**
  - **Chemotherapy regimens for patients who are not candidates for cisplatin-based therapy**
    - ◊ **Carboplatin AUC 5 or AUC 6 day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)**
    - ◊ **Carboplatin AUC 5 or AUC 6 day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)**
- **Pembrolizumab 200 mg and cisplatin-based doublet chemotherapy every 3 weeks for 4 cycles and then continued as single-agent pembrolizumab as adjuvant treatment after surgery (category 1);[3]** Systemic Therapy Following Surgical Resection
  - **Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² days 1 and 8 (squamous histology)**
  - **Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)**
- **Durvalumab 1500 mg and platinum-based doublet chemotherapy every 3 weeks for 4 cycles and then continued as single-agent durvalumab as adjuvant treatment after surgery (for patients with no known *EGFR* mutations or *ALK* rearrangements) (category 1);[4]** Systemic Therapy Following Surgical Resection
  - **Platinum-doublet chemotherapy options include:**
    - ◊ **Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1 (squamous histology)**
    - ◊ **Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8 (squamous histology)**
    - ◊ **Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)**
    - ◊ **Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)**
  - **Chemotherapy regimens for patients who are not candidates for cisplatin-based therapy**
    - ◊ **Carboplatin AUC 5 day 1, gemcitabine 1250 mg/m² days 1 and 8 (squamous histology)**

See Evidence Blocks on EB-2

Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors
Adjuvant Chemotherapy
Systemic Therapy Following Surgical Resection

[a] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR* exon 19 deletion or exon 21 L858R; *ALK, RET, or ROS1* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

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PERIOPERATIVE SYSTEMATIC THERAPY

Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors

Preferred (nonsquamous)

- Cisplatin 75 mg/m^2 day 1, pemetrexed 500 mg/m^2 day 1 every 21 days for 4 cycles[5]

Preferred (squamous)

- Cisplatin 75 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8, every 21 days for 4 cycles[6]
- Cisplatin 75 mg/m^2 day 1, docetaxel 75 mg/m^2 day 1 every 21 days for 4 cycles[7]

Other Recommended

- Cisplatin 50 mg/m^2 days 1 and 8; vinorelbine 25 mg/m^2 days 1, 8, 15, and 22, every 28 days for 4 cycles[8]
- Cisplatin 100 mg/m^2 day 1, vinorelbine 30 mg/m^2 days 1, 8, 15, and 22, every 28 days for 4 cycles[9,10]
- Cisplatin 75–80 mg/m^2 day 1, vinorelbine 25–30 mg/m^2 days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m^2 day 1, etoposide 100 mg/m^2 days 1–3, every 28 days for 4 cycles[9]

See Evidence Blocks on EB-1

Useful in Certain Circumstances

- Chemotherapy regimens for patients who are not candidates for cisplatin-based therapy
  - Carboplatin AUC 6 day 1, paclitaxel 200 mg/m^2 day 1, every 21 days for 4 cycles[11]
  - Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m^2 days 1 and 8, every 21 days for 4 cycles[12] (squamous histology)
  - Carboplatin AUC 5 day 1, pemetrexed 500 mg/m^2 day 1 every 21 days for 4 cycles[13] (nonsquamous histology)

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

Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors
Adjuvant Chemotherapy
Systemic Therapy Following Surgical Resection

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PERIOPERATIVE SYSTEMATIC THERAPY

Adjuvant Chemotherapy

- For stage IB and IIA (T2b, N0) and negative margins (R0), adjuvant chemotherapy is recommended for high-risk features.[b]
- For stage IIB (T1 abc–T2a, N1), stage IIB (T3, N0; T2b, N1), stage IIIA (T1–2, N2; T3, N1; T4, N0–1), stage IIIB (T3–4, N2) and negative margins (R0), adjuvant chemotherapy is recommended as a category 1.
- All chemotherapy regimens listed below can be used for sequential chemotherapy/RT.
- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3–4, N2]). See Principles of Molecular and Biomarker Analysis (NSCL-H).

See Evidence Blocks on EB-1

Preferred (nonsquamous)

- Cisplatin 75 mg/m^2 day 1, pemetrexed 500 mg/m^2 day 1 every 21 days for 4 cycles[5]

Preferred (squamous)

- Cisplatin 75 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8, every 21 days for 4 cycles[6]
- Cisplatin 75 mg/m^2 day 1, docetaxel 75 mg/m^2 day 1 every 21 days for 4 cycles[7]

Other Recommended

- Cisplatin 50 mg/m^2 days 1 and 8; vinorelbine 25 mg/m^2 days 1, 8, 15, and 22, every 28 days for 4 cycles[8]
- Cisplatin 100 mg/m^2 day 1, vinorelbine 30 mg/m^2 days 1, 8, 15, and 22, every 28 days for 4 cycles[9,10]
- Cisplatin 75–80 mg/m^2 day 1, vinorelbine 25–30 mg/m^2 days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m^2 day 1, etoposide 100 mg/m^2 days 1–3, every 28 days for 4 cycle[9]

Useful in Certain Circumstances

- Chemotherapy regimens for patients who are not candidates for cisplatin-based therapy
  - Carboplatin AUC 6 day 1, paclitaxel 200 mg/m^2 day 1, every 21 days for 4 cycles[11]
  - Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m^2 days 1 and 8, every 21 days for 4 cycles[12] (squamous histology)
  - Carboplatin AUC 5 day 1, pemetrexed 500 mg/m^2 day 1 every 21 days for 4 cycles[13] (nonsquamous histology)

Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors
Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors
Systemic Therapy Following Surgical Resection

[b] Examples of high-risk features may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, 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.

References

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PERIOPERATIVE SYSTEMIC THERAPY

Systemic Therapy Following Surgical Resection[a,c]

- **Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3–4, N2]).**
  See Principles of Molecular and Biomarker Analysis (NSCL-H).
- **Patients with completely resected tumors ≥4 cm or node-positive NSCLC should be evaluated for additional systemic therapy.**

- **Alectinib 600 mg twice daily for 24 months[14]**
  - **For patients with NSCLC positive for *ALK* rearrangements (category 1).**
- **Osimertinib 80 mg daily for 3 years[15]**
  - **For patients with NSCLC positive for *EGFR* (exon 19 deletion, exon 21 L858R) mutations who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy (category 1).**
- **Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[16]**
  - **For patients with NSCLC with PD-L1 ≥1% and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors (category 1).**
  - **Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to IV atezolizumab.**
- **Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks**
  - **For up to a year for patients with NSCLC negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors (category 1).[17] The benefit for patients with PD-L1 <1% is unclear.**
  - **For up to 39 weeks for patients who received previous neoadjuvant pembrolizumab + chemotherapy (category 1).[3]**
- **Durvalumab 1500 mg every 4 weeks for up to 12 cycles[4]**
  - **For patients who received previous neoadjuvant durvalumab + chemotherapy and no known *EGFR* mutations or *ALK* rearrangements (category 1).**
- **Nivolumab 480 mg every 4 weeks for up to 13 cycles[2]**
  - **For patients who received previous neoadjuvant nivolumab + chemotherapy and no known *EGFR* mutations or *ALK* rearrangements (category 1).**
  - **Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.**

See Evidence Blocks on EB-2

Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors
Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors
Adjuvant Chemotherapy

[a] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR* exon 19 deletion or exon 21 L858R; *ALK, RET, or ROS1* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

[c] In general, perioperative therapy should be given as a single regimen and change of immunotherapy is not recommended.

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CONCURRENT CHEMORADIATION REGIMENS

Concurrent Chemoradiation Regimens[a]

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,b,c,d,e]
- **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,b,c,d,e,f]
- **Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT**[4,b,c,d,e,g]
- **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,b,c,d,e]

Preferred (squamous)

- **Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT**[6,b,c,d,e,g]
- **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,b,c,d,e]

Consolidation Therapy 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,h,i] **(category 1 for stage III; category 2A for stage II) (except tumors that are positive for *EGFR* exon 19 deletion or exon 21 L858R mutations)**
- **Osimertinib 80 mg once daily until disease progression (category 1 for stage III; category 2A for stage II) if *EGFR* exon 19 deletion or L858R**[9,i]

See Evidence Blocks for Stage II Disease on EB-3 and Stage III Disease on EB-4

[a] For patients with superior sulcus tumors, the recommendation is for 2 cycles concurrent with RT 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.
[b] Regimens can be used as preoperative/adjuvant chemotherapy/RT.
[c] Regimens can be used as definitive concurrent chemotherapy/RT.
[d] For eligible patients, durvalumab may be used after noted concurrent chemotherapy/RT regimens.
[e] For eligible patients, osimertinib may be used after noted concurrent chemotherapy/RT regimens in patients with *EGFR* exon 19 deletion or L858R.
[f] If using durvalumab or osimertinib, additional chemotherapy after radiation is not recommended. If not using durvalumab or osimertinib, an additional 4 cycles of pemetrexed 500 mg/m² may be used.
[g] If using durvalumab or osimertinib, additional chemotherapy after radiation is not recommended. If not using durvalumab or osimertinib, an additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6 may be used.
[h] In patients with tumors that are positive for *EGFR* exon 19 deletion of exon 21 L858R mutations there is risk of toxicity when TKI is administered in temporal proximity to immunotherapy.
[i] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy or, if *EGFR* exon 19 deletion or L858R, osimertinib is recommended.

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CANCER SURVIVORSHIP CARE[1-3]

Monitoring and Managing Survivorship Needs During Systemic Therapy

- Symptom/patient-reported outcome monitoring
  - NCCN Guidelines for Palliative Care (PAL-2)
  - ESMO Clinical Practice Guideline – The Role of Patient-Reported Outcome Measures in the Continuum of Cancer Clinical Care
- Identification and management of cancer-related complications and side effects of therapy
  - NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease
  - NCCN Guidelines for Management of Immunotherapy-Related Toxicities
  - NCCN Guidelines for Cancer-Related Fatigue
  - NCCN Guidelines for Antiemesis
- Psychosocial evaluation and referrals: NCCN Guidelines for Distress Management
- Addressing the Stigma of Lung Cancer (American Lung Association)
- Financial toxicity/social determinants of health (SDOH) monitoring and referrals
  - Financial Advocacy Services Guidelines (Association of Cancer Care Centers)
  - Financial Toxicity and Cancer Treatment (National Cancer Institute)
- Palliative care referrals: NCCN Guidelines for Palliative Care
- Care coordination for optimization of comorbid conditions, eg, referral for pulmonary rehabilitation for patients with COPD or pulmonary hypertension

NSCLC Long-Term Follow-up Care

- Cancer surveillance (NSCL-17)
- Immunizations
  - Annual influenza vaccination
  - Herpes zoster vaccine
  - Pneumococcal vaccination with revaccination as appropriate
  - COVID vaccination as per the guidance of the Centers for Disease Control and Prevention (CDC)
  - Hepatitis vaccination
- NCCN Guidelines for Survivorship
- Lung cancer-specific exercise recommendations
  - Consider perioperative pulmonary rehabilitation for patients with comorbid COPD and those who have undergone lung surgery[4,5]
- Smoking cessation: NCCN Guidelines for Smoking Cessation
- Chronic cancer pain management: NCCN Guidelines for Adult Cancer Pain
- Psychosocial evaluation and referrals
- Financial toxicity/SDOH monitoring and referrals
- Care coordination with primary care clinicians
- Fatigue:
  - NCCN Guidelines for Cancer-Related Fatigue
  - Cancer-Related Fatigue in Lung Cancer: A Research Agenda: An Official American Thoracic Society Research Statement[6]

Continued

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CANCER SURVIVORSHIP CARE

Counseling Regarding Health Promotion and Wellness[7]
- **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[8,9]

These recommendations are for individuals at average risk for cancer; patients at high risk should be individualized.
- **Colorectal Cancer: NCCN Guidelines for Colorectal Cancer Screening**
- **Prostate Cancer: NCCN Guidelines for Prostate Cancer Early Detection**
- **Breast Cancer: NCCN Guidelines for Breast Cancer Screening and Diagnosis**

[7] American Cancer Society Guideline for Diet and Physical Activity for Cancer Prevention: https://www.cancer.org/cancer/risk-prevention/diet-physical-activity/acs-guidelines-nutrition-physical-activity-cancer-prevention.html.
[8] Memorial Sloan Kettering Cancer Center Screening Guidelines: https://www.mskcc.org/cancer-care/risk-assessment-screening/screening-guidelines.
[9] American Cancer Society Guidelines for the Early Detection of Cancer: http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer?sitearea=PED.

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

Molecular Diagnostic Studies in NSCLC

- 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 IHC analyses, which are distinct from IHC studies utilized to identify tumor type and lineage.
- Clinicopathologic features should not be used to select patients for testing.
- 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 Clinical Laboratory Improvement Amendments (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
  - Understanding what constitutes an informative versus a null result. A positive finding for a known oncogenic driver is considered an informative result. Absence of a known oncogenic driver, including results that show only "passenger" alterations, might be considered null depending on the context of the specimen limitations and clinical situation. Specifically, technical issues related to tumor cellularity in tissue testing or burden of disease in circulating tumor DNA (ctDNA) testing are considerations in interpretation of findings. Additional considerations are elaborated in sections below.
- 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 ctDNA) can be a surrogate sample (NSCL-H 8 of 8).
- 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.
      - – Broad-based genomic testing approaches that efficiently utilize limited biopsy tissue while maximizing diagnostic genomic information are most commonly NGS-based. NCCN acknowledges that many currently available NGS-based assays used to fully genotype NSCLC are larger than the 50-gene limit threshold utilized by Current Procedural Terminology (CPT) coding convention; as a result, utilization of panels >50 genes may be practical to follow these recommendations. Either a single assay or a combination of a limited number of assays may be appropriate.
      - – Although broad-based genomic testing approaches are preferred, in some clinical situations rapid testing may be warranted and should be followed up with broad-based genomic testing.

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Testing Methodologies (continued)**
  - ◊ **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, 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-20 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 and the potential for mutations outside of the testing scope of the specific assay must be considered.**
  - ◊ **Any method that interrogates sequences other than a subset of highly specific alterations (eg, NGS) 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. FISH may have better sensitivity for gene amplification events in some circumstances.**
- **Specimen Selection**
  - ▸ **Testing platforms using tissue and peripheral blood are available.**
  - ▸ **Testing using tissue sample requires acquisition of a suitable sample.**
    - ◊ **Alterations detected using NSCLC tumor tissue can be most directly attributed to the tumor.**
    - ◊ **If an assay has a technical failure related to an insufficient quantity, consideration of an alternate testing modality or procurement of additional tissue is recommended to achieve broad molecular profiling.**
  - ▸ **Testing using peripheral blood (most commonly plasma-based testing of ctDNA) can be utilized in conjunction with tissue-based testing to achieve genotyping for recommended biomarkers.**
    - ◊ **Many, but not all, ctDNA tests use NGS-based technology. The technical advantages and limitations of ctDNA testing are further elaborated below.**

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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; 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 TKI therapy is a consideration for NSCLC stage IB–IIIC. 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 21 p.L861Q, exon 18 p.G719X, and exon 20 p.S768I mutations), 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 *(EGFR*ex20*)* 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 *EGFR*ex20 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.**
        - ▪ ***EGFR*ex20 insertions/duplications are associated with responsiveness to specific targeted subsequent therapy agents designed for *EGFR*ex20 events. The most commonly represented *EGFR*ex20 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 targeted therapy.**
        - ▪ **Because some *EGFR*ex20 mutations are or may be sensitive to first- and third-generation inhibitors, the specific sequence of *EGFR*ex20 insertion mutations remains important. Some assays will identify the presence of an *EGFR*ex20 insertion without specifying the sequence, and additional testing to further clarify the *EGFR*ex20 insertion may be indicated for therapy selection.**
        - ▪ **Targeted PCR-based approaches for detection of EGFR variants under-detect *EGFR*ex20 insertion events; therefore, NGS-based strategies are preferred.**
    - ◊ **Testing Methodologies: Real-time PCR 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.**
    - **Molecular testing for *ALK* rearrangement mutations should be performed when TKI therapy is a consideration for NSCLC stage IB–IIIB. While the testing process may be technically easier on a resection specimen, initial diagnostic biopsy specimens are also acceptable for testing for this indication.**
    - **The presence of an *ALK* rearrangement is associated with responsiveness to oral ALK TKIs.**
    - **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.**
    - **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.**
  - ***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 (most commonly p.V600E, but rarely p.V600K, p.V600D, or other changes) 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 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.**

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Molecular Targets for Analysis (continued)**
  - ***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.**
    - ◊ **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 oral KRAS G12C inhibitors used for subsequent therapy, which were 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 and real-time PCR 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.**
  - ***ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2)/HER2*** **Gene Mutations: *ERBB2* encodes for HER2, a receptor tyrosine kinase found on the surface of normal epithelial cells that is often overexpressed or mutated in a variety of human malignancies.**
    - ◊ **A spectrum of genomic alterations involving *ERBB2* have been identified in multiple tumor types, including mutations and amplifications, and less commonly, other alterations.**
    - ◊ **Mutations in *ERBB2* are most commonly insertion/duplication events in exon 20, and less commonly, other activating mutations are observed.**
    - ◊ **Activating mutations in *ERBB2* are associated with responsiveness to anti-HER2 targeted therapy agents.**
      - – **While some mutations are known to be activating, including mutations in the extracellular domain (eg, p.S310X) and exon 20 insertion/duplication mutations, not all single-nucleotide or double-nucleotide changes in *ERBB2* are activating and not all potentially activating mutations were studied in pivotal trials.**
    - ◊ **Testing methodologies: While targeted PCR techniques can be utilized to examine *ERBB2* mutations, the diversity and spectrum of mutations are best surveyed using NGS-based approaches.**

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Molecular Targets for Analysis (continued)**
  - **HER2 protein overexpression: HER2, encoded by *ERBB2*, can be overexpressed in a variety of malignancies.**
    - **HER2 overexpression is defined as 3+ tumor cell staining, based on IHC.**
    - **At this time, there is no recommendation regarding specific IHC antibody clone for HER2 staining in NSCLC.**
    - **Scoring criteria for anti-HER2 monoclonal antibody/antibody-drug conjugate (ADC) therapy is currently based on criteria initially applied in gastric carcinoma, which utilizes different scoring criteria than that utilized for breast carcinoma and employs different scoring criteria for small biopsy specimens versus resections.**
  - ***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.**
- **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 routinely recommended, 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 certain oncogenic drivers should take precedence over treatment with an immune checkpoint inhibitor.**

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **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.**
- **Testing in the Setting of Progression on Targeted Therapy:**
  - **For any patient with progression on targeted therapy, histologic transformation (such as small cell) is a possible mechanism of resistance. Tissue biopsy of a progressing lesion should be considered to evaluate morphology and biomarker analysis.**
  - **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*; 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 subclonal 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 may impact the 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. Assay methodology selection can impact the ability to identify subclonal events in this setting.**

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Circulating Tumor DNA (ctDNA) Testing:**
  - **ctDNA testing should not be used in lieu of a histologic tissue diagnosis.**
  - **ctDNA is not routinely recommended in settings other than advanced/metastatic disease. For stages I–III, tissue-based testing is preferred. Metastatic disease confined to the thorax may have a higher yield with tissue-based testing.**
  - **Some laboratories offer testing for molecular alterations examining nucleic acids in peripheral circulation, most commonly in processed plasma.**
  - **Studies have demonstrated ctDNA and tissue testing to have very high specificity. Both ctDNA and tissue testing have appreciable false-negative rates, supporting the complementarity of these approaches, and data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection.**
    - ◊ **Limitations of ctDNA testing that can impact interpretation include:**
      - **Low tumor fraction/ctDNA; some assays include a measure of ctDNA fraction, which can aid in identification of situations in which low ctDNA fraction might suggest compromised sensitivity**
      - **The presence of mutations from sites other than the target lesion, most commonly clonal hematopoiesis of indeterminate potential (CHIP) or post-chemotherapy marrow clones. *KRAS* and *TP53* can be seen in either of these circumstances**
      - **The inherent ability of the assay to detect fusions or other genomic variation of relevance**
    - ◊ **Limitations of tissue testing that can impact interpretation include:**
      - **Low tumor percent in a sample not sufficiently mitigated by tumor enrichment or high analytic sensitivity methods**
      - **The inherent ability of the assay to detect fusions or other genomic variation of relevance**
- **Germline Testing**
  - **Consider referral to genetic counseling if there is suspicion for a germline alteration detected on somatic 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[a,b]	Capmatinib[1] Tepotinib[2] Crizotinib[3,4]
FGFR alterations[c]	Erdafitinib[5]

[a] 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 ≥10 is consistent with high-level *MET* amplification.
[b] In patients with *EGFR*-mutant NSCLC who develop high-level *MET* amplifications, administration of these agents with continuation of osimertinib is acceptable.
[c] For oncogenic or likely oncogenic *FGFR* mutations, refer to definitions at oncokb.org.

[1] Wolf J, Seto T, Han JY, et al; GEOMETRY mono-1 Investigators. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. N Engl J Med 2020;383:944-957.
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[5] Pant S, Schuler M, Iyer G, et al. Erdafitinib in patients with advanced solid tumours with FGFR alterations (RAGNAR): An international, single-arm, phase 2 study. Lancet Oncol 2023;24:925-935.

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MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

EGFR Exon 19 Deletion or Exon 21 L858R

- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous)[7]
  - Erlotinib + ramucirumab[8]
  - Erlotinib + bevacizumab[c] (nonsquamous)[9]
  - Amivantamab-vmjw + lazertinib[10]
- Subsequent therapy
  - Osimertinib[11]
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[12]
  - Datopotamab deruxtecan-dlnk (nonsquamous)[13]

EGFR S768I, L861Q, and/or G719X

- First-line therapy
  - Afatinib[1,14]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,15]
- Subsequent therapy
  - Osimertinib[11]

EGFR Exon 20 Insertion Mutation

- First-line therapy
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[16]
- Subsequent therapy
  - Amivantamab-vmjw[17]
  - Sunvozertinib[18]

KRAS G12C Mutation[d]

- Subsequent therapy
  - Sotorasib[19]
  - Adagrasib[20]

ALK Rearrangement

- First-line therapy
  - Alectinib[21,22]
  - Brigatinib[23]
  - Ceritinib[24]
  - Crizotinib[21,25]
  - Ensartinib[26]
  - Lorlatinib[27]
- Subsequent therapy
  - Alectinib[28,29]
  - Brigatinib[30]
  - Ceritinib[31]
  - Ensartinib[32]
  - Lorlatinib[33]

ROS1 Rearrangement

- First-line therapy
  - Crizotinib[34]
  - Entrectinib[35]
  - Repotrectinib[36]
  - Taletrectinib[37]
- Subsequent therapy
  - Lorlatinib[38]
  - Entrectinib[35]
  - Repotrectinib[36]
  - Taletrectinib[37]

BRAF V600E Mutation

- First-line therapy
  - Dabrafenib/trametinib[39]
  - Encorafenib/binimetinib[40]
  - Dabrafenib[41]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[41,42]
  - Encorafenib/binimetinib[40]

NTRK1/2/3 Gene Fusion

- First-line/Subsequent therapy
  - Larotrectinib[43]
  - Entrectinib[44]
  - Repotrectinib[45]

MET Exon 14 Skipping Mutation[d]

- First-line therapy/Subsequent therapy
  - Capmatinib[46]
  - Crizotinib[47]
  - Tepotinib[48]

RET Rearrangement

- First-line therapy
  - Selpercatinib[49]
  - Pralsetinib[50]
- Subsequent therapy
  - Cabozantinib[51,52]

ERBB2 (HER2) Mutation

- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[d,53]
  - Ado-trastuzumab emtansine[d,54]
  - Zongertinib[55]

NRG1 Gene Fusion

- Subsequent therapy
  - Zenocutuzumab-zbco[56]

HER2-positive IHC 3+

- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[57]

c-Met/MET (≥50% IHC 3+ and *EGFR* wild-type)

- Subsequent therapy
  - Telisotuzumab vedotin-tllv (nonsquamous)[58]

See Evidence Blocks on EB-5

PD-L1 ≥50% First-Line Therapy

PD-L1 ≥1%–49% First-Line Therapy

[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 (eg, chest, abdomen, pelvis) 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 (eg, chest, abdomen, pelvis) 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] For agents with a similar mechanism of action, it is not recommended to switch between these drugs at the time of progression.

References

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

PD-L1 ≥50% FIRST-LINE THERAPY (PS 0–2)	
Adenocarcinoma, Large Cell, NSCLC NOS	**Squamous Cell Carcinoma**
Preferred • Pembrolizumab (category 1)[59,60] • (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[61,62] • Atezolizumab[e] (category 1)[63] • Cemiplimab-rwlc (category 1)[64] • Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1)[65] Other Recommended • Carboplatin + paclitaxel + bevacizumab[c,f] + atezolizumab[e] (category 1)[66] • Carboplatin + albumin-bound paclitaxel + atezolizumab[e,67] • Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[68] • Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[65] • Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[69] • Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 2B)[69] Useful in Certain Circumstances • Nivolumab + ipilimumab (category 1)[70]	Preferred • Pembrolizumab (category 1)[59,60] • Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[71] • Atezolizumab[e] (category 1)[63] • Cemiplimab-rwlc (category 1)[64] • Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[65] Other Recommended • Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[68] • Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[69] • Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine (category 2B)[69] Useful in Certain Circumstances • Nivolumab + ipilimumab (category 1)[70]
PD-L1 ≥50% FIRST-LINE THERAPY (PS 3–4)[g]	
Best supportive care (NCCN Guidelines for Palliative Care)	

See Evidence Blocks on EB-6

PD-L1 ≥1%–49% First-Line Therapy

Continuation Maintenance

[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 (eg, chest, abdomen, pelvis) 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 (eg, chest, abdomen, pelvis) 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.
[e] Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to IV atezolizumab.
[f] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[g] Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status.

References

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MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

PD-L1 ≥1%–49% FIRST-LINE THERAPY (PS 0–2)

Adenocarcinoma, Large Cell, NSCLC NOS	Squamous Cell Carcinoma
Preferred • (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[61,62] • Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1)[65] Other Recommended • Carboplatin + paclitaxel + bevacizumab[c,f] + atezolizumab[e] (category 1)[66] • Carboplatin + albumin-bound paclitaxel + atezolizumab[e,67] • Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[68] • Nivolumab + ipilimumab (category 1)[70] • Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[65] • Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 1)[69] • Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 1)[69] Useful in Certain Circumstances • Pembrolizumab (category 2B)[h,59,60]	Preferred • Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[71] • Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[65] Other Recommended • Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[68] • Nivolumab + ipilimumab (category 1)[70] • Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel[69] • Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine[69] Useful in Certain Circumstances • Pembrolizumab (category 2B)[h,59,60]

PD-L1 ≥1%–49% FIRST-LINE THERAPY (PS 3–4)[g]

Best supportive care (NCCN Guidelines for Palliative Care)

See Evidence Blocks on EB-7
PD-L1 ≥50% First-Line Therapy
Continuation Maintenance

[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 (eg, chest, abdomen, pelvis) 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 (eg, chest, abdomen, pelvis) 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.
[e] Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to IV atezolizumab.
[f] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[g] Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status.
[h] Pembrolizumab monotherapy can be considered in PD-L1 1%–49%, when there are contraindications to combination chemotherapy.

References

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MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[b]

PD-L1 ≥50% CONTINUATION MAINTENANCE	
Adenocarcinoma, Large Cell, NSCLC NOS	**Squamous Cell Carcinoma**
• Pembrolizumab (category 1)[i] • Pembrolizumab + pemetrexed (category 1)[j] • Atezolizumab[e] and bevacizumab[c,f] (category 1)[k] • Atezolizumab[e,l] • Nivolumab + ipilimumab (category 1)[m] • Cemiplimab-rwlc (category 1)[n] • Cemiplimab-rwlc[o] ± pemetrexed[p] (category 1) • Durvalumab[q] ± pemetrexed[r]	• Pembrolizumab (category 1)[i,s] • Atezolizumab[e,l] • Nivolumab + ipilimumab (category 1)[m] • Cemiplimab-rwlc (category 1)[n,o] • Durvalumab[q]
PD-L1 ≥1%–49% CONTINUATION MAINTENANCE	
Adenocarcinoma, Large Cell, NSCLC NOS	**Squamous Cell Carcinoma**
• Pembrolizumab (category 2B)[i] • Pembrolizumab + pemetrexed (category 1)[j] • Atezolizumab[e] and bevacizumab[c,f] (category 1)[k] • Atezolizumab[e,l] • Nivolumab + ipilimumab (category 1)[m] • Cemiplimab-rwlc[o] ± pemetrexed[p] (category 1) • Durvalumab[q] ± pemetrexed[r]	• Pembrolizumab[i,s] • Nivolumab + ipilimumab (category 1)[m] • Cemiplimab-rwlc (category 1)[o] • Durvalumab[q] See Evidence Blocks on EB-8

References

[b] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease (eg, chest, abdomen, pelvis) 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.
[e] Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to IV atezolizumab.
[f] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[i] If pembrolizumab monotherapy given.
[j] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[k] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
[l] If atezolizumab/carboplatin/albumin-bound paclitaxel given (category 1 following atezolizumab alone).
[m] If nivolumab + ipilimumab ± chemotherapy given.
[n] If cemiplimab-rwlc monotherapy given.
[o] If cemiplimab-rwlc combination therapy given.
[p] If cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) given.
[q] If tremelimumab-actl combination therapy given. Refer to categories of evidence for first-line regimen.
[r] If tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed given. Refer to categories of evidence for first-line regimen.
[s] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.

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

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)	
NO contraindications to PD-1 or PD-L1 inhibitors[d] AND NO *EGFR* exon 19 deletion or L858R; *ALK*, *RET*, or *ROS1* rearrangements	**Contraindications to PD-1 or PD-L1 inhibitors[d] OR *EGFR* exon 19 deletion or L858R; *ALK*, *RET*, or *ROS1* rearrangements**
Preferred • Pembrolizumab/carboplatin/pemetrexed[e] (category 1)[1,2] • Pembrolizumab/cisplatin/pemetrexed[e] (category 1)[2] • Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin)[e] (category 1)[3] Other Recommended • Atezolizumab[f]/carboplatin/paclitaxel/bevacizumab[e,g,h,i,j] (category 1)[4] • Atezolizumab[f]/carboplatin/albumin-bound paclitaxel[e,5] • Nivolumab/ipilimumab[e,6] • Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin)[e] (category 1)[7] • Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)[e] (category 1)[3] • Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[e] (category 1)[8] • Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed[e] (category 1)[8]	Useful in Certain Circumstances • Bevacizumab[g]/carboplatin/paclitaxel[h,i,j] (category 1)[9] • Bevacizumab[g]/carboplatin/pemetrexed[h,i,j,9,10] • Bevacizumab[g]/cisplatin/pemetrexed[h,i,j,11] • Carboplatin-combination therapy (category 1) ▸ Combination options include: albumin-bound paclitaxel,[12] docetaxel,[13] etoposide,[14,15] gemcitabine,[16] paclitaxel,[17] or pemetrexed[18] • Cisplatin-combination therapy (category 1) ▸ Combinations options include: docetaxel,[13] etoposide,[19] gemcitabine,[17,20] paclitaxel,[21] or pemetrexed[20] • Gemcitabine/docetaxel[22] • Gemcitabine/vinorelbine[23] • Albumin-bound paclitaxel[24,25] • Docetaxel[26,27] • Gemcitabine[28-30] • Paclitaxel[31-33] • Pemetrexed[34]
ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 3–4)[f,k]	
Best supportive care (NCCN Guidelines for Palliative Care)	

See Evidence Blocks on EB-9

Maintenance Therapy NSCL-K (3 of 5) Subsequent Therapy NSCL-K (4 of 5)

[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 is 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; some oncogenic drivers (ie, *EGFR* exon 19 deletion or L858R; *ALK, RET*, or *ROS1* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

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

[f] Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to IV atezolizumab.

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

[h] Bevacizumab should be given until progression.

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

[j] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

[k] Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status.

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

SQUAMOUS CELL CARCINOMA (PS 0–2)

NO contraindications to PD-1 or PD-L1 inhibitors[d] AND NO *EGFR* exon 19 deletion or L858R; *ALK*, *RET*, or *ROS1* rearrangements	Contraindications to PD-1 or PD-L1 inhibitors[d] OR *EGFR* exon 19 deletion or L858R; *ALK*, *RET*, or *ROS1* rearrangements
Preferred • Pembrolizumab/carboplatin/paclitaxel[e] (category 1)[35] • Pembrolizumab/carboplatin/albumin-bound paclitaxel[e] (category 1)[35] • Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)[e] (category 1)[3] Other Recommended • Nivolumab/ipilimumab[e,7] • Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[e,7] • Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[e,8] (category 1) • Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/gemcitabine[e,8] (category 1)	Useful in Certain Circumstances • Carboplatin/albumin-bound paclitaxel (category 1)[12] • Carboplatin/docetaxel (category 1)[13] • Carboplatin/gemcitabine (category 1)[16] • Carboplatin/paclitaxel (category 1)[17] • Carboplatin/etoposide[14,15] • Cisplatin/docetaxel (category 1)[13] • Cisplatin/etoposide (category 1)[19] • Cisplatin/gemcitabine (category 1)[19,20] • Cisplatin/paclitaxel (category 1)[21] • Gemcitabine/docetaxel[22] • Gemcitabine/vinorelbine[23] • Albumin-bound paclitaxel[24,25] • Docetaxel[26,27] • Gemcitabine[28-30] • Paclitaxel[31-33] See Evidence Blocks on EB-10

SQUAMOUS CELL CARCINOMA (PS 3–4)[f,k]

Best supportive care (NCCN Guidelines for Palliative Care)

Maintenance Therapy NSCL-K (3 of 5) Subsequent Therapy NSCL-K (4 of 5)

[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; some oncogenic drivers (ie, *EGFR* exon 19 deletion or L858R; *ALK, RET*, or *ROS1* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

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

[f] Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to IV atezolizumab.

[k] Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – MAINTENANCE[l]

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)	SQUAMOUS CELL CARCINOMA (PS 0–2)
Continuation maintenance • Bevacizumab (category 1) • Pemetrexed (category 1) • Bevacizumab/pemetrexed[m] • Pembrolizumab/pemetrexed (category 1)[n] • Atezolizumab[f]/bevacizumab (category 1)[o] • Nivolumab/ipilimumab[p] • Atezolizumab[f,q] • Gemcitabine (category 2B) • Cemiplimab-rwlc[r] ± pemetrexed[s] (category 1) • Durvalumab[t] ± pemetrexed[u] Switch maintenance • Pemetrexed	Continuation maintenance • Pembrolizumab[v] • Nivolumab/ipilimumab[p] • Gemcitabine (category 2B) • Cemiplimab-rwlc[r] (category 1) • Durvalumab[t] See Evidence Blocks on EB-11
ADENOCARCINOMA, LARGE CELL, NSCLC NOS, SQUAMOUS CELL CARCINOMA (PS 3–4)	
Best supportive care (NCCN Guidelines for Palliative Care)	

Subsequent Therapy NSCL-K (4 of 5) Continued

[f] Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to IV atezolizumab.
[l] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease (eg, chest, abdomen, pelvis) with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
[m] If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
[n] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[o] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
[p] If nivolumab + ipilimumab ± chemotherapy given.
[q] If atezolizumab/carboplatin/albumin-bound paclitaxel given.
[r] If cemiplimab-rwlc combination therapy given.
[s] If cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) given.
[t] If tremelimumab-actl combination therapy given.
[u] If tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed given.
[v] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – SUBSEQUENT[d,l]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)	SQUAMOUS CELL CARCINOMA (PS 0–2)
Preferred (no previous IO): Systemic immune checkpoint inhibitors[e] • Nivolumab[w] (category 1) • Pembrolizumab[x] (category 1) • Atezolizumab[f] (category 1) Preferred (*EGFR* exon 19 deletion or L858R) • Datopotamab deruxtecan-dlnk Other Recommended (no previous IO or previous IO):[y] • Docetaxel • Pemetrexed • Gemcitabine • Ramucirumab/docetaxel • Albumin-bound paclitaxel • Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+) • Telisotuzumab vedotin-tllv (c-Met/MET ≥50% IHC 3+ and *EGFR* wild-type)	Preferred (no previous IO): Systemic immune checkpoint inhibitors[e] • Nivolumab[w] (category 1) • Pembrolizumab[x] (category 1) • Atezolizumab[f] (category 1) Other Recommended (no previous IO or previous IO):[y] • Docetaxel • Gemcitabine • Ramucirumab/docetaxel • Albumin-bound paclitaxel • Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+) See Evidence Blocks on EB-12

ADENOCARCINOMA, LARGE CELL, NSCLC NOS, SQUAMOUS CELL CARCINOMA (PS 3–4)
Best supportive care (NCCN Guidelines for Palliative Care)

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – PROGRESSION[d,l]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS[e,y]	SQUAMOUS CELL CARCINOMA[e,y]
• Options for PS 0–2: nivolumab,[w] pembrolizumab, atezolizumab[f]; datopotamab deruxtecan-dlnk (*EGFR* exon 19 deletion or L858R); fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+); telisotuzumab vedotin-tllv (c-Met/MET ≥50% IHC 3+ and *EGFR* wild-type), 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.	• Options for PS 0–2: nivolumab,[w] pembrolizumab, atezolizumab[f]; fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+); 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.

[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; some oncogenic drivers (ie, *EGFR* exon 19 deletion or L858R; *ALK, RET*, or *ROS1* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

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

[f] Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to IV atezolizumab.

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

[w] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

[x] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.

[y] If not previously given.

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All recommendations are category 2A unless otherwise indicated.

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EVIDENCE BLOCKS FOR NEOADJUVANT AND ADJUVANT THERAPY

Chemotherapy Regimens
(NSCL-E [3 of 6]) and (NSCL-E [4 of 6])

	Neoadjuvant	Adjuvant
Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles		
Cisplatin 100 mg/m² day 1; vinorelbine 30 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles		
Cisplatin 75–80 mg/m² day 1; vinorelbine 25–30 mg/m² days 1 + 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		
Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1, 8, every 21 days for 4 cycles (squamous)		
Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles (squamous)		
Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles (nonsquamous)		

Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
(NSCL-E [3 of 6]) and (NSCL-E [4 of 6])

Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles		
Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1, 8, every 21 days for 4 cycles (squamous)		
Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles (nonsquamous)		

All regimens can be used for sequential chemotherapy/RT

See NSCL-E

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EVIDENCE BLOCKS FOR TARGETED THERAPIES AND IMMUNOTHERAPIES FOR RESECTABLE NSCLC

Neoadjuvant Therapy
(NSCL-E [2 of 6])

Nivolumab/gemcitabine (squamous)/(carboplatin or cisplatin)	
Nivolumab/paclitaxel/(carboplatin or cisplatin)	
Nivolumab/pemetrexed (nonsquamous)/(carboplatin or cisplatin)	
Pembrolizumab/cisplatin/gemcitabine (squamous)†	*
Pembrolizumab/cisplatin/pemetrexed (nonsquamous)†	*
Durvalumab/carboplatin/paclitaxel (squamous)¶	*
Durvalumab/gemcitabine/(cisplatin or carboplatin) (squamous)¶	*
Durvalumab/pemetrexed/(cisplatin or carboplatin) (nonsquamous)¶	*

Adjuvant Therapy
(NSCL-E [5 of 6])

Osimertinib	
Pembrolizumab‡	*
Atezolizumab	
Pembrolizumab§	
Alectinib	*
Durvalumab#	*
Nivolumab**	*

* Evidence Block development in progress
† Followed by single agent adjuvant pembrolizumab after surgery
‡ For those who received previous neoadjuvant pembrolizumab/chemotherapy
§ For those who received previous adjuvant chemotherapy
¶ Followed by single agent adjuvant durvalumab after surgery
# For those who previously received neoadjuvant durvalumab/chemotherapy
** For those who previously received neoadjuvant nivolumab/chemotherapy

See NSCL-E

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EVIDENCE BLOCKS FOR CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY
STAGE II DISEASE

Concurrent Chemotherapy/RT Regimens	Neoadjuvant	Definitive	Adjuvant
Cisplatin/etoposide with concurrent thoracic RT			
Carboplatin AUC 5/pemetrexed with concurrent thoracic RT (nonsquamous)			
Cisplatin/pemetrexed with concurrent thoracic RT (nonsquamous)			
Cisplatin/pemetrexed with concurrent thoracic RT (nonsquamous) + additional 4 cycles of pemetrexed	—		
Paclitaxel/carboplatin AUC 2 with concurrent thoracic RT			
Paclitaxel/carboplatin AUC 2 with concurrent thoracic RT + additional 2 cycles of paclitaxel and carboplatin AUC 6	—		

Consolidation Therapy After Definitive Concurrent Chemotherapy/RT	
Durvalumab	
Osimertinib	*

See Evidence Blocks for Stage III Disease on EB-4

*Evidence Block development in progress

See NSCL-F

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EVIDENCE BLOCKS FOR CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY STAGE III DISEASE

Concurrent Chemotherapy/RT Regimens	Neoadjuvant	Definitive	Adjuvant
Cisplatin/etoposide with concurrent thoracic RT			
Carboplatin AUC 5/pemetrexed with concurrent thoracic RT (nonsquamous)			
Cisplatin/pemetrexed with concurrent thoracic RT (nonsquamous)			
Cisplatin/pemetrexed with concurrent thoracic RT (nonsquamous) + additional 4 cycles of pemetrexed	—		
Paclitaxel/carboplatin AUC 2 with concurrent thoracic RT			
Paclitaxel/carboplatin AUC 2 with concurrent thoracic RT + additional 2 cycles of paclitaxel and carboplatin AUC 6	—		

Consolidation Therapy After Definitive Concurrent Chemotherapy/RT	
Durvalumab	
Osimertinib	*

*Evidence Block development in progress

See NSCL-F

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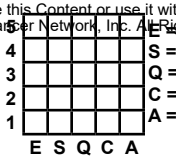

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EVIDENCE BLOCKS FOR TARGETED THERAPIES FOR METASTATIC NSCLC

ALK Rearrangement Positive

First-Line Therapy (NSCL-27)

Alectinib	
Brigatinib	
Ceritinib	
Crizotinib	
Ensartinib	*
Lorlatinib	

Subsequent Therapy (NSCL-28)

Alectinib	
Brigatinib	
Ceritinib	
Ensartinib	*
Lorlatinib	

EGFR Exon 20 Insertion Mutation Positive

First-Line Therapy (NSCL-25)

Amivantamab-vmjw/carboplatin/pemetrexed (nonsquamous)	*

Subsequent† Therapy (NSCL-25)

Amivantamab-vmjw	
Sunvozertinib	*

ERBB2 (HER2) Mutation Positive

Subsequent Therapy (NSCL-36)

Fam-trastuzumab deruxtecan-nxki	
Ado-trastuzumab emtansine	
Zongertinib	*

MET Exon 14 Skipping Mutation Positive

First-Line/Subsequent† Therapy (NSCL-34)

Capmatinib	
Crizotinib	
Tepotinib	

BRAF V600E Positive

First-Line/Subsequent† Therapy (NSCL-32)

Dabrafenib/trametinib	
Encorafenib/binimetinib	*
Vemurafenib	
Dabrafenib	

KRAS G12C Positive

Subsequent Therapy (NSCL-26)

Sotorasib	
Adagrasib	

NTRK1/2/3 Fusion Positive

First-Line/Subsequent† Therapy (NSCL-33)

Entrectinib	
Larotrectinib	
Repotrectinib	*

RET Rearrangement Positive

First-Line Therapy (NSCL-35)

Pralsetinib	
Selpercatinib	

RET Rearrangement Positive

Subsequent Therapy (NSCL-35)

Cabozantinib	

EGFR Mutation Positive (eg, *Exon 19* Deletion or *L858R*)

First-Line Therapy (NSCL-21) and (NSCL-24)

Afatinib	
Dacomitinib	
Erlotinib	
Gefitinib	
Osimertinib	
Erlotinib/ bevacizumab	
Erlotinib/ ramucirumab	
Osimertinib/ pemetrexed/ (cisplatin or carboplatin) (nonsquamous)	*
Amivantamab-vmjw/lazertinib	*

Subsequent Therapy (NSCL-22) and (NSCL-23)

Osimertinib	
Afatinib/cetuximab	
Amivantamab-vmjw/carboplatin/ pemetrexed (nonsquamous)	*
Datopotamab deruxtecan-dlnk	*

NRG1 Gene Fusion Positive

Subsequent Therapy (NSCL-37)

Zenocutuzumab-zbco	*

ROS1 Rearrangement Positive

First-Line Therapy (NSCL-30)

Crizotinib	
Entrectinib	
Repotrectinib	*
Taletrectinib	*

Subsequent Therapy (NSCL-31)

Entrectinib	
Lorlatinib	
Repotrectinib	*
Taletrectinib	*

†If not previously given

*Evidence Block development in progress

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Metastatic Nonsquamous and Squamous NSCLC, PD-L1 Expression ≥ 50%
(NSCL-J [2 of 6])

Atezolizumab	
Atezolizumab/carboplatin/paclitaxel/bevacizumab (nonsquamous)	*
Atezolizumab/carboplatin/albumin-bound paclitaxel (nonsquamous)	*
Pembrolizumab	
Cemiplimab-rwlc	
Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)	
Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin) (nonsquamous)	
Pembrolizumab/(albumin-bound paclitaxel or paclitaxel)/carboplatin (squamous)	
Pembrolizumab/pemetrexed/(carboplatin or cisplatin) (nonsquamous)	
Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed (nonsquamous)	
Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/gemcitabine (squamous)	
Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel	*
Nivolumab/ipilimumab	*
(Nivolumab/ipilimumab)/pemetrexed/(carboplatin or cisplatin) (nonsquamous)	*
(Nivolumab/ipilimumab)/paclitaxel/carboplatin (squamous)	*

*Evidence Block development in progress

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Metastatic Nonsquamous NSCLC, PD-L1 ≥ 1%-49%

First-Line Therapy
(NSCL-J [3 of 6])

Atezolizumab/carboplatin/albumin-bound paclitaxel	
Atezolizumab/carboplatin/paclitaxel/bevacizumab	
Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)	
Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin)	
Nivolumab/ipilimumab	
Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin)	
Pembrolizumab/pemetrexed/(carboplatin or cisplatin)	
Pembrolizumab	
Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel	
Tremelimumab-actl/durvalumab/(carboplatin or cisplatin/ pemetrexed	

Metastatic Squamous Cell NSCLC, PD-L1 ≥ 1% -49%

First-Line Therapy
(NSCL-J [3 of 6])

Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)	
Nivolumab/ipilimumab	
Nivolumab/ipilimumab/paclitaxel/carboplatin	
Pembrolizumab/(albumin-bound paclitaxel or paclitaxel)/carboplatin	
Pembrolizumab	
Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel	
Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/gemcitabine	

*Evidence Block development in progress

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Maintenance Therapy for Metastatic NSCLC PD-L1 ≥50% (NSCL-J [4 of 6])

Atezolizumab	
Atezolizumab/bevacizumab (nonsquamous)	*
Pembrolizumab	
Pembrolizumab/pemetrexed (nonsquamous)	*
Nivolumab/ipilimumab	
Cemiplimab-rwlc	
Cemiplimab-rwcl/pemetrexed (nonsquamous)	
Durvalumab	
Durvalumab/pemetrexed (nonsquamous)	

Maintenance Therapy for Metastatic NSCLC PD-L1 ≥1%-49% (NSCL-J [4 of 6])

Atezolizumab (nonsquamous)	
Atezolizumab/bevacizumab (nonsquamous)	
Cemiplimab-rwlc/pemetrexed (nonsquamous)	
Cemiplimab-rwlc	
Durvalumab	
Durvalumab/pemetrexed (nonsquamous)	
Pembrolizumab	*
Pembrolizumab/pemetrexed (nonsquamous)	
Nivolumab/ipilimumab	

*Evidence Block development in progress

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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC ADENOCARCINOMA

First-line Systemic Therapy

Atezolizumab/carboplatin/albumin-bound paclitaxel	
Atezolizumab/carboplatin/paclitaxel/ bevacizumab	
Albumin-bound paclitaxel	
Bevacizumab/carboplatin/paclitaxel	
Bevacizumab/carboplatin/pemetrexed	
Bevacizumab/cisplatin/pemetrexed	
Carboplatin/albumin-bound paclitaxel	
Carboplatin/docetaxel	
Carboplatin/etoposide	
Carboplatin/gemcitabine	
Carboplatin/paclitaxel	
Carboplatin/pemetrexed	
Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)	
Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin)	
Cisplatin/docetaxel	
Cisplatin/etoposide	

Cisplatin/gemcitabine	
Cisplatin/paclitaxel	
Cisplatin/pemetrexed	
Docetaxel	
Gemcitabine	
Gemcitabine/docetaxel	
Gemcitabine/vinorelbine	
Nivolumab/ipilimumab	
Nivolumab/ipilimumab/pemetrexed/ (carboplatin or cisplatin)	
Paclitaxel	
Pembrolizumab/carboplatin/pemetrexed	
Pembrolizumab/cisplatin/pemetrexed	
Pemetrexed	
Tremelimumab-actl/durvalumab/carboplatin/ albumin-bound paclitaxel	
Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed	

*Evidence Block development in progress

See NSCL-K

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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC SQUAMOUS CELL CARCINOMA

First-line Systemic Therapy

Carboplatin/albumin-bound paclitaxel	
Carboplatin/docetaxel	
Carboplatin/etoposide	
Carboplatin/gemcitabine	
Carboplatin/paclitaxel	
Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin)	
Cisplatin/docetaxel	
Cisplatin/etoposide	
Cisplatin/gemcitabine	
Cisplatin/paclitaxel	
Gemcitabine/docetaxel	
Gemcitabine/vinorelbine	

Nivolumab/ipilimumab	
Nivolumab/ipilimumab/paclitaxel/ carboplatin	
Pembrolizumab/carboplatin/albumin-bound paclitaxel	
Pembrolizumab/carboplatin/paclitaxel	
Tremelimumab-actl/durvalumab/ (carboplatin or cisplatin)/gemcitabine	
Tremelimumab-actl/durvalumab/ carboplatin/albumin-bound paclitaxel	
Albumin-bound paclitaxel	
Docetaxel	
Gemcitabine	
Paclitaxel	

See NSCL-K (2 of 5)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

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EVIDENCE BLOCKS FOR MAINTENANCE THERAPY FOR ADVANCED OR METASTATIC ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA

Maintenance Therapy for Adenocarcinoma

Atezolizumab	
Atezolizumab/bevacizumab	
Bevacizumab	
Bevacizumab/pemetrexed	
Cemiplimab-rwlc/ pemetrexed	
Cemiplimab-rwlc	

Durvalumab	
Durvalumab/ pemetrexed	
Gemcitabine	
Nivolumab/ ipilimumab	
Pemetrexed	
Pembrolizumab/ pemetrexed	

Maintenance Therapy for Squamous Cell Carcinoma

Cemiplimab-rwlc	
Docetaxel	
Durvalumab	
Nivolumab/ipilimumab	
Gemcitabine	
Pembrolizumab	

See NSCL-K (3 of 5)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

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EVIDENCE BLOCKS FOR SUBSEQUENT SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA

Subsequent Systemic Therapy for Adenocarcinoma

Atezolizumab	
Docetaxel	
Gemcitabine	
Nivolumab	
Pembrolizumab	
Pemetrexed	
Ramucirumab/docetaxel	
Albumin-bound paclitaxel	*
Fam-trastuzumab deruxtecan-nxki	*
Telisotuzumab vedotin-tllv	*
Datopotamab deruxtecan-dlnk	*

Subsequent Systemic Therapy for Squamous Cell Carcinoma

Atezolizumab	
Docetaxel	
Gemcitabine	
Nivolumab	
Pembrolizumab	
Ramucirumab/docetaxel	
Albumin-bound paclitaxel	*
Fam-trastuzumab deruxtecan-nxki	*

*Evidence Block development in progress

See NSCL-K (4 of 5)

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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

[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.

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ABBREVIATIONS

3D-CRT	3-dimensional conformal radiation therapy
4D-CT	4-dimensional computed tomography
ABC	active breathing control
ADC	antibody-drug conjugate
AIS	adenocarcinoma in situ
AUC	area under the curve
BAC	bronchioloalveolar carcinoma
BED	biologically effective dose
CBC	complete blood count
CBCT	cone-beam CT
CHIP	clonal hematopoiesis of indeterminate potential
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPT	Current Procedural Terminology
CRT	conformal radiation therapy
ctDNA	circulating tumor DNA
CTV	clinical target volume
DLCO	diffusing capacity of the lung for carbon monoxide
EBUS	endobronchial ultrasound
ENI	elective nodal irradiation
EUS	endoscopic ultrasound
FDG	fluorodeoxyglucose
FEV1	forced expiratory volume in the first second
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
GGO	ground-glass opacity
GTV	gross tumor volume
H&P	history and physical
H1 blocker	histamine-1 blocker
H2 blocker	histamine-2 blocker
ICRU	International Commission on Radiation Units and Measurements
IFI	involved field irradiation
IGRT	image-guided radiation therapy
IGTA	image-guided thermal ablation
IHC	immunohistochemistry
IMPT	intensity-modulated proton therapy
IMRT	intensity-modulated radiation therapy
IO	immuno-oncology
IPF	idiopathic pulmonary fibrosis
ITV	internal target volume
LDCT	low-dose computed tomography
LVEF	left ventricular ejection fraction
MIA	minimally invasive adenocarcinoma
MLD	mean lung dose
NGS	next-generation sequencing
NOS	not otherwise specified
NSCC	non-small cell carcinoma
NSCLC	non-small cell lung cancer
NUT	nuclear protein in testis

Continued

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ABBREVIATIONS

OAR	organ at risk
PCR	polymerase chain reaction
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PFT	pulmonary function test
PORT	postoperative radiotherapy
PS	performance status
PTV	planning target volume
ROSE	rapid on-site evaluation
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
SABR	stereotactic ablative radiotherapy
SBRT	stereotactic body radiation therapy
SCLC	small cell lung cancer
SDOH	social determinants of health
SRS	stereotactic radiosurgery
SRT	stereotactic radiation therapy
SUV	standardized uptake value
SVC	superior vena cava
TBNA	transbronchial needle aspiration
TKI	tyrosine kinase inhibitor
TNM	tumor node metastasis
TTF-1	thyroid transcription factor-1
TTNA	transthoracic needle aspiration
UIP	usual interstitial pneumonia
VATS	video-assisted thoracic surgery
VEGF	vascular endothelial growth factor
VMAT	volumetric modulated arc therapy
VUS	variant of uncertain significance
WBRT	whole brain radiation therapy

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

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Discussion

This discussion corresponds to the NCCN Guidelines for Non-Small Cell Lung Cancer. MS-2, MS-61, and MS-74 through MS-91 were updated on April 10, 2024. The rest of the discussion was last updated on April 13, 2023.

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Discussion update in progress

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Overview

Lung cancer is the leading cause of cancer-related deaths in the United States.[1,2] In 2024, an estimated 234,580 new cases (116,310 in males and 118,270 in females) of lung and bronchial cancer will be diagnosed, and 125,070 people (65,790 males and 59,280 females) will die because of the disease.[1] It is estimated that 25.4% of patients with lung and bronchial cancers are alive 5 years or more after diagnosis; this includes patients with non-small cell lung cancer (NSCLC) and those with small cell lung cancer (SCLC) in the United States from 2013 through 2019.[3] The overall 5-year relative survival rate among those with adenocarcinoma histology was 32.2%.[3] Since 2006, the incidence of lung cancer has decreased annually by 2.5% in males and 1% in females.[1] It is estimated that 81% of lung cancer deaths in 2024 will be caused directly by cigarette smoking.[1]

There have been significant improvements in the treatment of lung cancer, including advances in screening; minimally invasive techniques for diagnosis and treatment; radiation therapy (RT), including stereotactic ablative radiotherapy (SABR); as well as new targeted therapies and immunotherapies.[4-9] The availability of these new treatments is associated with improved survival rates for patients with NSCLC. From 2015 to 2016, 2-year relative survival for NSCLC was 42% compared with 34% from 2009 to 2010.[10] Patients with NSCLC who are eligible for targeted therapies or immunotherapies are now surviving longer; 5-year survival rates range from 15% to 62.5%, depending on the biomarker.[9,11-27] Therefore, biomarker testing is critical to guide treatment selection and ensure optimal outcomes in patients with NSCLC, particularly for those with advanced or metastatic disease.

Discussion Update in progress

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Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Guidelines for Non-Small Cell Lung Cancer, an electronic search of the PubMed database was performed to obtain key literature in NSCLC published since the previous Guidelines update, using the 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. Data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-fat-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men*, *women*, *female*, and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Risk Factors

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths.[2,28-32] Approximately 350 people die every day from lung cancer in the United States; most of these deaths (81%) are caused by cigarette smoking.[33] Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).[31,34] 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). Individuals who do not smoke also have an increased relative risk (RR = 1.24) of developing lung cancer if they are exposed to tobacco smoke from those who smoke, termed *second-hand smoke*; other studies have reported a modest risk (hazard ratio [HR], 1.05).[29,34-37]

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).[38,39] The International Agency for Research on Cancer lists several agents known to cause lung cancer, including arsenic, asbestos, beryllium, cadmium, chromium, coal smoke, diesel fumes, nickel, silica, soot, and uranium.[40-42] Asbestos is a known

Discussion under construction in progress

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carcinogen that increases the risk for lung cancer in people exposed to airborne fibers, especially in individuals who smoke cigarettes. It is estimated that about 3% to 4% of lung cancers are caused by asbestos exposure.[43] Asbestos also causes pleural mesothelioma (see the NCCN Guidelines for Mesothelioma: Pleural, 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.[44] In women who received estrogen alone, the incidence or risk of death from lung cancer did not increase.[45]

Smoking Cessation

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.[30] Of patients aged 20 to 49 years who were recently diagnosed with lung cancer, 81% of men and 72% of the women had smoked.[46] Active smoking causes lung cancer; individuals who formerly smoked are at increased risk for lung cancer compared with those who have never smoked. There is a causal relationship between active smoking and lung cancer and also between other cancers (eg, bladder, cervical, colorectal, esophageal, gastric, kidney, laryngeal, oral cavity, ovarian cancer, pancreatic, pharyngeal) and other diseases and conditions.[30] Smoking harms nearly every organ in the body; individuals who smoke have increased mortality compared with those who do not smoke.[47] Those who do not smoke, but live with someone who smokes, have an increased risk for lung cancer due to secondhand smoke.[35]

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).[48-51] The 5 A's framework is a useful tool (that is, Ask, Advise, Assess, Assist, Arrange).[52] It is in the best interest of patients to quit smoking tobacco. Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival.[53] Some surgeons will not operate on individuals who currently smoke, because active smoking may increase postoperative pulmonary complications.[54] 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.[55] The American Cancer Society (ACS) has resources on *How to Quit Using Tobacco.*

Agents that can be used to promote smoking cessation include nicotine replacement (eg, gum, inhaler, lozenge, nasal spray, patch), bupropion sustained release, and varenicline.[56,57] 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.[58] Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.[59-61] The effectiveness of varenicline for preventing relapse has not been clearly established.[62] 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.[63-66] Other side effects of varenicline include nausea, abnormal dreams, insomnia, and headache.[61,67,68] Bupropion may also be

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associated with similar serious neuropsychiatric symptoms. Nicotine replacement has fewer adverse effects than varenicline or bupropion.[69] In spite of the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.[69]

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.[2,70,71] The feasibility of lung cancer screening was assessed 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, early detection, and prompt treatment.

The National Lung Screening Trial (NLST) (ACRIN Protocol A6654), a phase 3 randomized trial, assessed the risks and benefits of low-dose CT scans compared with chest radiographs for detecting lung cancer in more than 53,000 individuals with a long-term history of smoking cigarettes—including those who currently or previously smoked.[72] The NLST showed that screening individuals with high-risk factors using low-dose CT decreased the mortality rate from lung cancer by 20%.[73] Individuals who currently or previously smoked cigarettes were categorized as high risk for lung cancer if they had a 30 or more pack-year smoking history (individuals who previously smoked had quit smoking up to 15 years before enrollment), were 55 to 74 years of age, and had no evidence of lung cancer.[72,74] NELSON, a phase 3 randomized trial, assessed low-dose CT screening in 15,789 individuals at high risk for lung cancer based on age and smoking history; 85% were men.[75] Individuals were aged 50 to 74 years and currently smoked or had quit smoking within the last 10 years. At 10 years of follow-up, NELSON demonstrated a reduction in lung cancer mortality in men of 24% (cumulative rate ratio for death from lung cancer: 0.76; 95% CI, 0.61–0.94; *P* = .01).

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 individuals who either currently or previously smoked cigarettes based on clinical trial data (see the NCCN Guidelines for Lung Cancer Screening, available at www.NCCN.org).[75-80] 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 two 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).[81-84] NSCLC accounts for more than 80% of all lung cancer cases, and it includes two major types: 1) nonsquamous, including adenocarcinoma, large-cell carcinoma, and other subtypes; and 2) squamous cell (epidermoid) carcinoma.[85] Adenocarcinoma is the most common subtype of lung cancer seen in the United States and is also the most frequently occurring histology in individuals who have never smoked cigarettes. The lung adenocarcinoma classification was developed by an international panel and adopted by WHO (see the *Pathologic Evaluation of Lung Cancer* in this Discussion).[81-84,86] All NSCLC should be classified according to subtype using the WHO Guidelines.[81,82,84] The guidelines contain an extensive pathology section (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC and *Pathologic Evaluation of Lung Cancer* in this Discussion). 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.[87]

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Diagnostic Evaluation

Incidental Lung Nodules

Lung cancer screening is recommended for early diagnosis in asymptomatic patients at high risk for cancer.[72,75] 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.[88] 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.[89] 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.[90]

The diagnostic algorithm for incidental pulmonary nodules in the NCCN Guidelines for NSCLC incorporates information from the NCCN Guidelines for Lung Cancer Screening. The diagnostic algorithms for incidental solid and subsolid lung nodules, which are detected on chest CT, use cutoff thresholds of 6 mm for a positive scan result based on the Fleischner criteria (see the NCCN Guidelines for NSCLC).[91-95] 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 a preferred recommendation in the NCCN Guidelines unless contrast enhancement is needed for better diagnostic resolution.

Solid and subsolid nodules are the two 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.[92,93] 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.[93,96-98] 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.[86,93,96,97,99-101] 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.[99,102,103] 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).[89,92,93]

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.[73] 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.[104-106]

Larger Tumors

The NCCN Guidelines recommend that the diagnostic strategy should be individualized for each patient depending on the size and location of the

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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 about whether a biopsy (including what type of biopsy) or surgical excision is appropriate depend on several factors as outlined in the NSCLC algorithm, which were revised by the NCCN Panel for the 2023 update (Version 1) (see *Principles of Diagnostic Evaluation* in the NCCN Guidelines for NSCLC). For example, the NCCN Panel clarified that a preoperative biopsy may be useful for patients with early-stage NSCLC (ie, clinical stage IB or more) who may be candidates for systemic therapy before surgery (also known as neoadjuvant, induction, or preoperative therapy).[107] 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 do a wedge or intraoperative core needle biopsy). The preferred biopsy technique depends on the disease site and is described in the NSCLC algorithm. 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.[108]

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, robotic bronchoscopy, or mediastinoscopy (see *Principles of Diagnostic Evaluation* in the NCCN Guidelines for NSCLC). Clinicians use both noninvasive and invasive methods when staging patients.[109] The panel decided that a preoperative bronchoscopy may also be preferred for tissue diagnosis and/or mediastinal staging (EBUS). EBUS provides access to nodal stations 2R/2L, 3P, 4R/4L, 7, 10R/10L, 11 to 13, 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, bi-lobectomy, or pneumonectomy. If a preoperative or intraoperative tissue diagnosis appears risky or unreliable, multidisciplinary evaluation—that includes interventional radiology, thoracic surgery, and interventional pulmonology—is recommended to determine the safest and most efficient approach, or to provide consensus that a biopsy is too risky or difficult and that anatomic resection can occur without tissue confirmation of lung cancer.

Pathologic Evaluation of Lung Cancer

Pathologic evaluation is done to determine whether patients have primary lung cancer or metastatic cancer, classify the histologic subtype of the lung cancer, determine the extent of invasion, establish whether the surgical margins contain cancer (ie, positive or negative margins), and conduct biomarker diagnostic studies to assess for certain somatic, disease-associated variants/mutations (eg, *EGFR* mutations) or immune biomarkers (eg, PD-L1) (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).[110] Targeted therapy is potentially very effective in patients with NSCLC and specific driver mutations, such as *EGFR* mutations; therefore, tissue needs to be conserved for molecular testing

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(see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[7,111-120] All specimens should be assessed morphologically, including routine staining approaches such as hematoxylin and eosin (H&E) histology (or relevant stains for cytology specimens). Cytology may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.[121] Ideally, a diagnosis of NSCLC can be done using H&E findings, clinical findings, imaging studies, and the patient's history, which will conserve tissue for molecular analyses. If necessary, immunohistochemistry (IHC) should be used to distinguish adenocarcinoma, squamous cell carcinoma, metastatic malignancy, and primary pleural mesothelioma (particularly for pleural samplings) (see *Immunohistochemistry for Diagnosis of NSCLC* in this Discussion).[122] Typically, treatment is not recommended until the patient has been diagnosed with NSCLC.

Preoperative evaluations include examination of the following: bronchial brushings, bronchial washings, sputum, FNA biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy.[108,123] Minimally invasive techniques can be used to obtain specimens in patients with advanced unresectable NSCLC;[124,125] however, diagnosis may be more difficult when using small biopsies and cytology.[100] When available, rapid on-site evaluation (ROSE) may be used to ensure that transbronchial needle aspirates or EBUS specimens are adequate for diagnosis and biomarker testing.[126-130] The mediastinal lymph nodes are systematically sampled to determine the staging and therapeutic options. Other lung diseases also need to be ruled out, such as tuberculosis, sarcoidosis, and coccidioidomycosis.[131-133] 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.[82-84,134] The classification for lung adenocarcinoma was determined by an international panel and adopted by the WHO (see *Adenocarcinoma* in this Discussion).[82-84,86] The classification recommends IHC and molecular studies (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).[82,135] The use of general categories—such as non-small cell carcinoma (NSCC) or NSCC not otherwise specified (NOS)—should be minimized, because more effective treatment can be selected when the histology is known.

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 (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC). All NSCLC should be classified according to subtype using the WHO Guidelines.[82,84] 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. 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.

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

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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. Molecular testing is recommended if any adenocarcinoma component is present in a biopsy specimen that is otherwise squamous. 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. Large cell carcinoma cannot be accurately identified using small samples because of challenges with complete assessment of the lesion.[86] Immunohistochemical stains that exclude adenocarcinoma (TTF1, Napsin A) and squamous cell carcinoma (p40, p63) need to be used before making a diagnosis of large cell carcinoma; mucin stain is also recommended to assess for occult glandular differentiation. Carcinoid tumors are treated using the neuroendocrine guidelines and not the NSCLC guidelines; however, they 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 distinguish typical carcinoids from atypical carcinoids by assessing for necrosis (see the NCCN Guidelines for Small Cell Lung Cancer, available at www.NCCN.org.)

The NCCN NSCLC Panel recommends molecular testing for eligible patients with metastatic NSCLC because FDA-approved agents for lung cancer are available for actionable biomarkers (see *Testing for Molecular Biomarkers* in this Discussion). Molecular testing is recommended for patients with metastatic adenocarcinoma, large cell carcinoma, and NSCLC NOS. Testing may be considered for patients with metastatic squamous cell carcinoma.[136,137] The NCCN NSCLC Panel also recommends PD-L1 IHC testing (category 1) in all patients with metastatic NSCLC because FDA-approved immunotherapy agents are available for this immune biomarker (see *Testing for Immune Biomarkers* in this Discussion).[138]

Adenocarcinoma

Most lung carcinomas are adenocarcinomas. 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 variants (see the NCCN Guidelines for NSCLC). Both AIS and MIA are associated with excellent survival if they are resected. The terms *AIS* and *MIA* should not be used for small samples because of challenges with complete assessment of the lesion.[86] The categories of BAC or mixed subtype adenocarcinoma are no longer used to classify adenocarcinoma.[86] The classification for lung adenocarcinoma was developed by an international panel and adopted by WHO.[82-84,86] The lung 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 (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).[135]

Immunohistochemistry for Diagnosis of NSCLC

To diagnose NSCLC in small tissue samples, judicious use of IHC 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).[122,125,139] Note that the specific IHC analyses used to identify tumor type and lineage (eg, adenocarcinoma vs. squamous cell carcinoma) are distinct from the IHC analyses used to determine whether patients are candidates for anaplastic lymphoma kinase (*ALK*) inhibitor therapy or PD-L1 inhibitor therapy. If necessary, IHC should be used to distinguish adenocarcinoma, squamous

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cell carcinoma, metastatic malignancy, and primary pleural mesothelioma (particularly for pleural samplings).[122] IHC is useful for assessing poorly differentiated NSCLC in small biopsy and/or cytology specimens.[86,140]

Adenocarcinomas are usually positive for thyroid transcription factor-1 (TTF-1), whereas squamous cell carcinomas are often negative for TTF-1 and positive for p40 (or alternatively p63).[86] Napsin A positivity occurs in more than 80% of lung adenocarcinomas and may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.[141,142] Note that p63 can co-stain with TTF-1 or Napsin A in adenocarcinoma. 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. Thus, two markers may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.[86,140]

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 useful 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.[140] However, TTF-1 is also positive in tumors such as thyroid cancer and rarely in a few other organ systems.[143] In addition, thyroglobulin and PAX8 are positive in tumors from patients with thyroid cancer, while they are negative in lung cancer. Immunomarkers that may be useful to assess for metastatic carcinoma to the lung include those for 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.

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).[108,140,144] 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.[145,146] Many SCLCs also stain positively for markers of neuroendocrine differentiation, including insulinoma-associated protein 1 (INSM1), CD56/NCAM, 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. CD56/NCAM, INSM1, chromogranin, and synaptophysin are used to identify neuroendocrine tumors if morphologic suspicion of neuroendocrine differentiation exists.[147] One positive marker is sufficient if the staining is not ambiguous in more than 10% of the tumor cells (TCs).

Malignant pleural mesothelioma is a rare disease (see the NCCN Guidelines for Mesothelioma: Pleural, available at www.NCCN.org).[148-150] 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 pleural mesothelioma include WT-1, calretinin, cytokeratin 5/6, and D2-40 (podoplanin antibody)

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(negative in adenocarcinoma).[148-151] 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).

Staging

The AJCC Cancer Staging Manual (8th edition) is effective for all cancer cases recorded on or after January 1, 2018.[152,153] The lung cancer staging system was revised by the International Association for the Study of Lung Cancer (IASLC)[154-156] and was adopted by the AJCC.[152,153,157,158] The definitions for TNM and the stage grouping for the eighth edition are summarized in Tables 1 and 2 of the staging tables (see *Staging* in the NCCN Guidelines for NSCLC). The descriptors of the TNM classification scheme are summarized in Table 3 of the staging tables.[159] 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+);[160] advanced or metastatic disease is stage IV. Pathologic staging uses both clinical staging information (which is noninvasive and includes medical history and physical [H&P] examination, and imaging) and other invasive staging procedures (eg, thoracotomy, examination of lymph nodes using mediastinoscopy).[161]

From 2012 to 2018, the overall 5-year relative survival rate for adenocarcinoma was 29.6% in the United States; the 5-year survival rate for squamous cell carcinoma was 23%.[162] The corresponding 5-year relative survival rates for adenocarcinoma were 70.1% for localized, 44.7% for regional, 9.6% for distant, and 20% for unstaged.[162] 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.[163] 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%.[164] 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* in this Discussion). The NSCLC Panel recommends testing for certain molecular and immune biomarkers in all appropriate patients with 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.[18-25] Biomarker testing is recommended in eligible patients with stage IV disease, including M1a, M1b, and M1c. Testing for certain biomarkers is now also recommended in eligible patients with resectable early-stage NSCLC (see *Combined Modality Therapy* in this Discussion).

Predictive molecular biomarkers include *ALK* rearrangements, *BRAF* p.V600E point mutations, *EGFR* mutations, v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (*ERBB2*) (also known as human epidermal growth factor receptor 2 [*HER2*]) mutations, Kirsten RAt Sarcoma virus (*KRAS*) mutations, mesenchymal-epithelial transition factor exon 14 (*MET*ex14) skipping mutations, neurotrophic tyrosine receptor kinase 1/2/3 (*NTRK1/2/3)* gene fusions, rearranged during transfection (*RET*) rearrangements, and *ROS* proto-oncogene 1 (*ROS1)*

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gene rearrangements; PD-L1 expression is the predictive immune biomarker (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). For the 2023 update (Version 1), the NCCN NSCLC Panel added testing recommendations for *ERBB2 (HER2)* mutations. Emerging predictive molecular biomarkers include high-level *MET* amplifications (see *Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC* in the NCCN Guidelines for NSCLC). Targeted agents are available for patients with NSCLC who have high-level *MET* amplifications.[165-170] However, there are less data to support using these agents and they may not be FDA approved for NSCLC; therefore, they are referred to as emerging biomarkers. In 2020, the NCCN Panel deleted tumor mutational burden (TMB) as an emerging immune biomarker based on clinical trial data and other issues (see *TMB* in this Discussion).[171,172]

The NCCN NSCLC Panel recommends molecular testing based on clinical trial data, but strongly advises broader molecular profiling, to identify these and other rare driver mutations 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.[173] Several online resources are available that describe NSCLC driver events, such as *My Cancer Genome*. Resources are available to assess whether the *HER2* mutations are oncogenic or likely to be oncogenic (see oncoKB.org).[174]

The presence of *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations is predictive of treatment benefit from EGFR tyrosine kinase inhibitor (EGFR TKI) therapy, such as osimertinib (see *EGFR Mutations* in this Discussion).[175,176] Previously, these mutations were referred to as *sensitizing EGFR* mutations; however, the specific mutations are now described. The presence of *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations does not appear to be prognostic of survival for patients with NSCLC, independent of therapy.[177] Molecular testing is also recommended in eligible patients with metastatic NSCLC for less common *EGFR* mutations—such as *EGFR* S768I, L861Q, and G719X alterations—based on data showing the efficacy of certain EGFR TKIs (see *NSCLC with EGFR Alterations* in this Discussion). The panel also recommends testing for *EGFR* exon 20 insertion mutations in eligible patients with metastatic NSCLC based on data showing the efficacy of novel agents as subsequent therapy options (see *NSCLC with EGFR Alterations* in this Discussion).[178,179] All of these *EGFR* mutations can be assessed in the same assay, if the assay has been appropriately validated (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). Because targeted polymerase chain reaction (PCR)-based methods for detecting *EGFR* mutations may under-detect *EGFR* exon 20 insertions, NGS-based strategies are preferred. The phrase *subsequent* therapy is used in these NCCN Guidelines instead of *second-line or beyond* therapy, because the line of therapy may vary depending on previous treatment with targeted agents.

ALK rearrangements predict for benefit from targeted therapy such as alectinib, brigatinib, or lorlatinib (see *ALK Gene Rearrangements* in this Discussion). Testing for *ALK* rearrangements and *EGFR* mutations is recommended (category 1 for both) for patients with metastatic nonsquamous NSCLC or NSCLC NOS so that patients with these driver mutations can receive effective treatment with targeted agents (see *Systemic Therapy for Advanced or Metastatic NSCLC* in this Discussion and the NCCN Guidelines for NSCLC).[173,180-183] Testing for the other actionable mutations—including *BRAF* p.V600E, *ERBB2 (HER2)* mutations, *KRAS*, *MET*ex14 skipping, *NTRK1/2/3*, *RET*, and *ROS1*—is also recommended for nonsquamous NSCLC or NSCLC NOS because effective targeted agents are available.

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Patients with metastatic NSCLC squamous cell carcinoma can also have actionable biomarkers, such as *EGFR* mutations, although at a lower incidence than those with metastatic NSCLC adenocarcinoma.[136,137,184,185] Molecular testing for actionable alterations can be considered in patients with metastatic squamous cell carcinoma based on the effectiveness of targeted therapies.[184,185] The NCCN Panel recommends that molecular testing be considered in all patients with metastatic NSCLC squamous cell carcinoma and not just those with certain characteristics, such as those who have never smoked cigarettes, with small biopsy specimens, and with mixed histology.

For patients with metastatic nonsquamous NSCLC, the NCCN NSCLC Panel currently recommends that a minimum of the following biomarkers should be assessed, including *ALK* rearrangements, *BRAF* mutations, *EGFR* mutations, *ERBB2 (HER2)* mutations, *KRAS* mutations, *MET*ex14 skipping mutations, *NTRK1/2/3* fusions, *RET* rearrangements, *ROS1* rearrangements, and PD-L1 expression levels; molecular testing can be considered in those with metastatic squamous cell carcinoma. This list of recommended biomarkers has been revised as new oncogenic driver mutations were identified and new agents were approved. The NCCN NSCLC Panel also recommends molecular testing in eligible patients with metastatic NSCLC for *EGFR* exon 20 insertion mutations and for less common *EGFR* mutations, such as *EGFR* S768I, L861Q, and G719X. Patients with metastatic NSCLC may have other somatic genomic alterations for which targeted therapies may be available even if they are not FDA approved for NSCLC, such as high-level *MET* amplifications; these are referred to as emerging biomarkers (see *Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC* in the NCCN Guidelines for NSCLC).[165-170] In 2020, the NCCN Panel deleted TMB as an emerging immune biomarker based on clinical trial data and other issues (see *TMB* in this Discussion).[171] 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 or commercial laboratories.[186] 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).

ALK, *BRAF* p.V600E, *EGFR*, *KRAS*, *MET*ex14 skipping mutations, *RET* rearrangements, and *ROS1* rearrangements do not usually overlap; thus, testing for *KRAS* mutations may identify patients who will not benefit from further molecular testing (also known as tiered testing approaches).[185,187-191] 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).[192]

Information about biomarker testing and plasma circulating tumor DNA (ctDNA) testing (so-called “liquid biopsy”) for actionable mutations is included in the algorithm (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). Briefly, the panel feels that plasma ctDNA testing should not be used to diagnose NSCLC; tissue should be used to diagnose NSCLC. Standards and guidelines for plasma ctDNA testing for somatic variants/mutations have not been published, 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]).[193,194] For example, an *IDH1* mutation identified by plasma ctDNA 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 ctDNA findings.[195] In addition, CHIP can be identified following prior chemotherapy or radiotherapy, further confounding interpretation of variants such as in *TP53*.[196] Given the previous caveats,

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careful consideration is required to determine whether ctDNA findings reflect a true oncogenic driver or an unrelated finding. For the 2023 update (Version 1), the NCCN Panel added a caveat that many, but not all, ctDNA tests use next-generation sequencing (NGS)-based technology.[197]

However, plasma ctDNA 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.[198,199] Data suggest that plasma ctDNA testing is a useful minimally invasive test that can be used to identify *ALK*, *BRAF*, *EGFR*, *HER2*, *MET* exon 14 skipping, *RET, ROS1*, and other oncogenic biomarkers that would not otherwise be identified in patients with metastatic NSCLC.[197,200-202] Molecular testing of plasma ctDNA should be done using clinically validated tests.[197]

Testing for Molecular Biomarkers

Molecular testing is used to test for oncogenic genomic driver events for which targeted therapies are available; these somatic genomic alterations (also known as molecular biomarkers) include gene mutations and fusions.[203] Testing for certain biomarkers is also recommended for eligible patients with resectable early-stage and locally advanced NSCLC (see *Surgery Followed by Adjuvant Therapy* in this Discussion). The panel defines broad molecular profiling for NSCLC as molecular testing that identifies all of the classic actionable biomarkers described in the algorithm [eg, *ALK*, *BRAF*, *EGFR*, *ERBB2 (HER2)*, *KRAS*, *MET*ex14 skipping*, NTRK1/2/3*, *RET*, *ROS1]*—using either a single assay or a combination of a limited number of assays—and optimally also identifies the emerging biomarkers (eg, high-level *MET* amplifications) (see *Summary of the Guidelines Updates* and *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). Tiered *KRAS* testing approaches, based on the low prevalence of co-occurring biomarkers, are acceptable (see *KRAS Mutations* in this Discussion).[173,204] Broad genomic profiling may be used to assess for mechanisms of resistance in patients who have had disease progression on targeted therapy. In addition, broad molecular profiling may be used to distinguish separate primary lung cancers from intrapulmonary metastases (see *Multiple Lung Cancers* in this Discussion). Broad genomic profiling may also help determine eligibility for certain molecularly driven clinical trials.

The various 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. 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 somatic genomic alterations.[205-213] It is important to recognize that NGS requires quality control as much as any other diagnostic technique; because it is design 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, which can detect more than 50 point mutations; NGS platforms can detect even more biomarkers. However, multiplex PCR systems do not typically detect gene fusions. *ROS1* and *ALK* gene rearrangements can be detected using fluorescence in situ hybridization (FISH), NGS, and other methods (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).

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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: *ALK* rearrangements, *BRAF* mutations, *EGFR* mutations, *ERBB2 (HER2)* mutations, *KRAS* mutations, *MET*ex14 skipping mutation*s, NTRK1/2/3* gene fusions, *RET* rearrangements, and *ROS1* rearrangements. Both FDA and laboratory-developed test platforms are available that evaluate these and other analytes. Broad molecular profiling is also recommended to identify emerging biomarkers for which effective therapy may be available, such as high-level *MET* amplifications. Although clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with specific somatic, disease-associated variants/mutations (eg, *EGFR* mutations), these features should not be used to select patients for testing. 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 or commercial laboratories.

Several systems are available to classify the pathogenicity of variants. One classification system uses 1) variants with strong clinical significance (Tier I); 2) variants with potential clinical significance (Tier II); 3) variants of unknown clinical significance (Tier III); and 4) variants that are benign or likely benign (Tier IV).[111] Another classification system uses pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely not pathogenic (likely benign), and not pathogenic (benign); this schema is most commonly applied to germline alterations, with some adoption in somatic testing interpretation.[214,215] Laboratories that adopt either approach (or others) typically do not report alterations that are classified as not pathogenic/Tier IV. Certain molecular testing methods—such as NGS or Sanger—can identify VUS alterations, while targeted assays generally do not detect them. The NCCN Guidelines note that any variant that is classified as VUS should not be used to select targeted therapy even if the VUS occurs in a gene in which other variants are clinically actionable (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).

***ALK* Gene Rearrangements**

About 5% of patients with NSCLC have *ALK* gene rearrangements.[120] Patients with *ALK* rearrangements are resistant to EGFR TKIs but have similar clinical characteristics to those with *EGFR* mutations, such as adenocarcinoma histology and either a light or never smoking history.[216] The NCCN NSCLC Panel recommends testing for *ALK* rearrangements in patients with metastatic nonsquamous NSCLC based on data showing the efficacy of alectinib, brigatinib, ceritinib, crizotinib, or lorlatinib for *ALK* rearrangements and on FDA approvals.[217-221] If patients appear to have squamous cell NSCLC, then *ALK* testing can be considered because *ALK* rearrangements also occur in squamous cell NSCLC, although at a lower rate than nonsquamous NSCLC.[136,137] For the 2023 update (Version 1), the NCCN Panel now recommends testing for *ALK* rearrangements, in addition to *EGFR* mutations, in eligible patients with resectable early-stage NSCLC (stages IB–IIIA, stage IIIB [only T3,N2]) to assess whether adjuvant therapy with atezolizumab or pembrolizumab is an option. PD-L1 inhibitors are less beneficial in patients with some oncogenic drivers (ie, *EGFR* exon 19 deletions, *EGFR* exon 21 L858R mutations, or *ALK* rearrangements).[184]

The different testing methods for *ALK* rearrangements are described in the algorithm (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). A molecular diagnostic FISH test has been approved by the FDA for detecting *ALK* rearrangements. Rapid prescreening with IHC to assess for *ALK* rearrangements can be done.[183,191,222-229] An IHC assay for *ALK* rearrangements has also been approved by the FDA. NGS can also be used to assess whether *ALK* rearrangements are present, if the platform has been appropriately

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designed and validated to detect *ALK* rearrangements.[230-232] If an actionable oncogenic genetic variant occurs in a patient, usually only one variant is present.[185,187-191,233,234] Therefore, tiered approaches may identify patients who will not benefit from further molecular testing (see *KRAS Mutations* in this Discussion).

The NCCN Panel has preference stratified the first-line therapy options for patients with *ALK* rearrangement–positive metastatic NSCLC. Alectinib, brigatinib, or lorlatinib are recommended as preferred first-line monotherapy options for patients with *ALK* rearrangement–positive metastatic NSCLC (see *NSCLC with ALK Rearrangements* in this Discussion). Ceritinib is an "other recommended" option, whereas crizotinib is "useful in certain circumstances." Data suggest that patients with *ALK* rearrangement–positive metastatic NSCLC do not respond to single-agent immune checkpoint inhibitors (ICIs).[184]

Patients typically have disease progression after first-line therapy with alectinib, brigatinib, ceritinib, crizotinib, or lorlatinib; subsequent therapy recommendations are described in the algorithm and often include continuing the first-line targeted therapies, depending on the type of progression [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion and the NCCN Guidelines for NSCLC]. Patients with *ALK* rearrangements often have brain metastases after progression on the initial targeted therapies. Treatment of limited brain lesions—clinical trials have included up to 3–5 progressing sites—in patients with NSCLC differs from that recommended in the NCCN Guidelines for Central Nervous System Cancers, because patients with NSCLC and brain lesions often have long-term survival; therefore, the potential neurocognitive issues that may occur with whole brain RT are a concern.[235] Clinicians are using whole brain RT less often in patients with NSCLC and limited brain lesions.[236] For multiple lesions, whole brain RT is recommended; stereotactic radiosurgery (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).[237-240]

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. The *BRAF* p.V600E mutation occurs in 1% to 2% of patients with lung adenocarcinoma; it is the most common of the *BRAF* point mutations when considered across all tumor types.[188,241] Rare *BRAF* mutations include p.V600K, p.V600D, and other mutations. Patients with *BRAF* p.V600E mutations typically either currently or previously smoked cigarettes, whereas those with *EGFR* mutations or *ALK* rearrangements typically have never smoked.[242] Mutations in *BRAF* typically do not overlap with *EGFR* mutations, *MET*ex14 skipping mutations, *RET* rearrangements, *ALK* rearrangements, or *ROS1* rearrangements.[188,189] Testing for *BRAF* mutations is recommended in patients with metastatic nonsquamous NSCLC. Testing may be considered in patients with metastatic NSCLC squamous cell carcinoma because *BRAF* mutations also occur in squamous cell NSCLC, although at a lower rate than nonsquamous NSCLC.[136,137,188,189] 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* p.V600E mutations and on FDA approval (see *NSCLC with BRAF V600E Mutation* in this Discussion).[188] The NCCN Panel has preference stratified the first-line therapy options for patients with *BRAF* p.V600E mutation–positive metastatic NSCLC. Dabrafenib plus trametinib is a preferred treatment

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option for patients with *BRAF* p.V600E mutations. If combination therapy with dabrafenib plus trametinib is not tolerated, single-agent therapy with dabrafenib or vemurafenib are treatment options; therefore, these agents are categorized as "useful in certain circumstances."[188,189,243] Chemotherapy regimens used for initial systemic therapy (eg, carboplatin plus paclitaxel) are also "useful in certain circumstances." In patients with *BRAF* p.V600E mutation–positive metastatic NSCLC, the response rate is about 24% to single-agent ICIs.[184]

EGFR Mutations

The NCCN NSCLC Panel recommends testing for *EGFR* mutations, including common and uncommon mutations, in eligible patients with metastatic NSCLC based on clinical trial data as described in the following sections. Molecular testing for *EGFR* mutations is also recommended for eligible patients with resectable stage IB to IIIA and stage IIIB (only T3,N2) NSCLC to determine whether adjuvant therapy with osimertinib is an option (see *Surgery Followed by Adjuvant Therapy: Trial Data and NCCN Recommendations* in this Discussion).

EGFR Exon 19 Deletions and EGFR Exon 21 L858R Mutations

In patients with NSCLC, the two most commonly found *EGFR* gene mutations are deletions in exon 19 (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 afatinib, dacomitinib, erlotinib, gefitinib, and osimertinib (see *Targeted Therapies* in this Discussion).[244] Because these *EGFR* mutations are sensitive to the EGFR TKIs, they were previously referred to as sensitizing *EGFR* mutations; however, the specific mutations are now described. These common *EGFR* mutations are found in approximately 10% of white patients with NSCLC and up to 50% of Asian patients.[245] Other less common mutations (approximately 10%), which are also sensitive to EGFR TKIs, include exon 20 p.S768I, exon 21 p.L861Q, and/or exon 18 p.G719X (see *EGFR S768I, L861Q, and G719X Mutations* in this section and *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[246,247] Data suggest that patients harboring tumors without these specific *EGFR* mutations should not be treated with EGFR TKIs in any line of therapy, although there are exceptions.

Most patients with the common *EGFR* mutations have adenocarcinoma histology and either have never smoked cigarettes or previously lightly smoked. Data suggest that *EGFR* mutations can occur in patients with adenosquamous carcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.[248] Patients with pure squamous cell carcinoma are less likely to have the common *EGFR* mutations; those with adenosquamous carcinoma may have mutations.[136,137,248] However, smoking status, ethnicity, and histology should not be used in selecting patients for testing. The NCCN Panel recommends that molecular testing be considered in all patients with metastatic NSCLC squamous cell carcinoma because these patients may also have actionable biomarkers, such as *EGFR* mutations, although at a lower incidence than those with metastatic NSCLC adenocarcinoma.[136,137,184,185]

The predictive effects of the *EGFR* exon 19 deletions and *EGFR* exon 21 L858R mutations are well-defined. Patients with these common *EGFR* mutations have a significantly better response to afatinib, dacomitinib, erlotinib, gefitinib, or osimertinib.[244] Data show that EGFR TKI therapy is as effective as first-line monotherapy in patients with advanced NSCLC and common *EGFR* mutations (see *Targeted Therapies* in this Discussion).[249-254] Progression-free survival (PFS) is longer with use of EGFR TKI monotherapy in patients with the common *EGFR* mutations when compared with cytotoxic systemic therapy, although overall survival

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is not statistically different for afatinib, erlotinib, or gefitinib.[249,250,255,256] Patients with *EGFR* exon 20 insertion mutations are usually resistant to afatinib, dacomitinib, erlotinib, or gefitinib, although there are rare exceptions (eg, p.A763_Y764insFQEA) (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[257-262] Patients typically have disease progression after first-line EGFR TKI monotherapy; subsequent therapy recommendations are described in the algorithm. The phrase *subsequent therapy* is used in these NCCN Guidelines instead of *second-line or beyond therapy*, because the line of therapy may vary depending on previous treatment with targeted agents.

Most patients with the common *EGFR* mutations become resistant to afatinib, erlotinib, or gefitinib; PFS is about 9.7 to 13 months.[250,256,263-265] *EGFR* p.Thr790Met (T790M) is an *EGFR* exon 20 mutation that is associated with acquired resistance to EGFR TKI therapy and has been reported in about 60% of patients with disease progression after initial response to afatinib, erlotinib, or gefitinib.[210,265-271] Studies suggest T790M may rarely occur in patients who have not previously received afatinib, erlotinib, or gefitinib.[272] Germline T790M confers a high risk for lung cancer regardless of smoking status.[273-275] Therefore, genetic counseling is recommended for patients if p.T790M is identified before treatment. Acquired resistance to EGFR TKIs may also be associated with histologic transformation from NSCLC to SCLC and with epithelial to mesenchymal transition.[276-280] The NCCN NSCLC Panel recommends that a tissue biopsy should be considered at progression to rule out SCLC transformation (approximately 6%) and to evaluate mechanisms of resistance.[277] Acquired resistance can also be mediated by other molecular events, such as acquisition of *ALK* rearrangement, *MET* or *ERBB2* amplification, and other biomarkers.[281]

The NCCN NSCLC Panel recommends testing for *EGFR* mutations (category 1) and other biomarkers in patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of afatinib, dacomitinib, erlotinib, gefitinib, or osimertinib and on FDA approvals (see *NSCLC with EGFR Alterations* in this Discussion).[18,249-254] Molecular testing can be considered for *EGFR* mutations and other biomarkers in patients with squamous cell carcinoma as previously described.

DNA mutational analysis is used to assess for EGFR status; IHC is not recommended for detecting *EGFR* mutations.[282-285] 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).[183,282] 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.[245,284,286-288] Mutation screening assays using multiplex PCR can simultaneously detect more than 50 point mutations.[289] NGS is a preferred method for detecting *EGFR* variants, because targeted PCR approaches may miss some *EGFR* exon 20 insertion mutations.[212]

The NCCN Panel has preference stratified the first-line therapy options for patients with *EGFR* mutation-positive (exon 19 deletion, exon 21 L858R) metastatic NSCLC. Osimertinib is a preferred first-line EGFR TKI option for patients with *EGFR*-positive metastatic NSCLC (see *NSCLC with EGFR Alterations* in this Discussion). Erlotinib (± bevacizumab or ramucirumab), afatinib, dacomitinib, or gefitinib 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 and disease progression on erlotinib (± bevacizumab or ramucirumab), afatinib, dacomitinib, or gefitinib.[264,290]

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EGFR S768I, L861Q, and G719X Alterations

Less common *EGFR* mutations (approximately 10%) that are also sensitive to first-, second-, and third-generation EGFR TKIs (eg, afatinib, erlotinib, gefitinib, osimertinib; classic EGFR TKIs) include exon 20 p.S768I, exon 21 p.L861Q, and exon 18 p.G719X (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[246,247,255,291] The NCCN NSCLC Panel recommends testing for *EGFR* S768I, L861Q, and G719X mutations in eligible patients with metastatic NSCLC based on data showing the efficacy of afatinib or osimertinib as preferred first-line therapy options for patients with *EGFR* S768I, L861Q, and G719X mutation-positive metastatic NSCLC (see *NSCLC with EGFR Alterations* in this Discussion).[255,291] Other recommended TKI options in this setting include dacomitinib, erlotinib, or gefitinib.[292,293]

EGFR Exon 20 Insertion Mutations

Exon 20 insertions are the third most common *EGFR* mutations; they occur in approximately 2% of patients with NSCLC and 4% to 12% of patients with *EGFR* mutations.[179,259,294,295] Although there are many different *EGFR* exon 20 insertion mutations, three are more common (insASV, insSVD, and insNPH).[179] Most patients with *EGFR* exon 20 insertion mutations have low response rates (≤9%) to afatinib, erlotinib, or gefitinib.[178,179] An exception is the p.A763_Y764insFQEA mutation; afatinib, erlotinib, or gefitinib are effective for patients with this *EGFR* exon 20 insertion.[257] When used at high doses (160 mg/day), osimertinib is associated with response rates of about 25% in patients with *EGFR* exon 20 insertion mutations, which is much lower than with *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations.[296] First-line platinum-based chemotherapy (± immunotherapy) is a recommended option for patients with *EGFR* exon 20 mutations (eg, carboplatin plus paclitaxel).[297-299] Patients with *EGFR* exon 20 insertion mutations who receive first-line platinum-based chemotherapy have shorter median overall survival (about 16 months) compared with patients with *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations who receive targeted therapy with afatinib, erlotinib, or gefitinib (about 39 months).[178,300,301] The response rates (0%–25%) to immunotherapy regimens vary, depending on the specific *EGFR* exon 20 insertion mutation.[179,302,303]

The NCCN NSCLC Panel recommends testing for *EGFR* exon 20 insertion mutations in eligible patients with metastatic NSCLC based on data showing the efficacy of amivantamab-vmjw or mobocertinib as subsequent therapy options for patients with *EGFR* exon 20 insertion mutation-positive metastatic NSCLC and on FDA approvals (see *NSCLC with EGFR Alterations* in this Discussion).[178,179] NGS is preferred for detecting *EGFR* exon 20 variants because PCR-based strategies may miss some variants (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).

ERBB2 (HER2) Mutations

For the 2023 update (Version 1), the NCCN Panel added content about *ERBB2 (HER2)* mutations (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). ERBB2 encodes for HER2, which is a receptor tyrosine kinase that is found on the surface of normal epithelial cells that is often overexpressed or mutated in various human malignancies, such as NSCLC. *ERBB2 (HER2)* alterations are commonly insertion or duplication events in exon 20 but other activating mutations are also observed. The panel added a caveat that while some *ERBB2 (HER2)* mutations are known to be activating, not all single- or double-nucleotide changes are activating. *ERBB2 (HER2)* exon 20 mutations occur in approximately 3% of patients (median age, 62 years) with advanced nonsquamous NSCLC.[304] Patients tend to be women who have never smoked cigarettes; they have a higher incidence of brain metastases than those with other actionable mutations.[304,305] Although

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clinicopathologic features—such as smoking status and histology—are associated with *ERBB2 (HER2)* activating mutations, these features should not be used to select patients for testing. For the 2023 update (Version 1), the NCCN Panel added testing recommendations for *ERBB2 (HER2)* mutations. NGS-based approaches are best able to survey the broad spectrum of genomic *ERBB2 (HER2)* alterations that may occur, although Sanger sequencing and targeted PCR approaches may also be used. The NCCN NSCLC Panel recommends testing for *ERBB2 (HER2)* mutations in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on clinical trial data and FDA approval of fam-trastuzumab deruxtecan-nxki [see *NSCLC with ERBB2 (HER2) Mutations* in this Discussion]. Testing for *ERBB2 (HER2)* mutations can be considered in patients with metastatic squamous cell carcinoma. Resources are available to assess whether the *ERBB2 (HER2)* mutations are oncogenic or likely to be oncogenic (see oncoKB.org). Data suggest that patients with *ERBB2* mutations respond to first-line immunotherapy regimens.[306]

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. Approximately 25% of patients with adenocarcinomas in a North American population have *KRAS* mutations; *KRAS* is the most common mutation in this population.[118,175,211,307,308] *KRAS* mutation prevalence is associated with cigarette smoking, unlike many of the other actionable mutations (eg, *EGFR* mutations, *ALK* rearrangements).[309] Patients with *KRAS* mutations appear to have a shorter survival than patients with wild-type KRAS; therefore, *KRAS* mutations are prognostic biomarkers.[192,308,310] *KRAS* mutations do not generally overlap with *EGFR*, *ROS1*, *BRAF*, and *ALK* genetic variants.[185,188-191,311] Therefore, a tiered approach using *KRAS* testing may identify patients who may not benefit from further molecular biomarker testing.[173,204] *KRAS* mutations may infrequently overlap with *EGFR* mutations or *RET* rearrangements.[312,313] In patients with *KRAS* mutation-positive metastatic NSCLC, data suggest the response rate is about 26% for single-agent ICIs.[184,314] First-line platinum-based chemotherapy (± immunotherapy) is a recommended option for patients with *KRAS* mutations (eg, carboplatin plus paclitaxel).

The NCCN NSCLC Panel recommends testing for *KRAS* mutations in eligible patients with metastatic NSCLC based on data showing the efficacy of adagrasib or sotorasib as subsequent therapy options for patients with *KRAS* p.G12C mutations and on FDA approvals (see *NSCLC with KRAS G12C Mutations* in this Discussion).[315-317] Responsiveness to adagrasib or sotorasib has not been assessed for mutations other than *KRAS* G12C. NGS, real-time PCR, and Sanger sequencing (ideally with tumor enrichment) are the most commonly used methods to assess for *KRAS* mutations (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).

MET Genomic Alterations

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 *MET*ex14 skipping mutations, MET gene copy number (GCN) gain or amplification, and MET protein overexpression.[187] *MET* genomic alterations do not typically overlap with *EGFR*, *ROS1*, *BRAF*, and *ALK* genetic variants.[318] However, *MET*ex14 skipping mutations and *MET* amplification may occur together. *MET*ex14 skipping mutations occur in 3% to 4% of patients with adenocarcinoma NSCLC and 1% to 2% of patients with other NSCLC histologies.[319,320] *MET*ex14 skipping mutations are more frequent in older women who have never smoked cigarettes.[321]

Several different types of *MET*ex14 skipping mutations may occur, such as mutations, base substitutions, and deletions, which makes it difficult to test for all of the mutations. NGS is the primary method of detecting *MET*ex14 skipping mutations; RNA-based NGS may have improved

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detection. IHC should not be used to detect *MET*ex14 skipping mutations. In patients with *MET*ex14 skipping mutation–positive metastatic NSCLC, data suggest the response rate is about 16% for single-agent ICIs, even with high PD-L1 levels.[184,322] Data suggest that patients with *MET* amplification respond to immunotherapy.[323]

The NCCN NSCLC Panel recommends testing for *MET*ex14 skipping mutations in eligible patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *MET*ex14 skipping mutations and on FDA approvals for capmatinib and tepotinib (see *NSCLC with MET Exon 14 Skipping Mutations* in this Discussion).[324,325] The NCCN Panel has preference stratified the first-line therapy options for patients with *MET*ex14 skipping mutation–positive metastatic NSCLC. The NCCN Panel voted that capmatinib or tepotinib are preferred first-line monotherapy options for patients with *MET*ex14 skipping mutation–positive metastatic NSCLC. The panel also voted that crizotinib or systemic therapy options (such as carboplatin plus paclitaxel) are useful in certain circumstances.

NTRK1/2/3 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.[326-328] 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 *NTRK1/2/3* fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers such as *EGFR*, *ALK*, or *ROS1*.[327] Various methods can be used to detect *NTRK1/2/3* gene fusions, including NGS, FISH, IHC, and PCR assays (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). NGS testing can detect a broad range of *NTRK* gene fusions; however, RNA-based NGS may improve detection. DNA-based NGS may not detect some *NTRK1* and *NTRK3* fusions; RNA-based NGS may be considered to assess for fusions.[329] In a clinical trial, *NTRK* gene fusions were detected with NGS (50 patients) and FISH (5 patients).[328] Larotrectinib and entrectinib are oral TKIs that inhibit TRK across a diverse range of solid tumors in patients with *NTRK* gene–fusion positive disease, regardless of age.[328,330]

The NCCN NSCLC Panel recommends *NTRK1/2/3* gene fusion testing in patients with metastatic NSCLC based on clinical trial data showing the efficacy of larotrectinib or entrectinib for patients with *NTRK* gene fusion–positive disease and on FDA approvals; however, clinical data are limited in NSCLC to support this recommendation (see *NSCLC with NTRK Gene Fusion* in this Discussion).[328,331]

RET Rearrangements

RET is a tyrosine kinase receptor that affects cell proliferation and differentiation. Rearrangements 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.[332,333] *RET* rearrangements occur in about 1% to 2% of patients with NSCLC and are more frequent in patients with adenocarcinoma histology.[332-336] In European patients, *RET* rearrangements occur in individuals who currently smoke cigarettes and those who have never nonsmoked.[334] *RET* rearrangements do not typically overlap with *EGFR*, *ROS1*, *BRAF*, *MET*ex14 skipping, and *ALK* genetic variants.[333] However, a few studies suggest that *RET* rearrangements may infrequently overlap with *EGFR* or *KRAS* mutations.[312,313] NGS, FISH, and RT-PCR can be used to detect *RET* rearrangements (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[333] NGS has high specificity; however, RNA-based NGS is preferable to DNA-based NGS for fusion detection. In

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patients with *RET*-positive metastatic NSCLC, data suggest the response rate is about 6% to single-agent ICIs.[184]

The NCCN NSCLC Panel recommends testing for *RET* rearrangements in eligible patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *RET* rearrangements and on FDA approvals for selpercatinib and pralsetinib.[337-340] Previously, the panel deleted vandetanib for patients with *RET* rearrangements because there are better therapy options.[341,342] The NCCN Panel has preference stratified the therapy options for patients with *RET* rearrangement-positive metastatic NSCLC. The NCCN Panel voted that selpercatinib or pralsetinib are preferred monotherapy options for patients with *RET* rearrangement-positive metastatic NSCLC; cabozantinib is useful in certain circumstances.

***ROS1* Rearrangements**

Although *ROS1* is a distinct receptor tyrosine kinase, it is very similar to ALK and members of the insulin receptor family.[343,344] It is estimated that *ROS1* gene rearrangements occur in about 1% to 2% of patients with NSCLC.[344-347] The NCCN NSCLC Panel recommends *ROS1* testing in patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of crizotinib, ceritinib, and entrectinib for patients with *ROS1* rearrangements.[190,344,348,349] *ROS1* testing can be considered in patients with metastatic squamous cell NSCLC because *ROS1* rearrangements also occur in metastatic squamous cell NSCLC, although at a lower rate than nonsquamous NSCLC.[136,137] Various methods can be used to detect *ROS1* rearrangements, including NGS, FISH, IHC, and PCR assays, although some methods are more effective (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[222,344,346,349-353] False-negative results may occur with FISH, IHC, PCR and DNA-based NGS.[354] RNA-based NGS may be considered to assess for fusions.

The NCCN NSCLC Panel recommends crizotinib, entrectinib, or ceritinib as first-line monotherapy options for patients with *ROS1*-positive metastatic NSCLC based on clinical trial data (see *NSCLC with ROS1 Rearrangements* in this Discussion). The NCCN Panel has preference stratified the first-line therapy options for patients with *ROS1*-positive metastatic NSCLC. The NCCN NSCLC Panel voted that crizotinib and entrectinib are 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.[330,348,349,355] Although entrectinib has better central nervous system (CNS) penetration than crizotinib, it is more toxic. The NCCN NSCLC Panel voted that ceritinib is an “other recommended” first-line therapy option for patients with *ROS1*-positive metastatic NSCLC. If *ROS1* rearrangements are discovered during first-line systemic therapy (eg, carboplatin plus 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 as a subsequent therapy option for select patients with *ROS1*-positive metastatic NSCLC and disease progression after treatment with crizotinib, entrectinib, or ceritinib (see *NSCLC with ROS1 Rearrangements* in this Discussion).[356] However, the panel clarified that entrectinib is recommended as a subsequent therapy option for patients with symptomatic brain lesions after progression on crizotinib or ceritinib.[357] Initial systemic therapy options that are used for adenocarcinoma or squamous cell carcinoma are also an option in this setting (eg, carboplatin plus paclitaxel). In patients with *ROS1*-positive metastatic NSCLC, data suggest the response rate is about 17% for single-agent ICIs.[184] Local therapy may be considered for limited progression.

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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.[358-360] Cemiplimab-rwlc, nivolumab, and pembrolizumab inhibit PD-1 receptors.[138,361,362] Atezolizumab and durvalumab inhibit PD-L1.[363,364] The NCCN NSCLC Panel recommends IHC testing for PD-L1 expression (category 1) 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 *Immune Checkpoint Inhibitors* in this Discussion).[138,365]

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 (also known as ICIs, immuno-oncology [IO] agents, immunotherapy).[366,367] 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.[366] Unique anti-PD-L1 IHC assays have been developed for each one of the different ICIs.[366,368-370] The definition of a positive or negative PD-L1 test result depends on the individual antibody, clone, and platform, which may be unique to each ICI.[370] Extensive effort has been undertaken to examine the cross-comparability of different clones with regard to each other to facilitate adoption of testing. While some clones for PD-L1 are FDA-approved for specific indications, using multiple IHC tests is not necessary if the individual IHC test has been validated against the FDA-approved clone. Testing for PD-L1 is not required for prescribing first-line therapy with certain ICI regimens—such as cemiplimab-rwlc monotherapy or atezolizumab with or without chemotherapy—or for subsequent therapy with single-agent nivolumab or atezolizumab.

The NCCN NSCLC Panel emphasizes that clinicians should obtain molecular testing results for actionable biomarkers before administering first-line ICI therapy, if clinically feasible, including *ALK, BRAF, EGFR, ERBB2 (HER2), KRAS, MET*ex14 skipping*, NTRK1/2/3, RET*, and *ROS1* variants. If it is not feasible to do molecular testing, then patients are treated as though they do not have driver oncogenes. Patients with metastatic NSCLC and PD-L1 expression levels of 1% or more—but who also have a targetable driver oncogene molecular variant—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 (lower response rates) in the first-line setting, targeted therapy is better tolerated, and these patients are less likely to respond to single-agent ICIs.[184,371-374]

TMB

TMB is an approximate measure of the total number of somatic mutations.[375] Theoretically, high TMB levels will correlate with high neoantigen levels that will activate an antitumor immune response.[376] TMB levels are typically high in patients with NSCLC who currently or previously smoked cigarettes. Low TMB is more commonly detected in individuals who have never smoked cigarettes.[329,377] Preliminary data for PFS from CHECKMATE 227, a phase 3 randomized trial with a complex design, suggested that TMB might be a useful immune biomarker for deciding whether to use immunotherapy in patients with metastatic NSCLC.[378] However, updated data from CHECKMATE 227 showed that overall survival was improved with nivolumab plus ipilimumab regardless of TMB or PD-L1 expression levels.[379] In addition, combining TMB with PD-L1 expression level also did not correlate with overall survival. Several trials have shown that high TMB levels do not correlate with PD-L1 expression levels in patients with NSCLC.[378-381] KEYNOTE 158, a phase 2 trial, assessed TMB levels in patients with solid tumors who received pembrolizumab as second-line therapy; however, none of the patients had

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NSCLC.[382] TMB does not identify patients who will respond to chemotherapy; therefore, TMB has limited value for assessing combination immunotherapy plus chemotherapy regimens.[376] TMB is also not an ideal immune biomarker because some patients with low TMB levels respond to immunotherapy and others with high levels do not respond to immunotherapy.[376]

In addition to the lack of clinical data to support use of TMB as an immune biomarker, there are technical problems with measuring TMB.[375] These problems include: 1) lack of agreement on the definition of a cut off for designating high TMB levels; and 2) lack of standardization of TMB measurements across laboratories.[375] PD-L1 expression level is a more useful immune biomarker than TMB for deciding how to use immunotherapy, because test results are obtained more quickly, less tissue is needed for testing, and data demonstrate relative reproducibility across platforms and individuals. In 2020, the NCCN Panel removed TMB as an emerging immune biomarker for patients with metastatic NSCLC based on clinical trial data, concerns about variable TMB measurements, and other issues as described here.[171,375,379] The NCCN Guidelines do not recommend measurement of TMB levels before deciding whether to use nivolumab plus ipilimumab regimens or to use other ICIs, such as pembrolizumab.[171]

Treatment Approaches

Surgery, RT, and systemic therapy are the three 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 care 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.[383]

Surgery

In general, surgery provides the best chance for cure in patients with stage I or II disease.[384] 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.[384-390] Although frailty is an increasingly recognized predictor of surgical and other treatment morbidity, a preferred frailty assessment system has not been established.[391-393]

The *Principles of Surgical Therapy* are described in the NSCLC algorithm and are summarized here. 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).[394] Patients with clinical stage IB or greater disease, or high-risk factors, should 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. A preoperative or intraoperative tissue diagnosis of lung cancer should be established before doing a lobectomy, bilobectomy, or pneumonectomy. If a preoperative or intraoperative tissue diagnosis appears risky or unreliable, multidisciplinary evaluation is recommended to determine the safest and

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most efficient approach, or to provide consensus that a biopsy is too risky or difficult and that anatomic resection can occur without prior tissue confirmation of lung cancer.

Lung-sparing anatomic resection (sleeve lobectomy [also known as sleeve resection]) is preferred over pneumonectomy, if anatomically appropriate and if margin-negative resection can be achieved; lobectomy or pneumonectomy should be done if physiologically feasible.[384,395,396] Sublobar resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients: 1) those who are not eligible for lobectomy; and 2) those with a peripheral nodule 2 cm or less with very low-risk features (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).[385,397-402] 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. Resection (including wedge resection) is preferred over ablation.[384,396] Wide wedge resection may improve outcomes.[403]

Patients with medically inoperable early-stage NSCLC may be candidates for definitive RT, preferably SABR, also known as stereotactic body RT (SBRT).[404,405] If SABR is considered for patients at high risk for surgical morbidity, a multidisciplinary evaluation is recommended (see *Stereotactic Ablative Radiotherapy* in this Discussion).[404,406-408]

Lymph Node Dissection

ACOSOG Z0030, a randomized phase 3 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.[409,410] 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.[409] Patients should have N1 and N2 node resection and mapping (American Thoracic Society map) with a minimum of three N2 stations sampled or a complete lymph node dissection.[152] The lymph node map from the IASLC may be useful.[411] Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease. For patients undergoing sublobar resection, the appropriate N1 and N2 lymph node stations should be sampled unless not technically feasible because sampling would substantially increase the surgical risk.

Thoracoscopic Lobectomy

Video-assisted thoracic surgery (VATS), which is also known as thoracoscopic lobectomy, is a minimally invasive surgical treatment (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).[412,413] Published studies suggest that thoracoscopic lobectomy has several advantages over lobectomy by thoracotomy.[414-418] Acute and chronic pain associated with thoracoscopic lobectomy is minimal; thus, this procedure requires a shorter length of hospitalization.[419,420] Thoracoscopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.[421-425] Thoracoscopic lobectomy is associated with less morbidity, fewer complications, and more rapid return to function than lobectomy by thoracotomy.[426-429]

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.[430-434] Thoracoscopic lobectomy has also been shown to

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improve discharge independence in older populations and patients at high risk.[435,436] Data show that thoracoscopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.[437,438] 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).[439-442] Robotic VATS seems to be more expensive with longer operating times than conventional VATS.[443,444]

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.[445,446] Randomized controlled trials suggest that surgery does not increase survival in these patients.[447,448] However, one of these trials (EORTC) only enrolled patients with unresectable disease.[448] 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.[449] Neoadjuvant (also known as preoperative or induction) systemic therapy is recommended for select patients with resectable NSCLC (see *Combined Modality Therapy* in this Discussion).

The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and is controversial.[450-452] Adding RT to induction regimens for patients with stage IIIA (N2) disease has been associated with higher pathological response but similar overall survival when compared with using preoperative chemotherapy (generally followed by postoperative RT).[452] For patients with completely resected stage IIIA (N2) NSCLC who received neoadjuvant or adjuvant chemotherapy, data from the LungART and PORT-C trials show that postoperative RT (also known as PORT) did not improve survival compared with no postoperative RT, although locoregional control was significantly improved.[450,453] Postoperative RT may be considered for select patients with negative margins and high-risk N2 disease (see *Chemoradiation* in this Discussion and *Principles of Radiation Therapy* in the algorithm). It is controversial whether pneumonectomy after preoperative chemoradiotherapy is appropriate.[447,454-460] 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. 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.[455,461]

The NCCN NSCLC Panel believes that surgery may be appropriate for select patients with N2 disease.[445,455,462] The NCCN Member Institutions were surveyed in 2021 regarding their approach to patients with N2 disease (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC). For example, more institutions now use neoadjuvant chemotherapy compared with neoadjuvant chemoradiation in patients with N2 disease. Many (66%) of the NCCN Member Institutions use induction chemotherapy, whereas 33% use induction chemoradiation.[463,464] Before surgery, most institutions require at least stable disease after induction therapy but do not require radiologic or pathologic response. All NCCN institutions consider surgery for single-station non-bulky N2 disease. However, 50% consider surgery for single-station bulky disease, 39% for multi-station non-bulky disease, and 21% for multi-station bulky disease.

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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.[465-475] These RT principles are summarized in this section. Whole brain RT and 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). For the 2023 update (Version 1), the NCCN NSCLC Panel revised some of the RT recommendations in the algorithm (see *Summary of the Guidelines Updates* and *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC). For example, recommendations about postoperative RT have been revised based on clinical trial data.[450,453,471-475]

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. RT recommendations 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) neoadjuvant or adjuvant therapy (also known as preoperative or postoperative therapy) for selected patients treated with surgery; 4) therapy for limited progression; and/or 5) palliative therapy for patients with incurable NSCLC.[408,450,453,476-483] The goals of RT are to maximize tumor control and to minimize treatment toxicity. Advanced technologies such as 4D-CT simulation, intensity-modulated RT/volumetric modulated arc therapy (IMRT/VMAT), image-guided RT (IGRT), motion management strategies, and proton therapy have been shown to reduce toxicity and increase survival in nonrandomized trials.[472,484-490] 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 older 3D-conformal RT (3D-CRT) technique despite higher tumor burden in patients treated with IMRT. However, IMRT yielded lower rates of severe pneumonitis compared with 3D-CRT (3.5% vs. 7.9%; P = .039).[491] CT-planned 3D-CRT is now considered to be the minimum technological standard, with IMRT preferred.

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.[492,493] Ideally, target delineation should be based on PET/CT that is obtained no more than 4 weeks before treatment because of the potential for rapid progression of NSCLC.[494,495] In the NSCLC algorithm, recommendations are provided for patients receiving chemoradiation (including those with compromised lung or cardiac function), photon beams, or IMRT (see the *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).[489,496-499] 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.[500]

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

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NSCLC algorithm (see Tables 2–5 in the NCCN Guidelines for NSCLC).[466,468,480,501-506] 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;[507,508] the ACR Practice Parameters and Technical Standards are also a helpful reference.[486,509,510] 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*).[511] 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.[512-516]

The normal tissue dose constraints for conventionally fractionated RT are 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).[473,517-522] These constraints are mainly empirical and have not, for the most part, been validated rigorously.[501,521,523-528] 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).[529,530] 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.[518,531-535] In this trial and subsequent retrospective analyses, higher dose to the heart and specific cardiac substructures, such as the coronary arteries, was associated with increased mortality.[535-541] Although optimal RT dose intensification remains a valid question, the NCCN Panel does not currently recommend a high dose of 74 Gy for routine use.[532,534,535,537-545]

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, preferably 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).[404,405,408,483,546,547] SABR is also an option for patients at high surgical risk who cannot tolerate a lobectomy because of a major medical comorbidity and/or severely limited lung function. After definitive RT (preferably SABR), adjuvant chemotherapy may be considered in patients with high-risk factors for recurrence (eg, large tumor size), similar to the postoperative setting.[406,548-550] Image-guided thermal ablation (eg, cryotherapy, microwave, radiofrequency ablation [RFA]) is an option for selected patients who are medically inoperable and will not receive SABR or definitive RT (see *Principles of Image-Guided Thermal Ablation Therapy* in the NCCN Guidelines for NSCLC).[384,551-557] Resection is recommended for patients with early-stage NSCLC who are medically fit

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(see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).[558] The indications for using preoperative or postoperative chemoradiation, systemic therapy, 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, with concurrent postoperative RT for patients with positive margins, or followed by postoperative RT in selected patients with high-risk features.

Definitive chemoradiation is recommended for patients with stage II to III disease who are not appropriate surgical candidates.[559] 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.[560] Involved-field RT (also known as involved-field irradiation or IFI) is recommended for treating nodal disease in patients with locally advanced NSCLC (over the older standard of elective nodal irradiation, or ENI).[561-568]

The optimal care 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).[445,447,452,459,569] Before surgical resection of stage IIIA NSCLC, induction systemic therapy or induction chemoradiotherapy is recommended to potentially shrink the tumor(s).[452,463] Preoperative systemic therapy and postoperative RT is an option for patients with resectable stage IIIA NSCLC with minimal N2 disease who can be treated with lobectomy.[451,464] Preoperative concurrent chemoradiation is recommended for resectable superior sulcus tumors and is an option for other resectable stage IIA to IIIA NSCLC.[503] In a 2021 survey of the NCCN Member Institutions, we found that 66% use induction chemotherapy, whereas 33% use induction chemoradiation before surgery for patients with stage IIIA N2 disease.[463,464] The NCCN NSCLC Panel recommends a preoperative RT dose of 45 to 54 Gy in 1.8 to 2 Gy fractions over 5 weeks.[451,570] Definitive RT doses delivered as preoperative chemo/RT can safely be administered and achieve promising nodal clearance and survival rates;[504-506,571] the risk of surgical complications after high-dose RT can be minimized with expert thoracic surgical techniques. About 50% of NCCN Member Institutions would consider pneumonectomy after preoperative chemotherapy, whereas only 25% do not consider pneumonectomy absolutely contraindicated after preoperative induction chemoradiation.

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.[504-506] 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. In postoperative RT, the clinical target volume (CTV) includes the bronchial stump and high-risk draining lymph node stations.[572] Standard RT doses after complete resection are 50 to 54 Gy in 1.8 to 2 Gy fractions over 5 to 6 weeks, but a boost may be considered to high-risk regions including areas of nodal extracapsular extension or microscopic positive margins.[467,573,574] Lung dose constraints should be more conservative, because tolerance appears to be reduced after surgery. The LungART

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and PORT-C trials provide useful guidelines for postoperative RT technique.[450,453,575] Highly conformal techniques (such as IMRT or proton therapy) to minimize lung and heart doses are preferred.

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) (see *Therapy for Recurrence and Metastases* in the algorithm).[483,576-578] 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 in 1–2 weeks), 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).[579-582] 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.[576,583] 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 limited metastatic sites or disease burden; management is evolving. Definitive local therapy to oligometastases (including brain and lung) achieves prolonged survival in a small proportion of well-selected patients with PS 0 to 2 who have also received radical therapy to the intrathoracic disease.[584] Definitive RT to oligometastases, particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.[585,586] In two 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.[587,588] Updated data from one of the trials also show 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).[589] 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).[590] 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.[587-589]

Stereotactic Ablative Radiotherapy

SABR (also known as SBRT) uses short courses of highly conformal and dose-intensive (ablative) RT precisely delivered to limited-size targets.[404,591-594] SABR has achieved good primary tumor control rates and overall survival that is higher than conventionally fractionated RT.[404] 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.[408,595-599] 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%.[405] 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.[384,405,499,557,558,598,600-605] 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.[546] 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.

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Although SABR is not proven equivalent to lobectomy for patients with operable early-stage NSCLC, some prospective series have shown similar overall survival and cancer-specific survival.[471,595,597,606] A combined analysis of two randomized trials (that individually did not complete accrual) compared SABR to lobectomy, with 3-year overall survival of 95% and 79%, respectively.[606] A single-arm SABR expansion cohort of one of the trials with longer follow-up compared non-randomly to a propensity-matched contemporary cohort treated with VATS lobectomy with mediastinal lymph node dissection and found 5-year overall survival of 87% and 84%, respectively.[471] These analyses do not provide sufficient data to change the standard of care for good surgical candidates but help to confirm the indication for SABR in patients with relative contraindications to surgery or those who refuse surgery. SABR can also be used for patients with limited lung metastases or limited metastases to other body sites.[592,599,607-613]

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, older, or refuse surgery after appropriate consultation (see the NCCN Guidelines for NSCLC).[384,599,601,606,614] If possible, biopsy should confirm NSCLC before use of SABR.[404,615,616] Decisions about whether to recommend SABR should be based on multidisciplinary discussion. If therapy is contemplated based on a clinical diagnosis without tissue confirmation of NSCLC, then multidisciplinary evaluation is required to provide consensus on the risk-benefit ratio of biopsy and/or the clinical diagnosis.[617,618] By analogy with surgical treatment, adjuvant chemotherapy may be considered after definitive RT, preferably SABR, in patients with high-risk factors for recurrence (eg, large tumor size).[406,548-550]

Locoregional recurrences can occur after SABR.[558,597,619-624] Late recurrences have been reported more than 5 years after SABR, highlighting the need for careful surveillance.[625,626] 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.[627,628] This careful follow-up is particularly relevant, because selected patients with recurrences after SABR may benefit from surgery or re-treatment with SABR.[625,629-633]

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).[404,596,598,605,634-644] In the United States, only regimens of 5 fractions or less meet the arbitrary billing code definition for SBRT; however, slightly more protracted ablative regimens are also appropriate.[644,645] Prescription doses do not completely describe the actual delivered doses.[646,647] These maximum dose constraints are for reference 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—defined variably as within 2 cm of the proximal bronchial tree and/or abutting mediastinal pleura—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).[406,637,648-650] The RTOG 0813 trial evaluated 5-fraction regimens and found no high-grade toxicities at 50 Gy in 5 fractions.[651,652]

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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 IVA, M1b* in the NCCN Guidelines for NSCLC).[394,585,586,599,653-656] SRS or SABR can be considered for select patients with stage M1c disease who have limited metastases that are amenable to treatment with definitive local therapy; clinical trials have included up to 3 to 5 metastatic sites.[653,654] For patients with disease progression on targeted therapy for *ALK* rearrangements, *ROS1* rearrangements, or the common *EGFR* mutations (ie, exon 19 deletion or exon 21 L858R), consideration of local therapy (eg, surgery or SABR [or SRS]) is recommended for limited progression.[657-660] Hypofractionated or dose-intensified conventional 3D-CRT is a less preferred option if an established SABR program is not available.[661-663] Nonrandomized clinical data indicate that local tumor control with SABR is higher than with image-guided thermal ablation techniques. Image-guided thermal ablation (ie, cryotherapy, microwave, radiofrequency) may be an option for selected patients who will not be receiving SABR or definitive RT.[384,408,557]

Whole Brain RT and Stereotactic Radiosurgery

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.[664,665] Control of brain metastases preserves neurocognitive function.[666,667] However, whole brain RT is itself associated with measurable declines in neurocognitive function in clinical trials, particularly with increasing dose and advanced age of the patient.[668-670] For limited brain 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.[667,671] Thus, SRS alone is recommended for patients with limited brain metastases.[237] 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.[236] 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%; $P < .001$). Resection followed by SRS to the cavity (instead of resection followed by whole brain RT) may decrease the risk of neurocognitive impairment.[672,673] A randomized trial demonstrated that using IMRT to avoid the hippocampus decreases memory impairment after whole brain RT.[674] 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.[675] 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.[676,677]

Treatment options for 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 Central Nervous System Cancers, available at www.NCCN.org). Selected patients include those with symptomatic lesions or whose tumor tissue is needed for diagnosis.[236,610,665,678-684] 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.[678,685-687] Treatment should be individualized for patients with recurrent or progressive brain lesions.[688] For extensive brain metastases, whole brain RT (with hippocampal avoidance if eligible) and memantine are recommended (see the NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).[237-240]

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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 medically inoperable or high-risk 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.[689-692] 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 With or Without Immunotherapy Followed by Surgery* in this Discussion).[445,693-699] A randomized trial found no difference in survival with preoperative versus postoperative chemotherapy.[700] The NCCN Guidelines state that patients with stage II or IIIA (T3,N1) disease may be treated with induction systemic therapy before surgery if they would have been candidates for adjuvant chemotherapy after surgery.[384,701] Concurrent chemoradiation is more efficacious than sequential chemoradiation for patients with unresectable stage III disease.[702-705] Cytotoxic chemotherapeutic agents can cause hair loss, which is distressing for patients. Hair loss varies depending on the systemic 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.[706-710]

For patients with stage IV disease who have a good PS, platinum-based chemotherapy with or without immunotherapy is beneficial.[711-718] 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 receiving systemic therapy alone.[719,720] Patients should receive treatment for debilitating symptoms.[664,721,722] A study also suggests that social support, such as being married, is as effective as systemic therapy.[723] Data suggest that systematic symptom monitoring during outpatient chemotherapy treatment increases overall survival when compared with usual care.[724-726] Surgery is rarely recommended for patients with stage IV disease. However, surgical resection of limited brain progression 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).[727] Definitive local therapy with surgical resection or RT is recommended for limited single-organ progression located in sites other than the brain if definitive thoracic therapy is feasible (see *Stage IVA, M1b* in the NCCN Guidelines for NSCLC).[394,584,587,589,599,653,654] The trials supporting the recommendations for combined modality therapy are discussed in the following sections.

Surgery Followed by Adjuvant Therapy

Chemotherapy

The International Adjuvant Lung Cancer Trial (IALT) assessed cisplatin-based postoperative therapy in patients with completely resected stage I, II, or III NSCLC.[690] 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.[728] Data show that postoperative chemotherapy prevents recurrences.

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The NCIC CTG JBR.10 trial and the ANITA trial compared the effectiveness of postoperative vinorelbine plus 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 plus cisplatin or to observation.[691] 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 was 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.[729] In patients with stage II disease receiving postoperative chemotherapy, median survival was 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 plus cisplatin or to observation.[692] Grade 3 and 4 toxicities were manageable in the chemotherapy group; seven 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.[692] 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 plus cisplatin to be the preferred regimen for completely resected early-stage NSCLC based on the number of trials and the amount of use;[730] however, most clinicians in the United States prefer to use regimens with less toxicity.[731,732]

A meta-analysis of 4584 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).[733] A subgroup analysis found that cisplatin plus vinorelbine also increased survival.[730] The benefit was greater in patients with stage II and III disease and with good PS. Postoperative chemotherapy benefited older patients up to 80 years of age.[389,734]

The CALGB 9633 trial assessed paclitaxel plus carboplatin in patients with stage IB (T2a,N0,M0) lung cancer.[735-737] In this trial, 344 patients were randomly assigned either to paclitaxel plus 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), although 3-year survival was significant (80% vs. 73%, *P*=.02).[736,737] Thus, the carboplatin and paclitaxel regimen is only recommended for early-stage disease if patients cannot tolerate cisplatin (see *Perioperative Systemic Therapy* in the NCCN Guidelines for NSCLC).[738] It is important to note that the CALGB trial was underpowered for patients with stage 1B disease.[739]

TREAT, a phase 2 randomized study, assessed cisplatin plus pemetrexed versus cisplatin plus vinorelbine as postoperative therapy for patients with completely resected stages IB to III NSCLC.[731] Data showed that cisplatin plus pemetrexed was an effective, less toxic regimen compared with cisplatin plus vinorelbine; in addition, patients were able to receive more cycles of cisplatin plus pemetrexed compared with cisplatin plus vinorelbine.[731] Overall survival at 3 years was similar between the arms (75% vs. 77%; *P* = .858).[740]

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The NCCN NSCLC Panel does not recommend postoperative chemotherapy for resected stage IA disease based on the trials described in the previous paragraphs.[741] Postoperative chemotherapy is recommended for high-risk, margin-negative, stage IB disease. Recommended chemotherapy regimens for preoperative and postoperative (perioperative) chemotherapy for patients with completely resected stages IB to III NSCLC are provided in the NCCN Guidelines; the regimens also include specific dosing (see *Perioperative Systemic Therapy* in the NCCN Guidelines for NSCLC).[689,741]

The NCCN NSCLC Panel has preference stratified all the systemic therapy regimens and decided that cisplatin plus pemetrexed is the preferred neoadjuvant or adjuvant option for nonsquamous NSCLC if patients are not candidates for ICIs (see *Perioperative Systemic Therapy* in the NCCN Guidelines for NSCLC).[731,740] Cisplatin plus gemcitabine or cisplatin plus docetaxel are the preferred perioperative chemotherapy options for patients with squamous cell NSCLC.[742,743] Other recommended options include cisplatin plus vinorelbine or cisplatin plus etoposide.[690-692] Perioperative therapy options for patients who are not candidates for cisplatin-based therapy are preference stratified as useful in certain circumstances and include: 1) carboplatin plus paclitaxel; 2) carboplatin plus gemcitabine; and 3) carboplatin plus pemetrexed (but only for nonsquamous NSCLC).[744-747] Neoadjuvant therapy is also known as preoperative (or induction) therapy; adjuvant therapy is also known as postoperative therapy.

Targeted Therapy

ADAURA, a phase 3 randomized trial, assessed adjuvant therapy with osimertinib versus placebo in 682 patients with resected stage IB to IIIA *EGFR* mutation-positive NSCLC.[748] At 24 months, 89% (95% CI, 85%–92%) of the osimertinib group and 52% (95% CI, 46%–58%) of the placebo group were alive and disease-free (overall HR for disease recurrence or death, 0.20; 99.12% CI, 0.14–0.30; $P < .001$). At 24 months, 98% (95% CI, 95%–99%) of the osimertinib group and 85% (95% CI, 80%–89%) of the placebo group were alive and did not have CNS disease (overall HR for disease recurrence or death, 0.18; 95% CI, 0.10–0.33). For patients with stage IB NSCLC, 88% (95% CI, 78%–94%) of the osimertinib group and 71% (95% CI, 60%–80%) of the placebo group were alive and disease-free at 24 months (overall HR for disease recurrence or death, 0.39; 95% CI, 0.18–0.76). For patients with stage II NSCLC, 91% (95% CI, 82%–95%) of the osimertinib group and 56% (95% CI, 45%–65%) of the placebo group were alive and disease-free at 24 months (overall HR, 0.17; 95% CI, 0.08–0.31). For those with stage IIIA NSCLC, 88% (95% CI, 79%–94%) of the osimertinib group and 32% (95% CI, 23%–41%) of the placebo group were alive and disease-free at 24 months (overall HR, 0.12; 95% CI, 0.07–0.20). Data were also reported for those who received adjuvant chemotherapy and those who did not; 60% (410/682) of patients received adjuvant chemotherapy.[749] Overall survival data are not yet available. Serious adverse events were reported in 16% (54/339) of patients receiving osimertinib versus 12% (42/343) receiving placebo. Ten patients (3%) receiving osimertinib had interstitial lung disease versus no patients in the placebo group. There were no deaths in the osimertinib group versus one in the placebo group.

The NCCN Panel recommends osimertinib as an adjuvant therapy option for eligible patients with completely resected (R0) stage IB to IIIA, and stage IIIB (only T3,N2) *EGFR* mutation-positive NSCLC who have previously received adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy based on clinical trial data and FDA approval.[748] Osimertinib is recommended in this setting for *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations, which are the most common *EGFR* mutations. Although it is technically easier to use a resected specimen to do molecular testing, it is also acceptable to use initial diagnostic biopsy specimens. For the 2023 update (Version 1), the NCCN

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Panel expanded the criteria to include patients with stage IIIB (only T3,N2) NSCLC based on differences between the AJCC staging systems for the 7th and 8Th editions (see Table 3 in the algorithm).[159] Although the 8th edition of the AJCC staging manual is currently being used, the clinical trial used the 7th edition.

Immunotherapy

Trial Data

IMpower010, a phase 3 randomized trial, assessed adjuvant therapy with atezolizumab versus best supportive care in 1005 patients with resected early-stage NSCLC and various PD-L1 levels who had received adjuvant chemotherapy.[750] In patients with resected stage II to IIIA NSCLC and PD-L1 of 1% or more, disease-free survival was improved in those receiving adjuvant atezolizumab compared with best supportive care (HR, 0.66; 95% CI, 0.5–0.88; *P* = .0039). Treatment-related grade 3 and 4 adverse events were reported in 11% (53/495) of patients; 4 deaths occurred (1%, 4/495). Atezolizumab is an ICI that inhibits PD-L1 receptors.

PEARLS/KEYNOTE 091, a phase 3 randomized trial, assessed adjuvant therapy with pembrolizumab versus placebo in 1177 patients with completely resected stage IB to IIIA NSCLC (based on AJCC 7th edition).[751] Most patients (86%) received adjuvant platinum-based chemotherapy after resection but had not received neoadjuvant chemotherapy or radiotherapy. In patients who received adjuvant chemotherapy after resection, the median disease-free survival was 53.6 months (95% CI, 39.2–not reached) in those receiving adjuvant pembrolizumab compared with 42.0 months (95% CI, 31.3–not reached) in those receiving placebo (HR, 0.76; 95% CI, 0.63–0.91). Grade 3 or worse events included hypertension (6%) and pneumonia (2%). In patients receiving pembrolizumab, there were four fatal (1%) treatment-related adverse reactions, including myocarditis and cardiogenic shock, septic shock and myocarditis, pneumonia, and sudden death. Pembrolizumab is an ICI that inhibits PD-1 receptors.

NCCN Recommendations

The NCCN Panel recommends atezolizumab as an adjuvant therapy option for eligible patients with completely resected (R0) stage IIB to IIIA, stage IIIB (only T3,N2), or high-risk stage IIA NSCLC and with PD-L1 of 1% or more who are negative for certain biomarkers—*EGFR* exon 19 deletions, *EGFR* exon 21 L858R mutations, and *ALK* rearrangements—and who have previously received adjuvant chemotherapy based on clinical trial data and FDA approval.[750] For the 2023 update (Version 2), the NCCN Panel added a recommendation for adjuvant pembrolizumab for eligible patients with completely resected stage IIB to IIIA, stage IIIB (only T3,N2), or high-risk stage IIA NSCLC who are negative for *EGFR* exon 19 deletions, *EGFR* exon 21 L858R mutations, or *ALK* fusions and who have previously received adjuvant chemotherapy.[751] The panel added a caveat that the benefit of adjuvant pembrolizumab is unclear for patients with PD-L1 levels less than 1%.

For the 2023 update (Version 1), the NCCN Panel expanded the molecular testing criteria to include *ALK* rearrangements because patients with *ALK* rearrangements, *EGFR* exon 19 deletions, or *EGFR* exon 21 L858R mutations have less benefit from ICIs.[184] Clinical trials are assessing whether ALK inhibitors are effective in this setting.[752-758] The NSCLC Panel also clarified that single-agent therapy with osimertinib is recommended if patients have both *EGFR* mutations and PD-L1 of 1% or more; the panel does not recommend using single-agent therapy with atezolizumab or combination therapy with osimertinib plus atezolizumab in this setting. The NCCN Panel also added a recommendation that patients should be evaluated for perioperative (neoadjuvant or adjuvant) therapy before surgery. For the 2023 update (Version 1), the NCCN Panel

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expanded the criteria to include patients with stage IIIB (only T3,N2) disease as previously described.

Preoperative Chemotherapy With or Without Immunotherapy 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 three arms.[698] IFCT 0002, 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.[700]

Several trials suggest that preoperative therapy is beneficial in patients with N2 disease.[445,452,697] Other trials suggest that preoperative therapy is beneficial in patients with earlier stage disease.[694,695,699] A randomized intergroup trial (SWOG 9900) evaluated preoperative paclitaxel plus 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 two arms.[699]

Scagliotti et al published a phase 3 trial of preoperative cisplatin plus 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 preoperative chemotherapy (HR, 0.63).[694] Song et al published a meta-analysis of 13 randomized clinical trials evaluating preoperative chemotherapy followed by surgery versus surgery alone in resectable NSCLCs (overall survival: HR, 0.84; 95% CI, 0.77–0.92; P = .0001).[693] These results are similar to those reported in another meta-analysis (HR, 0.89; 95% CI, 0.81–0.98; P = .02).[694] The benefit from preoperative chemotherapy is similar to that attained with postoperative chemotherapy.[694,698,700,733]

CheckMate 816, a phase 3 randomized trial, assessed neoadjuvant therapy with nivolumab plus platinum-doublet chemotherapy versus chemotherapy alone in 358 patients with resectable (tumors ≥4 cm or node positive) NSCLC (stage IB–IIIA resectable NSCLC using AJCC staging, 7th edition).[107] Chemotherapy regimens included 1) cisplatin plus either pemetrexed (nonsquamous only) or gemcitabine (squamous only); or 2) carboplatin plus paclitaxel (any histology). If their patients could not tolerate cisplatin, clinicians could substitute carboplatin-based regimens. Patients had good PS (0–1) and did not have *EGFR* or *ALK* alterations. The median event-free survival was 31.6 months (95% CI, 30.2–not reached) for nivolumab plus chemotherapy versus 20.8 months (95% CI, 14.0–26.7) for chemotherapy alone (HR, 0.63; 97% CI, 0.43–0.91; P=.005). The pathologic complete response was 24% (95% CI, 18%–31%) with nivolumab plus chemotherapy versus 2.2% (95% CI, 0.6%–5.6%) with chemotherapy alone (odds ratio 13.9; 99% CI, 3.49–55.7; P<.001). The major pathologic response was 36.9% with nivolumab plus chemotherapy versus 8.9% with chemotherapy alone (major pathologic response, ≤10% viable tumor in lung and lymph nodes). The overall response rate was 53.6% for nivolumab plus chemotherapy versus 37.4%

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with chemotherapy alone. Surgery was done for 83% of patients receiving nivolumab plus chemotherapy versus 75% of those receiving chemotherapy alone. Grade 3 to 4 treatment-related adverse events occurred in 33.5% of patients receiving nivolumab plus chemotherapy versus 36.9% of those receiving chemotherapy alone.

NADIM, a single-arm phase 2 study, assessed neoadjuvant therapy with nivolumab plus paclitaxel plus carboplatin in 46 patients with surgically resectable stage IIIA NSCLC; 41 patients had resection.[759,760] At 36 months, updated results show that overall survival was 81.9% (95% CI, 66.8%–90.6%).[759] TMB and PD-L1 levels were not predictive of survival. Grade 3 or higher adverse events were reported in 30% (14/46) of patients including increased lipase (3/46, 7%) and febrile neutropenia (3/46, 7%). None of the adverse events were associated with death or delays in surgery.

NCCN Recommendations

Based on clinical trial data, the NCCN Panel recommends that certain patients who are likely to receive adjuvant chemotherapy may instead be treated with preoperative (also known as induction or neoadjuvant) systemic therapy after surgical evaluation.[694,698,700,733] The NCCN Panel recommends nivolumab plus platinum-doublet chemotherapy as a neoadjuvant systemic therapy option for eligible patients with resectable (tumors ≥4 cm or node positive) NSCLC and no contraindications to treatment with PD-1/PD-L1 inhibitors based on clinical trial data and FDA approval.[107,760] For the 2023 update (Version 1), the panel added a recommendation that all patients should be evaluated for neoadjuvant therapy with strong consideration for those with node-positive disease or tumors 4 cm or more and no contraindications for ICIs. However, neoadjuvant therapy should not be used to attempt to induce resectability in patients who do not already meet criteria for resectability on initial evaluation. Some oncogenic drivers—such as *EGFR* exon 19 deletions, *EGFR* exon 21 L858R mutations, or *ALK* rearrangements—have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.[184] Testing for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements is recommended before administering neoadjuvant nivolumab plus platinum-doublet chemotherapy in eligible patients with stage IB (only tumors = 4 cm) to IIIA, or stage IIIB (only T3, N2) NSCLC. For the 2023 update (Version 1), the NCCN Panel expanded the criteria to include patients with stage IIIB (only T3,N2) NSCLC as previously described. The chemotherapy regimens that may be used with neoadjuvant nivolumab include: 1) cisplatin plus either pemetrexed (nonsquamous only), gemcitabine (squamous only), or paclitaxel (any histology); or 2) carboplatin plus either pemetrexed (nonsquamous only), gemcitabine (squamous only), or paclitaxel (any histology).[107]

Chemoradiation

The major controversies in NSCLC relate to the care 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 three 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.[761-766]

Two randomized trials assessed postoperative RT in patients with clinical stage I or II disease that was upstaged surgically to N2.[450,453] LungART, a phase 3 randomized trial, assessed postoperative RT versus no postoperative RT in 501 patients with completely resected stage IIIA (N2) NSCLC who had received either neoadjuvant (14%) or adjuvant chemotherapy (75%).[450] The median disease-free survival was 30.5 months (95% CI, 24–49) in the postoperative RT group versus 22.8 months (95% CI, 17–37) in the control group (HR, 0.86; 95% CI, 0.68–1.08; *P* = .18). Common grade 3 to 4 adverse events included pneumonitis

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(postoperative RT: 5% [13/241]; control: <1% [1/246]); lymphopenia (postoperative RT: 4% [9/241]; control: 0); and fatigue (postoperative RT: 3% [6/241]; control: <1%). Late-grade 3 to 4 cardiopulmonary toxicity occurred in 11% (26/241) of patients in the postoperative RT group versus 5% (12/246) in the control group. Three patients died in the postoperative RT group (2, pneumonitis; 1, sepsis).

PORT-C, a phase 3 randomized trial, assessed postoperative RT versus no postoperative RT in 394 patients with completely resected stage IIIA (N2) NSCLC who had received adjuvant chemotherapy.[453] The 3-year disease-free survival rates were 40.5% with postoperative RT versus 32.7% with no RT (median, 22.1 vs. 18.6 months) (HR, 0.84; 95% CI, 0.65–1.09; $P = .20$). The 3-year overall survival rates were 78.3% in patients receiving postoperative RT versus 82.8% with no RT (HR, 1.02; $P = .93$). The 3-year local recurrence only rates were 9.5% and 18.3%, respectively (Fine-Gray HR, 0.55; Gray test $P = .04$). No radiotherapy-related grade 4 or 5 adverse events were reported.

Data from the LungART and PORT-C trials show that postoperative RT (also known as PORT) did not improve survival compared with no postoperative RT, although locoregional control was significantly improved.[450,453] For the 2023 update (Version 1), the NCCN Panel clarified that postoperative RT may be considered for select patients with high-risk N2 disease such as extracapsular extension, multi-station involvement, inadequate lymph node dissection or sampling, and/or refusal of or intolerance to adjuvant systemic therapy.[450,453,761,767] To minimize potential lung and heart toxicities, highly conformal RT techniques such as IMRT or proton therapy are preferred.[466,530,768,769]

For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is more efficacious than RT alone.[762,763,765,766,770] Concurrent chemoradiation is more efficacious than sequential chemoradiation.[702-705,771] 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.[772,773] Sequential chemoradiation or RT alone is recommended for frail patients who cannot tolerate concurrent chemoradiation.[387,774]

JCOG0301, a phase 3 randomized trial, assessed chemoradiation using low-dose carboplatin versus RT alone in patients (>70 years) with unresectable NSCLC.[775] 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 chemoradiation 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 chemoradiation 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%]). In older patients receiving chemoradiation versus RT alone, long-term follow-up data for overall survival continue to support using chemoradiation (HR, 0.74; 95% CI, 0.55–0.99; $P = .024$).[776] Although the optimal sequence is not established, postoperative RT is generally administered after adjuvant chemotherapy or concurrently for positive resection margins.[466,468,469,768]

Concurrent chemoradiation regimens recommended for all histologies for initial treatment include 1) cisplatin plus etoposide; and 2) carboplatin plus paclitaxel (see *Concurrent Chemoradiation Regimens* in the NCCN Guidelines for NSCLC).[532,702,704,777-782] For nonsquamous NSCLC, additional recommended concurrent chemoradiation regimens include pemetrexed plus either carboplatin or cisplatin.[783-785] A weekly paclitaxel plus carboplatin regimen is another chemoradiation option.[532] The different

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options for preoperative, definitive, and postoperative chemotherapy/RT are described in detail in the algorithm. The NCCN NSCLC Panel has preference stratified all the systemic therapy regimens and decided that the following concurrent chemoradiation options are preferred for patients with NSCLC: 1) pemetrexed plus either carboplatin or cisplatin for nonsquamous NSCLC only; 2) carboplatin plus paclitaxel for all histologies; and 3) cisplatin plus etoposide for all histologies. The cisplatin plus vinblastine concurrent regimen is rarely used in the United States; therefore, it is not recommended in the NCCN Guidelines.

The recommended sequential chemoradiation options include cisplatin combined with pemetrexed (nonsquamous only), docetaxel, etoposide, gemcitabine, or vinorelbine. Carboplatin regimens are recommended for patients with comorbidities or those not able to tolerate cisplatin, including 1) carboplatin plus gemcitabine; 2) carboplatin plus paclitaxel; and 3) carboplatin plus pemetrexed (nonsquamous only). The NCCN NSCLC Panel has preference stratified all the systemic therapy regimens and decided that the following sequential chemoradiation options are preferred for patients with NSCLC: 1) pemetrexed plus cisplatin for nonsquamous NSCLC only; 2) cisplatin plus gemcitabine for squamous histology; and 3) cisplatin plus docetaxel for squamous histology.

Durvalumab

Durvalumab is a human ICI antibody that inhibits PD-L1 (see *PD-L1 Expression Levels* and *Immune Checkpoint Inhibitors* in this Discussion).[358-360,363] 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) but without disease progression after treatment with 2 or more cycles of definitive concurrent platinum-based chemoradiation.[363,786] Eligible patients received adjuvant durvalumab after treatment with concurrent chemoradiation (1–42 days). Most patients either currently or previously smoked cigarettes and did not have *EGFR* mutations; their PD-L1 status was typically less than 25% or unknown. 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.[787] An updated analysis of this trial reported that overall survival was increased after durvalumab consolidation (47.5 months; 95% CI, 38.4–52.6) compared with placebo (29.1 months; 95% CI, 22.1–35.1) (stratified HR for death, 0.72; 95% CI, 0.45–0.68).[16,786] After 5 years, 42.9% of patients who received durvalumab were alive versus 33.4% of those who received placebo.[13] In addition, 42.9% were alive after 5 years if they had received durvalumab and 33% were alive and free of disease progression compared with 19% of those who received placebo. The subgroup analyses were limited by small sample size and were not powered to assess efficacy. Patients receiving durvalumab received less subsequent immunotherapy (11.6%) compared with those who received placebo (28.3%).

The NCCN NSCLC Panel recommends durvalumab (category 1) as a consolidation immunotherapy option (regardless of PD-L1 status) for eligible patients (PS 0–1) with unresectable stage III NSCLC and without disease progression after treatment with definitive concurrent platinum-based chemoradiation based on this trial and FDA approval.[363,786] It is important to note that durvalumab is used as an adjuvant treatment option in this setting; it is not used as second-line therapy. Durvalumab may be used as a consolidation immunotherapy option after treatment with any of the concurrent chemoradiation regimens described in the algorithm (eg, cisplatin plus etoposide, carboplatin plus paclitaxel) (see *Concurrent Chemoradiation Regimens* in the NCCN Guidelines for NSCLC). Ten patients with stage II NSCLC were included in the PACIFIC trial, which used the older AJCC staging criteria (7th edition). Therefore, the NCCN

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NSCLC Panel also recommends durvalumab as a consolidation immunotherapy option (regardless of PD-L1 status) for eligible patients (PS 0–1) with unresectable stage II NSCLC and without disease progression after treatment with definitive concurrent platinum-based chemoradiation.

A few of the recommended concurrent chemoradiation regimens have an option for additional cycles (2 or 4) of chemotherapy after radiation, which is termed consolidation chemotherapy (see *Concurrent Chemoradiation Regimens* in the NCCN Guidelines for NSCLC).[503,532,778,783] If patients will be receiving durvalumab, the NCCN NSCLC Panel does not recommend 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, depending on the initial regimen.

Systemic Therapy

Chemotherapy

Patients with metastatic (stage IV) NSCLC (who have a good PS) benefit from chemotherapy, usually with a platinum-based regimen, which was the only treatment option for many years before the advent of targeted therapy and immunotherapy regimens.[715-717] If patients are not eligible for the targeted therapy or immunotherapy regimens, then chemotherapy regimens are recommended. Combination chemotherapy regimens produce 1-year survival rates of 30% to 40% and are more efficacious than single agents.[738,743,788-790] However, survival rates are higher for patients with stage IV NSCLC who are eligible for either the newer targeted therapy or immunotherapy regimens.[9,14-27] Phase 3 randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.[791,792] The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients.[743,793-799] Non–platinum-based regimens are also options, such as 1) gemcitabine plus vinorelbine, or 2) gemcitabine plus docetaxel.[800-803] The prognosis for stage IV inoperable lung cancer remains poor if patients are not candidates for targeted therapy or immunotherapy regimens.

In the United States, frequently used initial cytotoxic regimens for stage IV nonsquamous NSCLC include: 1) cisplatin (or carboplatin) plus pemetrexed; or 2) carboplatin plus paclitaxel with (or without) bevacizumab.[777,804,805] Gemcitabine plus cisplatin (or carboplatin) is often used for patients with stage IV squamous cell NSCLC.[790,795,804,805] These chemotherapy regimens are recommended based on phase 3 randomized trials (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).[790,806] 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).[807,808]

A phase 3 randomized trial assessed cisplatin plus pemetrexed versus cisplatin plus gemcitabine as first-line therapy in patients with stage IIIB or IV NSCLC.[790] For patients with adenocarcinoma who received cisplatin plus pemetrexed, median overall survival was 12.6 months compared with 10.9 months for those receiving cisplatin plus gemcitabine (HR, 0.84; 95% CI, 0.71–0.99; P = .03). In contrast, for patients with squamous cell NSCLC who received cisplatin plus pemetrexed, overall survival was 9.4 versus 10.8 months for those receiving cisplatin plus gemcitabine (HR, 1.23; 95% CI, 1.00–1.51; P = .05). Patients with nonsquamous NSCLC

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receiving cisplatin plus pemetrexed had less toxicity when compared with those receiving cisplatin plus gemcitabine.[809] 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 plus cisplatin as first-line therapy for patients with stage IIIB or IV NSCLC.[743] 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 plus vinorelbine (24.5%; *P* = .029); docetaxel plus 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).[790,810] There are no agents for the prevention of peripheral neuropathy, and few agents are useful for treatment.[811] The POINTBREAK trial showed that carboplatin plus pemetrexed plus bevacizumab is a reasonable option for patients with metastatic NSCLC and confirmed that taxane-based regimens are more toxic than pemetrexed-based regimens.[812] 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 plus paclitaxel does not increase survival in patients ≥ 65 years with advanced nonsquamous NSCLC.[813] However, another retrospective cohort study reported increased survival in older patients.[814] A combined analysis of the ECOG 4599 and POINTBREAK trials found a survival benefit with the addition of bevacizumab to carboplatin plus paclitaxel in patients < 75 years but no benefit in those > 75 years.[815]

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.[816,817] A phase 3 randomized trial in patients with advanced NSCLC reported that an albumin-bound paclitaxel plus carboplatin regimen is associated with less neurotoxicity and improved response rate, when compared with the control arm of paclitaxel plus carboplatin.[818] Based on the trial and FDA approval, the NCCN NSCLC Panel recommends an albumin-bound paclitaxel plus 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 actionable driver mutations (ie, *ALK*, *BRAF* p.V600E, *ERBB2, EGFR*, *KRAS*, *MET*ex14 skipping*, NTRK1/2/3, RET,* and *ROS1)*, PD-L1 expression less than 1%, and contraindications to PD-1 or PD-L1 inhibitors. Chemotherapy regimens may be used as first-line or subsequent therapy options in eligible patients with actionable driver mutations as shown in the algorithm, although they are generally not preferred options. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations. Recommended chemotherapy regimens are based on PS and include platinum agents (eg, cisplatin, carboplatin), taxanes (eg, paclitaxel, albumin-bound paclitaxel, docetaxel), vinorelbine, etoposide, pemetrexed, and gemcitabine. To clarify use of systemic therapy, the NCCN Guidelines list all the combination systemic therapy regimens and single agents that are

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recommended for patients with metastatic NSCLC based 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.[819] For nonsquamous NSCLC or NSCLC NOS, single-agent chemotherapy includes gemcitabine, pemetrexed, or taxanes; combination chemotherapy regimens include carboplatin plus paclitaxel or carboplatin plus pemetrexed.[820-822] Patients with a PS of 2 are often just treated with single-agent chemotherapy because of concerns about toxicity.[823] Treatment with carboplatin plus 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 plus pemetrexed arm.[820,824]

The NCCN NSCLC Panel has preference stratified all the systemic therapy regimens for patients with NSCLC. The newer chemotherapy plus 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 *Immune Checkpoint Inhibitors* 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 plus 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 do not include 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, the following regimens are not recommended in the NCCN Guidelines: carboplatin plus vinorelbine, cisplatin plus vinorelbine, etoposide, irinotecan, and vinorelbine. For patients with metastatic squamous cell NSCLC, the following regimens are not recommended in the NCCN Guidelines: carboplatin plus vinorelbine, cisplatin plus gemcitabine plus necitumumab, cisplatin plus vinorelbine, etoposide, irinotecan, and vinorelbine.

The NCCN NSCLC Panel voted unanimously to not recommend the necitumumab plus cisplatin plus gemcitabine regimen for patients with metastatic squamous cell NSCLC. 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 plus 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).[825] The stratified HR was 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 gemcitabine plus cisplatin (333 [62%] of 541). Although it has been suggested that adding necitumumab

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to cisplatin plus gemcitabine adds value and is cost-effective, the NCCN NSCLC Panel does not agree.[826]

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.[358-360] Cemiplimab-rwlc, nivolumab, and pembrolizumab inhibit PD-1 receptors;[361,362,138] atezolizumab and durvalumab inhibit PD-L1.[363,364] The single-agent immunotherapy or combination immunotherapy plus chemotherapy regimens are not recommended if patients have contraindications to immunotherapy, which may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents. PD-L1 inhibitors are less beneficial in patients with some oncogenic drivers (ie, *EGFR* exon 19 deletions, *EGFR* exon 21 L858R mutations, *ALK* rearrangements).[184] Monitoring is recommended during initial therapy with response assessment with CT, with or without contrast, of known or high-risk sites of disease after 2 cycles and then every 2 to 4 cycles. During maintenance or subsequent therapy, monitoring is also recommended with CT, with or without contrast, every 6 to 12 weeks. ICIs (also known as immunotherapy or IO agents) are associated with a delay in benefit when compared with targeted therapy or cytotoxic chemotherapy.

The NCCN NSCLC Panel recommends IHC testing for PD-L1 expression (category 1) before first-line treatment in all patients with metastatic NSCLC, regardless of histology, based on the efficacy of pembrolizumab with or without chemotherapy.[365] 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* rearrangements). Plasma-based ctDNA testing can be used to evaluate for genomic alterations if the assay has been validated and if the patient is unfit for invasive tissue sampling or if there is insufficient tissue for molecular analyses; however, plasma-based ctDNA testing is 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 (lower response rates) in the first-line setting, targeted therapy is better tolerated, and these patients are less likely to respond to single-agent ICIs.[184,371-373,827] 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 using osimertinib in combination with or following ICIs.[828,829] A few case reports suggest that patients treated with ICIs who have acquired resistance may have transformation to SCLC.[830]

In 2020, the NCCN Panel removed TMB as an emerging immune biomarker for patients with metastatic NSCLC based on clinical trial data, concerns about variable TMB measurements, and other issues as previously described (see *TMB* in this Discussion).[171,375,379] The NCCN Guidelines do not recommend measurement of TMB levels before deciding whether to use nivolumab plus ipilimumab regimens or other ICIs, such as pembrolizumab.[171]

The following content briefly summarizes the use of ICIs as first-line or subsequent therapy options in eligible patients with metastatic NSCLC; detailed information, including clinical trial data, is provided in subsequent sections.[831] ICIs may also be used in other settings; clinical trial data and appropriate use are described in greater detail elsewhere. For example,

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adjuvant atezolizumab or pembrolizumab are recommended following adjuvant chemotherapy for eligible patients with completely resected early-stage NSCLC (see *Surgery Followed by Adjuvant Therapy: Trial Data and NCCN Recommendations* in this Discussion).[750,751] Durvalumab is recommended as a consolidation immunotherapy option for eligible patients with unresectable stage II or III NSCLC and without disease progression after treatment with definitive concurrent chemoradiation (see *Chemoradiation* in this Discussion).[363]

Single-agent pembrolizumab, atezolizumab, or cemiplimab-rwlc are recommended (category 1; preferred) as first-line therapy options for eligible patients with metastatic NSCLC regardless of histology, PD-L1 expression levels of 50% or more, and negative test results for actionable driver mutations that have recommended first-line targeted therapies (ie, *ALK*, *BRAF* p.V600E, *EGFR*, *MET*ex14 skipping*, NTRK1/2/3, RET, ROS1).* The NCCN NSCLC Panel 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 actionable driver mutations.[832]

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 actionable driver mutations, 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 actionable driver mutations, regardless of PD-L1 expression levels. Combination therapy with pembrolizumab plus chemotherapy or with ABCP may be used as first-line or subsequent therapy options, although they are not preferred options, in eligible patients with actionable driver mutations as shown in the algorithm. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations. Continuation maintenance immunotherapy is recommended for 2 years, if tolerated, for all first-line immunotherapy (± chemotherapy) regimens.

If patients have disease progression on PD-1/PD-L1 inhibitor therapy (± chemotherapy), then using a PD-1/PD-L1 inhibitor is not recommended for subsequent therapy.[833] 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. Based on data in the second-line setting, PD-1 or PD-L1 inhibitor monotherapy appears to be less effective in patients with *EGFR* exon 19 deletions, *EGFR* exon 21 L858R mutations, or *ALK* rearrangements, regardless of PD-L1 expression levels.[358,362,827,834,835] 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%.[372] Patients with *ALK*-positive NSCLC and very high PD-L1 expression levels do not respond to pembrolizumab.[184,827] 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

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side effects (see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).[836,837] Atezolizumab, cemiplimab-rwlc, durvalumab, nivolumab, or pembrolizumab should be discontinued for patients with severe or life-threatening pneumonitis or myocarditis 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.[838-840]

Atezolizumab

Atezolizumab is a humanized monoclonal immunoglobulin G1 antibody that inhibits PD-L1, which improves antitumor immune response.[364] Immune-mediated adverse events may occur with ICIs, including atezolizumab.[834,841] 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 or myocarditis and should be discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information). The following sections describe the use of atezolizumab in eligible patients with metastatic NSCLC. The use of adjuvant atezolizumab following adjuvant chemotherapy for eligible patients with completely resected early-stage NSCLC is described in a different section (see *Surgery Followed by Adjuvant Therapy* in this Discussion).[750]

First-Line Therapy

IMpower110, a phase 3 randomized trial, compared first-line therapy with single-agent atezolizumab 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 TC [TC ≥50%] or PD-L1 stained tumor-infiltrating cells [IC] covering ≥10% of the tumor area [IC ≥ 10%]); patients were wild type for *EGFR* or *ALK* variants and most either currently or previously smoked cigarettes.[842,843] Patients receiving first-line atezolizumab monotherapy also received maintenance therapy with atezolizumab. Chemotherapy regimens for patients with nonsquamous NSCLC included cisplatin (or carboplatin) plus pemetrexed and maintenance therapy with pemetrexed; patients with squamous cell NSCLC received cisplatin plus gemcitabine and best supportive care as maintenance therapy. Atezolizumab monotherapy was associated with fatal adverse reactions in 3.8% of all patients (11/286, all 3 groups), including aspiration, COPD, 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%), COPD (2.1%), and pneumonitis (2.1%); 28% of patients had serious adverse reactions.

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.[842,844] Data suggest that different methods of testing for PD-L1 levels are not equivalent.[368,369] Based on an 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 analysis using the 22C3 pharmDx assay, median

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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).[842,844] 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%).

The NCCN NSCLC Panel recommends atezolizumab monotherapy (category 1; preferred) as a first-line therapy option for eligible patients with metastatic NSCLC based on clinical trial data and FDA approval.[842,843] 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 actionable driver mutations, regardless of histology; maintenance therapy with atezolizumab is also recommended in this setting. Cemiplimab-rwlc and pembrolizumab are also recommended first-line therapy options in this setting (category 1; preferred). The NCCN NSCLC Panel has preference stratified the ICI regimens and decided that atezolizumab, cemiplimab-rwlc, and pembrolizumab (all are category 1) are preferred first-line therapy options for eligible patients with metastatic NSCLC based on clinical trial data.[138,361,832,842]

IMpower150, a phase 3 randomized trial, compared first-line therapy with the ABCP regimen versus bevacizumab plus chemotherapy for patients with metastatic nonsquamous NSCLC.[841] 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 plus paclitaxel plus 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 plus bevacizumab (8.3 vs. 6.8 months; HR, 0.62; 95% CI, 0.52–0.74; *P* < .001). Some patients with *EGFR* mutations or *ALK* rearrangements (n = 108) and disease progression 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* rearrangements, PFS was also increased with ABCP compared with chemotherapy plus 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).[845] Therefore, the ABCP regimen may be an option for patients with *EGFR* mutations or *ALK* rearrangements and disease progression after initial therapy with TKIs.

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.[841] The ABCP regimen (also known as the quadruplicate regimen) is recommended as a first-line therapy option for patients with negative test results for actionable driver mutations (ie, *ALK*, *BRAF* p.V600E, *EGFR*, *MET*ex14 skipping, *NTRK1/2/3, RET,* and *ROS1),* regardless of PD-L1 expression levels. Combination therapy with the ABCP regimen may be used as a first-line or subsequent therapy option, although it is not a preferred option, in eligible patients with actionable driver mutations as shown in the algorithm. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations. Maintenance therapy with atezolizumab and bevacizumab is also recommended in this setting (category 1) (see *Maintenance Therapy* in this Discussion). The NCCN NSCLC Panel has 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

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ABCP, that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.[833,846-849]

IMpower130, a phase 3 randomized trial, compared atezolizumab plus carboplatin plus albumin-bound paclitaxel versus chemotherapy alone as first-line therapy in patients with metastatic nonsquamous NSCLC with no *EGFR* mutations or *ALK* rearrangements.[850] 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) in carboplatin plus albumin-bound paclitaxel arm (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 atezolizumab plus carboplatin plus albumin-bound paclitaxel (other recommended intervention) as a first-line therapy option for eligible patients with metastatic nonsquamous NSCLC based on clinical trial data.[850] Atezolizumab plus carboplatin plus albumin-bound paclitaxel is recommended as a first-line therapy option for patients with metastatic NSCLC and negative test results for actionable driver mutations, regardless of PD-L1 levels. The atezolizumab plus carboplatin plus albumin-bound paclitaxel regimen may be used as a first-line or subsequent therapy option, although it is not a preferred option, in eligible patients with actionable driver mutations as shown in the algorithm. Maintenance therapy with atezolizumab is also recommended in these settings. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations.

Subsequent Therapy

OAK, a phase 3 randomized trial, compared atezolizumab versus docetaxel in patients with metastatic NSCLC and disease progression during or after systemic therapy.[834,851] Most patients either currently or previously smoked cigarettes and had received platinum-based chemotherapy; 10% of patients were not reported because they had *EGFR* mutations and *ALK* rearrangements.[834,851] 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.[364,834,851] Nivolumab and pembrolizumab are also recommended subsequent therapy options in this setting (category 1; preferred). Testing for PD-L1 expression levels is not required for prescribing subsequent therapy with atezolizumab or nivolumab but may provide useful information. If patients have progressed on a PD-1/PD-L1 inhibitor, then using a PD-1/PD-L1 inhibitor is not recommended.

Cemiplimab-rwlc

Cemiplimab-rwlc is a recombinant human immunoglobulin G4 monoclonal antibody that inhibits PD-1 receptors, which improves antitumor immune response.[361] Immune-mediated adverse events may occur with ICIs, including cemiplimab-rwlc.[361] For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered

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based on the severity of the reaction. Cemiplimab-rwlc should also be permanently discontinued for patients with grades 2, 3, or 4 myocarditis and should be discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

EMPOWER-Lung 1, a phase 3 randomized trial, compared first-line therapy with single-agent cemiplimab versus platinum-based chemotherapy for patients with metastatic squamous or nonsquamous NSCLC, PD-L1 levels of 50% or more, and negative test results for *EGFR* mutations, *ALK* rearrangements, or *ROS1* rearrangements.[361] Patients receiving first-line cemiplimab also received maintenance therapy with cemiplimab. Median overall survival was not reached for patients receiving cemiplimab (95% CI, 17.9–not evaluable) versus 14.2 months (95% CI, 11.2–17.5) for chemotherapy (HR, 0.57; 95% CI, 0.42–0.77; *P*=.0002). The response rate was 39% (95% CI, 34%–45%) for those receiving cemiplimab versus 20% (95% CI, 16%–26%) for chemotherapy. Of patients treated with cemiplimab, 28% (98/355) had grade 3 to 4 adverse events compared with 39% (135/342) for those treated with chemotherapy. Treated-related deaths occurred in 2.5% (9/355) of patients receiving cemiplimab versus 2.0% (7/342) with chemotherapy. The cemiplimab-related deaths were due to autoimmune myocarditis, cardiac failure, cardiopulmonary failure, cardiorespiratory arrest, nephritis, respiratory failure, septic shock, tumor hyperprogression, and unknown reasons.

The NCCN NSCLC Panel recommends cemiplimab-rwlc monotherapy (category 1; preferred) as a first-line therapy option for eligible patients with metastatic NSCLC regardless of histology, PD-L1 levels of 50% or more, and negative test results for actionable driver mutations based on clinical trial data and FDA approval; maintenance therapy with cemiplimab-rwlc is also recommended.[361] Atezolizumab and pembrolizumab are also recommended first-line therapy options in this setting (category 1; preferred). The NCCN NSCLC Panel has preference stratified the ICI regimens and decided that atezolizumab, cemiplimab-rwlc, and pembrolizumab (all are category 1) are preferred first-line therapy options for eligible patients with metastatic NSCLC based on clinical trial data.[138,361,832,842]

EMPOWER-Lung 3, a randomized phase 3 trial, assessed first-line therapy with cemiplimab plus platinum-based chemotherapy versus platinum-based chemotherapy alone in 466 patients with advanced NSCLC, regardless of PD-L1 levels or histology. The chemotherapy regimens included 1) cemiplimab plus paclitaxel plus either cisplatin or carboplatin for either nonsquamous NSCLC or squamous cell histology; or 2) cemiplimab plus pemetrexed plus either cisplatin or carboplatin for nonsquamous NSCLC.[852] Patients received maintenance therapy if indicated. Most patients (85%) had stage IV NSCLC and 57% had nonsquamous NSCLC. Most patients either currently smoked cigarettes (55%) or had previously smoked (31%). Patients did not have *EGFR*, *ALK*, or *ROS1* mutations. The median overall survival was 21.9 months (95% CI, 15.5–not evaluable) with cemiplimab plus chemotherapy versus 13.0 months (95% CI, 11.9–16.1) with chemotherapy alone (HR, 0.71; 95% CI, 0.53–0.93; *P* = .01). Subgroup analysis showed that overall survival was similar between the groups for PD-L1 levels less than 1%, nonsquamous NSCLC, and other subgroups; however, the trial was not powered to detect differences in efficacy within the subgroups. Grade 3 or higher treatment-related adverse events occurred in 44% (136/312) of patients receiving cemiplimab plus chemotherapy, and 31% (48/153) of patients receiving chemotherapy alone. Immune-related adverse events occurred in 19% of patients receiving cemiplimab plus chemotherapy. Death occurred in 6.1% (19/312) of patients receiving cemiplimab plus chemotherapy versus 7.8% (12/153) of patients receiving chemotherapy alone. One patient died from immune-mediated pneumonitis.

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The NCCN NSCLC Panel recommends cemiplimab-rwlc plus platinum-based chemotherapy regimens as first-line therapy options (category 1; other recommended) for eligible patients with metastatic NSCLC—regardless of histology or PD-L1 levels and with negative test results for actionable driver mutations—based on clinical trial data and FDA approval; maintenance therapy with cemiplimab-rwlc with or without pemetrexed is also recommended.[852] Combination therapy with cemiplimab-rwlc plus platinum-based chemotherapy may be used as a first-line or subsequent therapy option, although it is not a preferred option, in eligible patients with actionable driver mutations as shown in the algorithm. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations. The NCCN Panel has preference stratified the cemiplimab-rwlc plus chemotherapy regimens and decided that they are other recommended first-line therapy options for eligible patients with metastatic NSCLC based on clinical trial data.[852]

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, depending on the setting. Nivolumab is a human immunoglobulin G4 monoclonal antibody that inhibits PD-1 receptors, which improves antitumor immune response.[358,362,138] PD-1 receptors are expressed on activated cytotoxic T cells.[358-360] 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.[853] Immune-mediated adverse events may occur with ICIs, including nivolumab or nivolumab plus ipilimumab.[379] 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 or myocarditis 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 nivolumab.[379]

First-Line Therapy

CheckMate 227, a phase 3 randomized trial with a complex design, compared first-line therapy with nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy for patients with metastatic nonsquamous or squamous NSCLC who had PD-L1 expression levels of 1% or more, PS 0 to 1, and no *EGFR* mutations or *ALK* rearrangements. First-line therapy with nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy alone was also compared for patients with PD-L1 expression levels less than 1%. In addition, first-line therapy with nivolumab plus ipilimumab or chemotherapy was compared as one of the co-primary analyses in patients who had high TMB levels (≥10 mutations/megabase).[378] Preliminary data for PFS from CHECKMATE 227 suggested that TMB might be a useful immune biomarker for deciding whether to use immunotherapy in patients with metastatic NSCLC.[378] However, updated data from CHECKMATE 227 showed that overall survival was improved with nivolumab plus ipilimumab regardless of TMB or PD-L1 expression levels.[379]

The PFS rate at 1 year was 42.6% for nivolumab plus ipilimumab versus 13.2% for chemotherapy alone. The median PFS for nivolumab plus 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

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for nivolumab plus ipilimumab was 45.3% versus 26.9% with chemotherapy alone; nivolumab plus ipilimumab was beneficial regardless of PD-L1 expression levels or histology. The rate of grade 3 or 4 adverse events was similar for nivolumab plus 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).[379] For patients with PD-L1 levels of 1% or more, the 4-year overall survival rate was 29% with nivolumab plus ipilimumab versus 18% for those receiving chemotherapy (HR, 0.76; 95% CI, 0.65–0.90).[854] For patients with PD-L1 levels less than 1%, the 4-year overall survival rate was 24% with nivolumab plus ipilimumab versus 10% for those receiving chemotherapy (HR, 0.64; 95% CI, 0.51–0.81).

The NCCN NSCLC Panel recommends nivolumab plus ipilimumab as a first-line therapy option for eligible patients with metastatic NSCLC based on clinical trial data and FDA approval.[378,379,381] Nivolumab plus ipilimumab is recommended for patients with metastatic NSCLC, regardless of PD-L1 levels or histology, negative test results for actionable driver mutations (ie, *ALK*, *BRAF* p.V600E, *EGFR*, *MET*ex14 skipping, *NTRK1/2/3, RET, ROS1),* and no contraindications to immunotherapy. For patients with PD-L1 levels of 1% or more, the NCCN recommendation is category 1 for nivolumab plus ipilimumab. Nivolumab plus ipilimumab is also a recommended option for patients with PD-L1 levels less than 1%. Maintenance therapy with nivolumab plus ipilimumab is also recommended. Combination therapy with nivolumab plus ipilimumab may be used as a first-line or subsequent therapy option, although it is not a preferred option, in eligible patients with actionable driver mutations as shown in the algorithm. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations.

The NCCN NSCLC Panel has preference stratified the systemic therapy regimens and decided that first-line therapy with nivolumab plus ipilimumab is “useful in certain circumstances” (eg, renal impairment) for patients with PD-L1 levels of 50% or more and is an “other recommended” first-line therapy option for patients with PD-L1 levels less than 50%. For the 2023 update (Version 1), the NCCN Panel revised the preference stratification for first-line therapy with nivolumab plus ipilimumab to an “other recommended” option from useful in certain circumstances in patients with PD-L1 levels of 1% to 49%. Previously, the NCCN Panel deleted TMB as an emerging immune biomarker based on clinical trial data and other issues (see *TMB* in this Discussion).[171] The NCCN Guidelines do not recommend measurement of TMB levels before deciding whether to use nivolumab plus ipilimumab regimens or to use other ICIs, such as pembrolizumab.[171]

CheckMate 9LA, a phase 3 randomized trial, compared first-line nivolumab plus 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* rearrangements.[855] For metastatic nonsquamous NSCLC, the chemotherapy was pemetrexed with either cisplatin or carboplatin; for metastatic squamous NSCLC, the chemotherapy was paclitaxel with carboplatin. Updated data show that the median overall survival with nivolumab plus ipilimumab plus chemotherapy was 15.8 months (95% CI, 13.9–19.7) versus 11.0 months (95% CI, 9.5–12.7) with chemotherapy alone regardless of histology or PD-L1 expression levels (HR, 0.72; 95% CI, 0.61–0.86).[856] In patients receiving nivolumab plus ipilimumab plus

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chemotherapy, the 2-year overall survival rate was 38% versus 26% in those receiving chemotherapy alone. Based on histology or PD-1 levels, overall survival was also significantly different in patients receiving nivolumab plus chemotherapy compared with chemotherapy alone. 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 plus ipilimumab plus chemotherapy versus 15% in those receiving chemotherapy alone. The death rate was 2% in each arm (nivolumab plus ipilimumab plus chemotherapy: 7/358; chemotherapy alone: 6/349). In the nivolumab plus ipilimumab plus 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.

The NCCN NSCLC Panel recommends nivolumab plus ipilimumab plus chemotherapy (category 1; other recommended) as first-line therapy options for eligible patients with metastatic NSCLC based on clinical trial data and FDA approval.[855,857] 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 actionable driver mutations; and no contraindications to PD-1/PD-L1 inhibitors. Maintenance therapy with nivolumab plus ipilimumab is also recommended. Combination therapy with nivolumab plus ipilimumab may be used as a first-line or subsequent therapy option, although it is not a preferred option, in eligible patients with actionable driver mutations as shown in the algorithm. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations. The panel has preference stratified the systemic therapy regimens 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 regardless of PD-L1 expression levels or histology.

Subsequent Therapy

CheckMate-057, a phase 3 randomized trial, compared nivolumab versus docetaxel as subsequent therapy for patients with metastatic nonsquamous NSCLC and disease progression on or after first-line chemotherapy.[358] 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).[358] 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%) for 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 NSCLC

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squamous cell and disease progression on or after first-line chemotherapy.[362] Median overall survival was 9.2 months (95% CI, 7.3–13.3) for nivolumab compared with 6.0 months (95% CI, 5.1–7.3) for docetaxel (HR, 0.59; 95% CI, 0.44–0.79; $P < .001$).[362] 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 three 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.[858] 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%). At 5 years, overall survival was 13.4% for patients receiving nivolumab versus 2.6% for those receiving docetaxel.[17]

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 and disease progression on or after first-line chemotherapy based on clinical trial data and FDA approval.[358,362,858,859] Testing for PD-L1 is not required for prescribing nivolumab but may provide useful information.[370] 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.[358,362,835,860] If patients have progressed on a PD-1/PD-L1 inhibitor, then using a PD-1/PD-L1 inhibitor is not recommended.

Immune-related adverse events, such as pneumonitis, may occur with nivolumab.[360,861-867] 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 or myocarditis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

Pembrolizumab

Pembrolizumab is a humanized immunoglobulin G4 monoclonal antibody that inhibits PD-1 receptors, which improves antitumor immune response.[362,138] 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.[366,367] 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.[366] Unique anti-PD-L1 IHC assays have been developed for each one of the different ICIs currently available.[366,370] The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.[370]

Immune-mediated adverse events may occur with ICIs, including pembrolizumab.[861,863,868] For patients with immune-mediated adverse

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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 or myocarditis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information). The following sections describe the use of pembrolizumab in eligible patients with metastatic NSCLC. The use of adjuvant pembrolizumab following adjuvant chemotherapy in eligible patients with completely resected NSCLC is described in a different section (see *Surgery Followed by Adjuvant Therapy* in this Discussion).[751]

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* rearrangements.[9,12,138] 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%).[138] An updated analysis of KEYNOTE-024 showed that median overall survival was 26.3 months (95% CI, 18.3 months–40.4) with pembrolizumab monotherapy compared with 13.4 months (95% CI, 9.4–18.3 months) with chemotherapy (HR, 0.62; 95% CI, 0.48–0.81).[12] The 5-year overall survival rate was 31.9% for pembrolizumab and 16.3% for chemotherapy. 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%).[9] 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* rearrangements.[832] Overall survival was 20.0 months (95% CI, 15.4–24.9) in patients with PD-L1 levels of 50% or more who received single-agent pembrolizumab compared with 12.2 months (95% CI, 10.4–14.2) with chemotherapy (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; for patients with PD-L1 levels of 50% or more, 5-year overall survival is about 29.6%.[19] Median overall survival was 22.3 months (95% CI, 17.1–32.3) for treatment-naïve patients. For patients with metastatic NSCLC receiving chemotherapy alone, 5-year overall survival is approximately 6%.[19]

The NCCN NSCLC Panel recommends IHC testing for PD-L1 expression (category 1) 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).[365] The 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 actionable driver mutations based on clinical trial data and FDA

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approval.[138,832,869] Maintenance therapy with pembrolizumab is also a recommended option in this setting (category 1). The NCCN NSCLC Panel has preference stratified the ICI regimens and decided that pembrolizumab, atezolizumab, and cemiplimab-rwlc (all are category 1) are all preferred single-agent options for eligible patients with metastatic NSCLC.[138,361,832,842] For patients who have disease progression on first-line therapy with single-agent pembrolizumab, subsequent therapy with initial cytotoxic systemic therapy regimens (eg, carboplatin plus 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 actionable driver mutations based on clinical trial data and FDA approval.[832,869] The NCCN NSCLC Panel decided that single-agent pembrolizumab is a useful intervention in patients with PD-L1 levels of 1% to 49% when there are contradictions to combination 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.

First-Line Combination Therapy

KEYNOTE-189, a phase 3 randomized trial, compared pembrolizumab added to carboplatin (or cisplatin) plus pemetrexed versus chemotherapy in patients with metastatic nonsquamous NSCLC.[711] Most patients received pembrolizumab plus carboplatin plus 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* rearrangements. The estimated rate of overall survival at one year was 69.2% (95% CI, 64.1%–73.8%) in patients receiving pembrolizumab plus 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.[870] 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 plus 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 FDA approval.[711,712] The NCCN NSCLC Panel has preference stratified the systemic therapy regimens and decided that these pembrolizumab plus chemotherapy regimens are preferred first-line options for eligible patients with metastatic nonsquamous NSCLC. These pembrolizumab plus 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 actionable driver mutations, regardless of their PD-L1 expression levels. Maintenance therapy with pembrolizumab plus pemetrexed is also a recommended option (category 1) in this setting. Combination therapy with pembrolizumab plus pemetrexed and either carboplatin or cisplatin may be used as a first-line or subsequent therapy option in eligible patients with actionable driver mutations as shown in the algorithm. However, targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20

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mutations or *KRAS* mutations. For patients with metastatic NSCLC and disease progression on combination therapy with PD-1/PD-L1 inhibitors plus chemotherapy, subsequent therapy with docetaxel (with or without ramucirumab), pemetrexed (nonsquamous only), albumin-bound paclitaxel, 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).[871] 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 plus 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 tumor proportion score (TPS) less than 1%. Grade 3 or higher adverse events were similar in both groups (pembrolizumab plus chemotherapy, 69.8% vs. chemotherapy alone, 68.2%). Because of adverse events, more patients discontinued treatment with pembrolizumab plus chemotherapy than with chemotherapy (13.3% vs. 6.4%, respectively). A pooled analysis of three randomized trials (ie, KEYNOTE-189, KEYNOTE-407, KEYNOTE-021) in patients with metastatic NSCLC and PD-L1 levels less than 1% showed that overall survival was improved in those receiving pembrolizumab plus chemotherapy versus chemotherapy alone (HR, 0.63; 95% CI, 0.50–0.79).[872]

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 and FDA approval.[871,873] Maintenance therapy with pembrolizumab is also a recommended option in this setting (category 1). The NCCN NSCLC Panel has preference stratified the systemic therapy regimens and decided that these pembrolizumab plus chemotherapy regimens are preferred for eligible patients with metastatic squamous cell NSCLC. 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 actionable driver mutations, regardless of their PD-L1 expression levels. The panel does not recommend pembrolizumab plus cisplatin with either paclitaxel or albumin-bound paclitaxel, because there are fewer data for this regimen. Combination therapy with pembrolizumab plus carboplatin and either paclitaxel or albumin-bound paclitaxel may be used as a first-line or subsequent therapy option in eligible patients with actionable driver mutations as shown in the algorithm. However, targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations.

Subsequent Therapy

KEYNOTE-010, a phase 3 randomized trial, assessed single-agent pembrolizumab in patients with previously treated advanced nonsquamous and squamous NSCLC who were PD-L1 positive (≥1%); most patients either currently or previously smoked cigarettes.[835] There were three 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;

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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 six treatment-related deaths occurred in patients receiving pembrolizumab (three at each dose) and five treatment-related deaths occurred in the docetaxel arm. Long-term data from KEYNOTE-010 show that 5-year survival for patients with metastatic NSCLC is approximately 15.6% for patients who received subsequent pembrolizumab monotherapy versus 6.5% for those receiving docetaxel. For patients with PD-L1 levels of 50% or more, 5-year overall survival was about 25% for patients receiving pembrolizumab versus 8.2% for those receiving docetaxel, respectively.[11]

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.[835,874,875] Nivolumab and atezolizumab are also recommended subsequent therapy options in this setting (category 1; preferred). 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).

Tremelimumab-actl and Durvalumab

Tremelimumab-actl is a monoclonal IgG2 antibody that enhances immune function by inhibiting CTLA-4 and preventing interactions with CD80/CD86; CTLA-4 inhibits T-cell activation.[876] Durvalumab is a human immunoglobulin G1 monoclonal antibody that inhibits PD-L1 binding to PD-1 and CD80, thus increasing immune function (see *Durvalumab* in this Discussion). Immune-mediated adverse events may occur with ICIs, including tremelimumab-actl and durvalumab.[876] For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered based on the severity of the reaction. Tremelimumab-actl and durvalumab should be permanently discontinued for patients with grades 2, 3, or 4 myocarditis and should be discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

POSEIDON, a phase 3 randomized trial, assessed three different first-line treatment arms in 1013 patients with metastatic NSCLC who did not have *EGFR* or *ALK* mutations.[877] The treatment arms included 1) tremelimumab plus durvalumab plus platinum-based chemotherapy; 2) durvalumab plus platinum-based chemotherapy; and 3) platinum-based chemotherapy alone; there were 675 patients in arms 1 and 3. The chemotherapy regimens included 1) tremelimumab plus durvalumab plus albumin-bound paclitaxel plus carboplatin for either nonsquamous NSCLC or squamous cell histology; 2) tremelimumab plus durvalumab plus pemetrexed plus either cisplatin or carboplatin for nonsquamous NSCLC; or 3) tremelimumab plus durvalumab plus gemcitabine plus either cisplatin or carboplatin for squamous cell histology. Most patients received the pemetrexed regimen. Most patients either currently smoked cigarettes (25%) or had previously smoked (57%). The median overall survival was 14 months (95% CI, 11.7–16.1) in patients receiving tremelimumab plus durvalumab plus chemotherapy versus 11.7 months (95% CI, 10.5–13.1) in patients receiving chemotherapy alone (HR, 0.77; 95% CI, 0.65–0.92; *P*=.003). Subgroup analysis showed that overall survival was similar between the groups for squamous cell histology and other subgroups.

In patients receiving tremelimumab plus durvalumab plus chemotherapy, grade 3 or 4 adverse events included neutropenia, anemia, leukopenia,

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lymphocytopenia, increased lipase levels, hyponatremia, and thrombocytopenia.[877] Common serious adverse events in patients receiving tremelimumab plus durvalumab plus chemotherapy included pneumonia (11%), anemia (5%), diarrhea (2.4%), thrombocytopenia (2.4%), pyrexia (2.4%), and febrile neutropenia (2.1%). Grade 3 to 4 immune-related adverse events occurred in 10% of patients receiving tremelimumab plus durvalumab plus chemotherapy versus 1.5% of those receiving chemotherapy alone. Treatment-related deaths occurred in 3.3% (11/330) of patients receiving tremelimumab plus durvalumab plus chemotherapy and 2.4% (8/333) receiving chemotherapy alone. An exploratory analysis suggests that tremelimumab plus durvalumab plus chemotherapy may be beneficial in patients with metastatic NSCLC who have *STK11*, *KEAP1,* or *KRAS* mutations; however, the sample size was too small to yield definitive conclusions.[878]

The NCCN NSCLC Panel recommends tremelimumab-actl plus durvalumab plus platinum-based chemotherapy regimens as first-line therapy options for eligible patients with metastatic NSCLC—regardless of histology or PD-L1 levels, and with negative test results for actionable driver mutations—based on clinical trial data and FDA approval; maintenance therapy with durvalumab with or without pemetrexed is also recommended.[877] Combination therapy with tremelimumab-actl plus durvalumab plus platinum-based chemotherapy may be used as a first-line or subsequent therapy option, although it is not a preferred option, in eligible patients with actionable driver mutations as shown in the algorithm. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations. The category assignment (ie, category 1, 2A, or 2B) for the tremelimumab-actl plus durvalumab plus platinum-based chemotherapy regimens varies depending on the histology, chemotherapy, and PD-L1 levels. The NCCN Panel has preference stratified the tremelimumab-actl plus durvalumab plus chemotherapy regimens and decided that they are other recommended first-line therapy options for eligible patients with metastatic NSCLC based on clinical trial data.[877]

Maintenance Therapy

Maintenance therapy refers to therapy given for patients with advanced NSCLC after 4 to 6 cycles of first-line therapy.[879] Patients are only candidates for maintenance therapy if their tumors have responded to their previous treatment 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, such as histologic type, presence of mutations or gene fusions, and 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; it is not recommended for patients with PS 3 to 4 or those with progression (see the NCCN Guidelines for NSCLC).[880] Monitoring is recommended during maintenance therapy with response assessment with CT, with or without contrast, of known or high-risk sites of disease every 6 to 12 weeks.

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). Use of continuation maintenance therapy depends on several factors, such as whether the patient had minimal toxicity during treatment.

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A drug vacation may be more appropriate for some patients.[810] 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.[808,810] 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).[807,808]

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).[881] Updated results from PARAMOUNT reported that continuation maintenance therapy with pemetrexed also improves overall survival (13.9 vs. 11.0 months).[882] 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.[881-883]

POINTBREAK, a phase 3 randomized trial, assessed bevacizumab plus carboplatin plus pemetrexed compared with bevacizumab plus carboplatin plus paclitaxel in patients with metastatic NSCLC; patients received maintenance therapy with either bevacizumab plus pemetrexed or bevacizumab alone.[812] PFS was 6 months with pemetrexed plus carboplatin plus bevacizumab versus 5.6 months with paclitaxel plus carboplatin plus bevacizumab.[812] 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 plus pemetrexed versus bevacizumab alone in patients with advanced nonsquamous NSCLC; the initial regimen was bevacizumab plus cisplatin plus pemetrexed.[884,885] An updated analysis reported that overall survival was 17.1 months with bevacizumab plus pemetrexed maintenance versus 13.2 months with bevacizumab alone (HR, 0.87; 95% CI, 0.63–1.21; P = .29).[884]

The NCCN NSCLC Panel recommends continuation maintenance therapy with bevacizumab plus pemetrexed in patients with nonsquamous NSCLC who initially received bevacizumab plus pemetrexed plus platinum regimen based on clinical trial data.[884,885] 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.[806,883,886] The 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.[833,846-849] 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.

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).[742,887] A phase 3 randomized trial from the CECOG assessed continuation maintenance therapy with gemcitabine versus best supportive care after an initial regimen of cisplatin plus gemcitabine.[888] The data showed a slight difference in PFS but no difference in overall survival (13 vs. 11 months, respectively; P = .195).

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The NCCN NSCLC Panel recommends gemcitabine (category 2B) as continuation maintenance therapy regardless of histology in patients with metastatic NSCLC, negative test results for actionable driver mutations, and PD-L1 expression less than 1%.

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.[810,889] 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.[890,891] The NCCN NSCLC Panel recommends switch maintenance therapy with pemetrexed in eligible patients with nonsquamous cell carcinoma; negative test results for actionable driver mutations, and PD-L1 expression less than 1% based on clinical trial data and FDA approval.[891,892]

The NCCN NSCLC Panel does not recommend erlotinib as switch maintenance therapy (or as subsequent therapy) for patients with nonsquamous NSCLC, good PS, and negative test results for actionable driver mutations based on results from IUNO, a randomized trial, and a revised indication from the FDA.[893] The NCCN NSCLC Panel also does not recommend switch maintenance therapy with erlotinib in patients with squamous cell NSCLC, because overall survival and quality of life were not improved.[742,894] A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after gemcitabine plus carboplatin or delayed until progression in patients with advanced NSCLC; however, many patients in the delayed chemotherapy arm did not receive docetaxel.[895] Previously, the panel deleted the recommendation for switch maintenance therapy with docetaxel for patients with squamous cell NSCLC because there are better options.[895,896]

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Targeted Therapy

Targeted therapies are available for the treatment of eligible patients with NSCLC.[182,897,898] For information about the use of targeted therapy in early-stage resectable NSCLC, see the *Surgery Followed by Adjuvant Therapy* and the *Neoadjuvant and Adjuvant Therapy* sections in this Discussion.

For information about targeted therapies for advanced or metastatic NSCLC with clinically actionable biomarkers, see the *Systemic Therapy for Advanced or Metastatic NSCLC* section in this Discussion.

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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).[91-95] 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 *Initial 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.[49,899-901] 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 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.[109,902-904] 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.[109] 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. Although mediastinal biopsy is generally preferred, the risks in selected patients may outweigh the benefits, such as patients who are medically inoperable. In patients with peripheral tumors (outer one third of the lung) 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.[905] Invasive mediastinal staging is recommended for central tumors. Mediastinal evaluation can be considered in patients with clinical stage IA disease (T1abc,N0). In patients with peripheral T2a, central T1abc, 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.[906] This strategy

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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 a chest CT scan plus mediastinoscopy was significantly more accurate (89% vs. 71%) than using a chest CT scan alone for identifying N2 disease. When using CT scans, node positivity is based on the size of the lymph nodes. Therefore, a 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 in 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.[907] 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.[902] 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 panel assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.[908] Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported.[909] 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.[910] 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%.[911] Kernstine et al compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.[912] 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.[913,914] When patients with early-stage disease are accurately staged using FDG PET/CT, inappropriate surgery is avoided.[915]

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.[109,916,917] However, FDG PET/CT is even more sensitive and is recommended by the panel.[915,918,919] PET/CT is typically done from the skull base to the knees; whole body PET/CT may also be done.

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.[109,920] 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.[921-924] 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.[925] In patients with positive nodes on CT or PET, EBUS-TNBA can be used to clarify the results.[926,927] In patients with negative findings on EBUS-TNBA, conventional mediastinoscopy can be done to confirm the results.[922,927-929] 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.[930]

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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 >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 provided 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 *Perioperative Systemic Therapy*, *Concurrent Chemoradiation Regimens*, *Molecular and Biomarker-Directed Therapy for Advanced or Metastatic Disease*, and *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). First-line targeted therapy options are recommended for eligible patients with metastatic NSCLC and positive test results for actionable driver mutations such as *ALK*, *BRAF* p.V600E, *EGFR*, *MET*ex14 skipping, *NTRK1/2/3, RET,* and *ROS1*. Second-line targeted therapy options are recommended for eligible patients with metastatic NSCLC and positive test results for *EGFR* exon 20 insertions or *KRAS* p.G12C mutations. First-line immunotherapy options are recommended for eligible patients with metastatic NSCLC and negative test results for actionable driver mutations. Immunotherapy options may be used as first-line or subsequent therapy options in eligible patients with actionable driver mutations as shown in the algorithm, although they are generally not preferred options.

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, preferably 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).[384,405,408,483,547,931] Image-guided thermal ablation (eg, cryotherapy, microwave, RFA) is an option for selected patients who are medically inoperable and not receiving SABR or definitive RT (see *Principles of Image-Guided Thermal Ablation Therapy* in the NCCN Guidelines for NSCLC).[384,551-557] 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 two 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

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options are organized according to the location of the tumor, such as the superior sulcus, chest wall, proximal airway, or mediastinum.[394] 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). Preoperative concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has shown 2-year survival in the 50% to 70% range.[394,503,505,932-934] The overall 5-year survival rate is approximately 40%.[503] For patients with resectable tumors (T3 invasion,N0–1) in the superior sulcus, the NCCN NSCLC Panel recommends preoperative concurrent chemoradiation followed by surgical resection and adjuvant chemotherapy plus either atezolizumab, pembrolizumab, or osimertinib, if patients have certain *EGFR* mutations or PD-L1 levels of 1% or more (see *Initial Treatment* for Superior Sulcus Tumors in the NCCN Guidelines for NSCLC). Patients with possibly resectable superior sulcus tumors should undergo preoperative concurrent chemoradiation before surgical re-evaluation (including CT with or without contrast ± PET/CT). For patients with unresectable tumors (T4 extension,N0–1) in the superior sulcus, definitive concurrent chemoradiation is recommended followed by durvalumab (category 1).[781,935]

Definitive concurrent chemoradiation is recommended for patients with medically inoperable stage II or III NSCLC. The NCCN NSCLC Panel recommends durvalumab (category 1) as a consolidation immunotherapy option for eligible patients with unresectable stage III NSCLC and without disease progression after treatment with definitive concurrent chemoradiation based on clinical trial data and FDA approval (see *Chemoradiation* in this Discussion and the NCCN Guidelines for NSCLC).[16,363,786] The panel also recommends durvalumab as a consolidation immunotherapy option (regardless of PD-L1 status) for eligible patients (PS 0–1) with unresectable stage II NSCLC but without disease progression after definitive concurrent platinum-based chemoradiation. 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 systemic therapy 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).[16,447,702,786] Additional chemotherapy (ie, consolidation chemotherapy) is an option if patients will not be receiving durvalumab.[532,778] However, consolidation chemotherapy is not recommended if patients will be receiving durvalumab, based on concerns that consolidation chemotherapy will increase the risk of pneumonitis if patients are also receiving durvalumab.

Multimodality therapy is recommended for most patients with stage III NSCLC.[774] 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. 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.[482,703] Recommended therapy for

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metastatic disease depends on whether disease is in a solitary site or is widespread.

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).[936] 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%.[937] 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.[768] For those with N2 nodes and negative margins, I chemotherapy (category 1) or sequential chemotherapy with RT is recommended. Adjuvant chemotherapy followed by adjuvant atezolizumab, pembrolizumab, or osimertinib is recommended for those with N0–1, depending on *EGFR* mutation levels and PD-L1 levels (see the NCCN Guidelines for NSCLC). In patients with synchronous solitary nodules (contralateral lung), the NCCN NSCLC Panel recommends treating them as two primary lung tumors if both are curable, even if the histology of the two tumors is similar.[938]

Multiple Lung Cancers

Patients with a history of lung cancer or those with biopsy-proven synchronous lesions may be suspected of or confirmed with having multiple lung cancers.[939,940] 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.[86,394,941,942] Lesions with different cell types, such as squamous cell or adenocarcinoma, are usually different primary tumors. However, lesions of the same cell type may not be metastases. 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).[943,944] Although criteria have been established for diagnosing multiple lung cancers, no definitive method has been established before treatment.[944-947] 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.[947] Data suggest that NGS testing may help determine whether separate lung nodules are clonally related.[948-950]

Broad molecular profiling can be used to assess multiple lung lesions (see *Summary of the Guidelines Updates* in the NCCN Guidelines for NSCLC). For example, tumors with non-overlapping, unique mutations are considered to be clonally unrelated, separate primary lung cancers even if they are histologically similar. Therefore, these tumors can be treated with local therapy (see *Multiple Lung Cancers* in the NCCN Guidelines for NSCLC). 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.[941,951-953] Patients should be evaluated in a multidisciplinary setting by thoracic surgeons, pulmonary medicine, 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).[940,941] VATS or SABR are reasonable options depending on the number and distribution of the tumors requiring local treatment.[954] Multiple lung nodules (eg, solid, subsolid nodules) may also be detected on CT scans; some of these

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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).[955]

For the 2023 update (Version 1), the NCCN NSCLC Panel revised the algorithm for multiple lung cancers. For example, the NCCN Panel added an initial recommendation for multidisciplinary evaluation for patients suspected of or confirmed with having multiple lung cancers. One of the goals during multidisciplinary evaluation for multiple lung cancers is to assess whether patients have lung nodules that can be observed instead of erroneously assuming that patients have stage IV NSCLC. The panel added the following caveats: lesions at low risk of becoming symptomatic can be observed, such as small subsolid nodules with slow growth. However, treatment should be considered if the lesion(s) show accelerating growth, increasing solid component, or increasing FDG uptake, even if the lesions are small.

Stage IIIB and IIIC NSCLC

Stage IIIB NSCLC comprises two unresectable groups, including: 1) T1–2,N3 tumors; and 2) T3–4,N2 tumors; stage IIIC NSCLC includes T3,N3 and 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).[956,957] 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).[447,702,781,786,958-960]

Durvalumab is recommended (category 1) as a consolidation immunotherapy option for eligible patients with unresectable stage III NSCLC and without disease progression after treatment with definitive concurrent chemoradiation (see *Chemoradiation* in this Discussion and the NCCN Guidelines for NSCLC).[16,363,786] If patients will be receiving durvalumab, additional f chemotherapy (ie, consolidation chemotherapy) is not recommended 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.[532,778] 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).[447,702,781,786,958-961] Again, durvalumab is recommended (category 1) as a consolidation immunotherapy option for eligible patients with unresectable stage III NSCLC and without disease progression after treatment with definitive concurrent chemoradiation.[16,363,786] Consolidation chemotherapy is an option for eligible patients.[532,778] However, consolidation chemotherapy is not recommended if patients will be receiving durvalumab.

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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).[962] 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 *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). Biomarker testing is recommended for patients with stage IVA disease (see *Predictive and Prognostic Biomarkers* in this Discussion).

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).[158] 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 sanguineous 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). Data suggest that most pleural or pericardial effusions are associated with unresectable disease in 95% of cases.[963] 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.[964,965]

Care 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 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.[584,966] 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 progression (eg, SRS to brain metastases or other sites, SABR for limited thoracic or other metastatic disease; surgery).[967,968]

Neoadjuvant or Adjuvant Therapy

Chemotherapy, Chemoradiation, Immunotherapy, and Targeted Therapy

On the basis of clinical studies,[690-692] the NCCN NSCLC Panel recommends cisplatin combined with docetaxel, etoposide, gemcitabine, or vinorelbine as neoadjuvant or adjuvant therapy options (also known as perioperative therapy) for all histologies in eligible patients with locally advanced disease. The NCCN NSCLC Panel has preference stratified all the systemic therapy regimens and decided that cisplatin plus

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pemetrexed is a preferred neoadjuvant or adjuvant therapy option (also known as preoperative and postoperative therapy) for nonsquamous NSCLC, whereas cisplatin plus either gemcitabine or docetaxel is preferred for squamous cell NSCLC (see *Perioperative Systemic Therapy* in the NCCN Guidelines for NSCLC).[738,743,790] 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.[738,969] These neoadjuvant or adjuvant regimens may also be used for sequential chemoradiation.[744-747]

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.[697,970-972] All three 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 plus 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.[971,972] The two 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.[973-975]

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 recommended option for patients with T2ab,N0 tumors and negative surgical margins who have high-risk features, including poorly differentiated tumors, vascular invasion, wedge resection, visceral pleural involvement, and unknown lymph node status (Nx) (see the NCCN Guidelines for NSCLC).[737,976] 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 an option for T2b,N0).[467,737]

The NCCN NSCLC Panel recommends atezolizumab as an adjuvant therapy option for eligible patients with completely resected (R0) stage IIB to IIIA, stage IIIB (only T3,N2), or high-risk stage IIA NSCLC and PD-L1 of 1% or more, and negative for *EGFR* exon 19 deletions, *EGFR L858R* mutations, or *ALK* rearrangements, who have previously received adjuvant chemotherapy based on clinical trial data and FDA approval (see *Surgery Followed by Adjuvant Therapy: Trial Data and NCCN Recommendations* in this Discussion).[750] For the 2023 update (Version 2), the NCCN Panel also recommends pembrolizumab as an adjuvant therapy option following adjuvant chemotherapy for eligible patients with completely resected early-stage NSCLC based on clinical trial data and FDA approval.[751] The panel recommends osimertinib as an adjuvant therapy option for eligible patients with completely resected (R0) stage IB to IIIA or stage IIIB (only T3,N2) NSCLC and *EGFR* exon 19 deletions or *EGFR L858R* mutations who have previously received adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy based on clinical trial data and FDA approval.[748] For patients who have these *EGFR* mutations and PD-L1 levels of 1% or more, the panel only recommends osimertinib; the panel does not recommend using 1)

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single-agent therapy with either atezolizumab or pembrolizumab; or 2) combination therapy with osimertinib plus atezolizumab or pembrolizumab.

The NCCN NSCLC Panel recommends adjuvant chemotherapy (category 1) followed by atezolizumab, pembrolizumab, or osimertinib for eligible patients with the appropriate biomarkers, negative surgical margins, and stage IIB disease, including 1) T1abc–T2a,N1; 2) T2b,N1; or 3) T3,N0 disease.[733,977] 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). After an R2 resection, options 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.[768] Postoperative chemotherapy or chemoradiation 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. For patients with negative margins (R0), treatment options include either 1) chemotherapy (category 1) followed by atezolizumab, pembrolizumab, or osimertinib for eligible patients with the appropriate biomarkers; or 2) sequential chemotherapy and consider RT.[733]

For stage IIIA superior sulcus tumors (T4 extension,N0–1) that become resectable after preoperative concurrent chemoradiation, resection followed by chemotherapy is recommended and then atezolizumab, pembrolizumab, or osimertinib, depending on biomarker status (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 completion of definitive dose chemoradiation without interruption, followed by consolidation immunotherapy 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 and then either atezolizumab, pembrolizumab, or osimertinib depending on biomarker status, if the surgical margins are negative. For patients with positive margins, options include 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.[768] Similar treatment plans are 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) and no apparent disease progression after initial treatment with induction systemic therapy with or without RT, surgery is recommended (see the NCCN Guidelines for NSCLC).[450] Alternatively, if the disease progresses, treatment options include either 1) local therapy using RT (if feasible) 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; neoadjuvant systemic therapy with nivolumab plus chemotherapy is an option before surgery. 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

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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.[978] Data from two randomized phase 3 trials, the LungART and PORT-C trials, show that postoperative RT (also known as PORT) did not improve survival compared with no postoperative RT, although locoregional control was significantly improved in patients with completely resected stage IIIA (N2) NSCLC who received neoadjuvant or adjuvant chemotherapy.[450,453] Postoperative RT may be considered for select patients with negative margins and high-risk N2 disease (see *Chemoradiation* in this Discussion and *Principles of Radiation Therapy* in the algorithm). Previous trials and meta-analyses had suggested that there was an apparent survival benefit of postoperative RT in patients with N2 nodal stage diagnosed surgically.[467,574,977,979,980]

PROCLAIM, a phase 3 randomized trial, assessed concurrent thoracic RT with cisplatin plus pemetrexed versus cisplatin plus etoposide followed by consolidation chemotherapy in patients with unresectable stage III nonsquamous NSCLC.[778] Both regimens were equivalent in terms of survival, but the cisplatin plus 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 Panel has preference stratified the concurrent chemoradiation regimens and decided that pemetrexed with either carboplatin or cisplatin are preferred concurrent chemoradiation regimens for eligible patients with nonsquamous NSCLC.[783,981,982] Other preferred concurrent chemoradiation regimens include 1) paclitaxel plus carboplatin; and 2) cisplatin plus etoposide;, these regimens may be used regardless of histology.[532,780] The NCCN NSCLC Panel deleted the cisplatin plus etoposide consolidation regimen based on the PROCLAIM trial.[778] Other consolidation chemotherapy regimens are an option for eligible patients receiving definitive chemoradiation; however, consolidation chemotherapy is not recommended if the patient will be receiving durvalumab.

Postoperative chemotherapy (category 1) followed by adjuvant atezolizumab, pembrolizumab, or osimertinib, depending on the biomarker status, is recommended for patients with T1–3, N2 disease and negative margins (see the NCCN Guidelines for NSCLC). Postoperative sequential chemotherapy with consideration of postoperative RT is recommended for select patients with negative margins and high-risk N2 disease such as extracapsular extension, multistation involvement, inadequate lymph node dissection or sampling, and/or refusal or intolerance of adjuvant systemic therapy.[450,453,767] Either concurrent or sequential chemoradiation may be used for postoperative therapy and positive margins, depending on the type of resection and the setting (eg, N2 disease). Concurrent chemoradiation is recommended for R2 resections, whereas either sequential or concurrent chemoradiation is recommended for R1 resections. Concurrent chemoradiation is often used for positive margins, but sequential is reasonable in frailer patients.[768] Cisplatin plus etoposide and carboplatin plus paclitaxel are chemoradiation regimens recommended by the NCCN NSCLC Panel for all histologies (see *Concurrent Chemoradiation Regimens* in the NCCN Guidelines for NSCLC).[780] When chemoradiation is recommended in the NCCN Guidelines, these regimens may be used for stage II to III disease.[468,469,702,703,781,784,785]

Surveillance

Because recurrence is common after treatment for NSCLC, surveillance is recommended in the NCCN Guidelines for eligible patients with no

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evidence of clinical or radiographic disease after definitive therapy. Data from randomized phase 3 trials are not available to clarify surveillance recommendations; therefore, the most appropriate schedules are controversial.[983-988] The surveillance recommendations were compiled by polling the NCCN NSCLC Panel regarding their practice patterns. Details regarding the specific surveillance schedules are outlined in the algorithm based on stage and the definitive treatment (see *Surveillance After Completion of Definitive Therapy* in the algorithm). 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.[73] 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).[73] Low-dose CT is recommended for screening individuals at high risk for lung cancer (see the NCCN Guidelines for Lung Cancer Screening, available at www.NCCN.org). 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 after definitive treatment) followed by annual low-dose non-contrast–enhanced CT and an H&P (see *Surveillance After Completion of Definitive Therapy* in the algorithm).[986,987,989-992] 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.[983] 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 suspicious areas with apparent "recurrent" disease is needed.[993] The NCCN NSCLC Panel recommends assessing patients with recurrences using PET/CT and brain MRI with contrast; if brain MRI is not possible, then CT with contrast of the head is recommended. 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 (see the NCCN Guidelines for Colorectal Cancer Screening, NCCN Guidelines for Breast Cancer Screening and Diagnosis, and NCCN Guidelines for Prostate Cancer Early Detection, available at www.NCCN.org). An analysis suggests that patients who survive lung cancer have a high symptom burden 1 year after diagnosis and therefore need management after treatment.[994]

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) obstruction, and severe hemoptysis—is described in the NCCN Guidelines (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for NSCLC).[664] An

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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.[995] After treatment for 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 somatic genomic alterations are present that can be treated with targeted therapy, and PS (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).

Management of distant metastases—localized symptoms; bone; and 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).[480,579,996] 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, select limited locoregional recurrences may be treated with curative intent therapy (re-resection preferred or RT or SABR) (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).[607,608,611,654,997-1000] 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.[477,631-633,1001-1004]

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).[1005] The FDA has approved the use of zoledronic acid and denosumab in patients with bone metastases from solid tumors.[1006,1007] 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.[182,1005,1008-1011]

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Systemic Therapy for Advanced or Metastatic NSCLC

For patients with advanced or metastatic NSCLC, the NCCN Guidelines recommend that histologic subtype should be determined before therapy so that an appropriate treatment can be selected. Smoking cessation counseling (if necessary) and palliative care should also be integrated into the disease management strategy. Data suggest that early palliative care is associated with higher quality of life in patients with metastatic NSCLC.[720]

Molecular testing for somatic, disease-associated oncogenic driver mutations or alterations should be conducted as part of broad molecular profiling, which is strongly recommended by the panel. Broad molecular profiling is defined as molecular testing that identifies all actionable molecular biomarkers specified in the NCCN Guidelines for NSCLC in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers. Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. The goal of broad molecular profiling is to identify driver alterations that can guide use of available targeted therapies or to appropriately counsel patients regarding potential clinical trials that may be available. Therefore, broad molecular profiling is considered a key component of improving care for patients with NSCLC.

Molecular testing via biopsy and/or plasma testing is recommended; combinations of tissue and plasma testing, either concurrently or in sequence, are acceptable. Evidence suggests that concurrent testing can improve time to test results and should be considered depending on the clinical situation.[197,1012-1017] Negative results (defined as the absence of a definitive driver mutation) by one method suggest that a complementary method may be used.

Molecular testing for *EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, METex14* skipping, *RET*, and *ERBB2 (HER2)* alterations is recommended in all patients with advanced or metastatic nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) and NSCLC not otherwise specified (NOS); *EGFR* mutation and *ALK* rearrangement testing are category 1 recommendations for patients with nonsquamous NSCLC or NSCLC NOS based on the data available to recommend targeted therapies for these biomarkers. As the cumulative incidence of targetable molecular alterations in squamous cell carcinoma across all alterations ranges from 2% to 10%,[136,137,184,185] the same molecular testing should be considered in all patients with advanced or metastatic NSCLC squamous cell carcinoma, and not just those with certain clinical characteristics, such as never smoking status and mixed histology.

If a clinically actionable biomarker is found, the NCCN Guidelines for NSCLC provide appropriate therapy recommendations. If results are unknown or pending, patients can be treated as if they do not have driver oncogenes. However, retrospective data indicate that the availability of molecular testing prior to treatment initiation is associated with longer overall survival (OS) in patients with advanced nonsquamous NSCLC.[1018] If patients require an urgent start to therapy, clinicians should consider holding immunotherapy for one cycle (ie, just use platinum-based chemotherapy regimens). Clinicians need to be aware of the long half-life of immune checkpoint inhibitors and the potential for higher rates of side effects when using certain targeted therapies, (such as osimertinib) in combination with or following checkpoint inhibitors.[828,829,1019,1020]

If a clinical actionable biomarker is discovered during first-line systemic therapy, then the planned systemic therapy (including maintenance therapy) can be either interrupted or completed before switching to the appropriate targeted therapy. Factors that can be considered to guide

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this decision include the level of toxicity that the patient is experiencing and whether a clinical or radiographic response has been observed.

Upfront programmed death ligand 1 (PD-L1) expression testing before first-line therapy is also a category 1 recommendation (regardless of histology) in patients with advanced or metastatic NSCLC to assess how immune checkpoint inhibitors (ICIs) could be used if no actionable molecular biomarkers are identified. Treatment options for advanced or metastatic NSCLC without actionable molecular biomarkers are stratified by PD-L1 level and include systemic therapy options such as immunotherapy with or without chemotherapy (see NSCL-37 and NSCL-38 in the NCCN Guidelines for NSCLC). Refer to the full Guidelines at www.NCCN.org for complete treatment recommendations for advanced or metastatic NSCLC based on PD-L1 levels in the absence of a clinically actionable marker.

In the NCCN Guidelines, targeted therapies with a first-line indication are recommended as initial therapy (rather than first-line ICIs) for patients with advanced or metastatic NSCLC and some (but not all) oncogenic drivers, regardless of PD-L1 levels. The rationale is that targeted therapies typically yield higher response rates (eg, osimertinib, 80%) than ICIs (poor response rates) in the first-line setting, and targeted therapy is better tolerated.[184,371,372,827,1021] It should be noted that targeted therapies are not available or recommended for NSCLC with certain actionable biomarkers in the first-line setting. For instance, patients with NSCLC with *KRAS* G12C mutations are likely to benefit from immunotherapy (with or without chemotherapy) in the first-line setting.[184,1022,1023] Targeted therapies are recommended only in the second-line setting or later for those with *KRAS* G12C mutations.

Monitoring is recommended during initial therapy with response assessment with CT (with or without contrast) of known or high-risk sites of disease (such as chest, abdomen, and pelvis) after 2 cycles and then every 2 to 4 cycles. Likewise, monitoring of known or high-risk sites of disease is also recommended during maintenance or subsequent therapy with CT (with or without contrast) every 6 to 12 weeks.

For complete treatment recommendations for advanced or metastatic NSCLC, see NSCL-19.

NSCLC with *EGFR* Alterations

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is altered in a subset of patients with NSCLC. The two most common *EGFR* alterations in NSCLC are deletions in exon 19 (with conserved deletion of the LREA sequence) and a point mutation in exon 21 (L858R); these represent approximately 85% to 90% of all *EGFR* alterations in NSCLC.[246] Both result in activation of the tyrosine kinase domain and are associated with sensitivity to small-molecule EGFR tyrosine kinase inhibitors (TKIs).[244] These *EGFR* alterations are found in approximately 10% of white patients with NSCLC and up to 19% of Black and 50% of Asian patients.[245,1024,1025]

Other less common *EGFR* mutations (approximately 10%) include exon 20 S768I, exon 21 L861Q, and/or exon 18 G719X.[246,247] These mutations have varying degrees of sensitivity to first- (erlotinib/gefitinib), second- (afatinib/dacomitinib), and third- (osimertinib) generation EGFR TKIs.[246,247,291-293,1026]

EGFR T790M is an *EGFR* exon 20 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 afatinib, erlotinib, or gefitinib.[210,265-271] If *EGFR* T790M is identified in the absence of prior EGFR TKI therapy, genetic counseling and possible germline genetic testing are warranted. Identification of germline *EGFR* T790M confers a high risk for lung cancer regardless of smoking status.[273-275]

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EGFR exon 20 insertion mutations are the third most common group of *EGFR* mutations; they occur in approximately 2% of patients with NSCLC and 4% to 12% of patients with *EGFR* mutations.[179,259,294,295] *EGFR* exon 20 insertion mutations are a heterogeneous group; while NSCLC with these variants generally have low response rates to early-generation EGFR TKIs, variable levels of response with newer therapies have been reported, depending on the variant.[178,179,257,1027]

Clinical Data: NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Mutations

Osimertinib is a third-generation oral EGFR TKI that is approved by the U.S. Food and Drug Administration (FDA) for the treatment of NSCLC with *EGFR* alterations.[1028,1029] Osimertinib monotherapy and osimertinib in combination with platinum and pemetrexed chemotherapy are both indicated for the first-line treatment of adults with metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutation.

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 (exon 19 deletion or L858R).[18,371,1030,1031] The median progression-free survival (PFS) was longer with osimertinib compared with either erlotinib or gefitinib (18.9 months vs. 10.2 months; hazard ratio [HR], 0.46; $P < .001$).[371] The median duration of response was longer with osimertinib compared with erlotinib or gefitinib (median response, 17.2 vs. 8.5 months).[371] Only 6% of patients receiving osimertinib had central nervous system (CNS) progression events when compared with 15% of those receiving erlotinib or gefitinib.[371] Grade 3 or higher adverse events (AEs) were reported in 34% of patients receiving osimertinib and 45% of those receiving erlotinib or gefitinib.[371] An updated analysis showed that median overall survival (OS) was 38.6 months with osimertinib compared with 31.8 months for either erlotinib or gefitinib (HR, 0.8; $P = .046$).[18]

FLAURA2, a phase 3 open-label randomized study, evaluated first-line therapy with osimertinib in combination with chemotherapy (pemetrexed and either cisplatin or carboplatin) versus osimertinib monotherapy in 557 patients with advanced NSCLC with *EGFR* exon 19 deletion or L858R.[1032] The histology was adenocarcinoma in 99% of the patient population. The median investigator assessed PFS was longer in patients who received osimertinib in combination with chemotherapy compared with those who received only osimertinib (25.5 vs. 16.7 months; HR, 0.62; $P < .001$). The median duration of response was also longer with osimertinib plus chemotherapy compared with osimertinib alone (24.0 vs. 15.3 months). The number of grade 3 AEs was higher with osimertinib plus chemotherapy than with osimertinib monotherapy and was primarily driven by known chemotherapy-related AEs.

Amivantamab-vmjw is a bispecific human antibody to EGFR and MET that has been studied in a variety of contexts of NSCLC with *EGFR* mutations.[178] For patients with advanced NSCLC and *EGFR* exon 19 deletion or L858R mutation whose disease progressed on or after osimertinib monotherapy, MARIPOSA-2, a phase 3 randomized trial, evaluated the efficacy of amivantamab-vmjw in combination with chemotherapy (carboplatin and pemetrexed) as subsequent therapy compared with chemotherapy.[1033] The median PFS was longer for the amivantamab-vmjw plus chemotherapy group than the chemotherapy group (6.3 months vs. 4.2 months; HR, 0.48; $P < .001$). The objective response rate was 64% with amivantamab-vmjw plus chemotherapy versus 36% with chemotherapy alone. No statistically significant difference in OS was reported in the interim analysis. The most common grade 3 or higher AEs were neutropenia, thrombocytopenia, anemia, and leukopenia.

Multiple studies have shown that other single-agent EGFR inhibitors and combination regimens also have efficacy in patients with advanced or

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metastatic NSCLC and *EGFR* alterations.[181,250,256,1034-1036] Erlotinib, gefitinib, and dacomitinib have all been approved by the FDA for the treatment of metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations.[1037-1039] Erlotinib in combination with either ramucirumab[1040] or bevacizumab[1036,1041] can also be considered as options.

Several studies have reported that programmed cell death protein 1 (PD-1)/PD-L1 inhibitor monotherapy in the second-line setting is less effective in *EGFR* exon 19 deletion or exon 21 L858R-positive NSCLC, regardless of PD-L1 expression.[358,827,834,835] Recent data also suggest that PD-1 inhibitor (pembrolizumab) in combination with chemotherapy as subsequent therapy may not have an OS or PFS benefit compared with chemotherapy alone in patients with metastatic NSCLC and *EGFR* exon 19 deletion or exon 21 L858R.[1042]

NCCN Recommendations: Advanced or Metastatic NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Mutations (NSCL-21, NSCL-22, and NSCL-23)

In the first-line setting, the NCCN NSCLC Panel recommends single-agent osimertinib as a preferred treatment option for patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutations. Single-agent erlotinib, afatinib, gefitinib, or dacomitinib are other recommended first-line treatment options. All of these are category 1 recommendations and are appropriate for patients with performance status 0–4.

The following combination regimens are also included in the NCCN Guidelines for NSCLC as “other recommended” options for advanced or metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutations in the first-line setting: osimertinib in combination with pemetrexed and either cisplatin or carboplatin (category 1; nonsquamous), erlotinib in combination with bevacizumab (nonsquamous and no recent history of hemoptysis), or erlotinib in combination with ramucirumab. An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

Targeted therapies are also recommended as an option if an *EGFR* exon 19 deletion or *EGFR* exon 21 L858R mutation is discovered during first-line systemic therapy. For patients receiving first-line ICIs with or without chemotherapy, oncologists should be aware of the long half-life of the ICI and potential AEs when using osimertinib (or other TKIs) in combination with or following ICIs.[828,829,1019,1020] For example, the rate of AEs, such as pneumonitis, is higher when osimertinib is initiated within 3 months of treatment with certain ICIs.[828]

In patients who experience disease progression after receiving first-line osimertinib, decisions about subsequent therapies are guided by disease symptoms as well as sites of progression. Changes in systemic therapy are generally recommended if patients have symptomatic systemic progression and/or multiple lesions. When considering second-line systemic therapy, ideally patients should be re-biopsied to rule out transformation to small cell histology, a phenomenon that occurs in approximately 5% EGFR TKI-resistant tumors.[265,278] Amivantamab-vmjw in combination with carboplatin and pemetrexed is a category 1 and preferred treatment option for patients with multiple lesions (if nonsquamous). Systemic therapy options such as chemotherapy (NSCL-K 1 of 5 or NSCL-K 2 of 5 in the NCCN Guidelines for NSCLC) are also recommended for patients with symptomatic systemic progression. Data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective in *EGFR* exon 19 deletion or exon 21 L858R NSCLC, irrespective of PD-L1 expression.[358,827,834,835]

Definitive local therapy has a role in the treatment of metastatic *EGFR*-positive NSCLC. For patients with a limited number of initial sites of metastasis (oligometastasis; limited number is not universally defined,

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but clinical trials have included 3-5 metastases), definitive local therapy (eg, stereotactic ablative radiotherapy [SABR] or surgery) should be considered as consolidation after initiating EGFR TKI therapy (local consolidative therapy) if not given prior to EGFR TKI therapy (see *Principles of Radiation Therapy* [NSCL-C] and NSCL-15 in the NCCN Guidelines for NSCLC). Local therapy may also be an appropriate subsequent therapy option for certain patients who have progressed after initial therapy with an EGFR TKI. For those with asymptomatic progression or symptomatic systemic progression that is limited in nature (oligoprogression), definitive local therapy (eg, SABR or surgery) should be considered for limited lesions regardless of prior TKI therapy; image-guided thermal ablation (IGTA) therapy may also be an option (see *Principles of Image-Guided Thermal Ablation Therapy* [NSCL-D] in the NCCN Guidelines for NSCLC). For those with CNS progression, definitive local therapy (eg, stereotactic radiosurgery [SRS] with or without surgical resection) should be considered for symptomatic lesions, and SRS should be considered for asymptomatic lesions at risk of symptomatic progression based on factors including size, location, and edema. See also the NCCN Guidelines for CNS Cancers on www.NCCN.org for additional recommendations.

If the patient experiences disease progression after treatment with osimertinib as well as chemotherapy with pemetrexed and either cisplatin or carboplatin then the subsequent therapy options listed on NSCL-K 4 of 5 in the NCCN Guidelines for NSCLC (such as chemotherapy) can be considered.

Clinical Data: NSCLC with EGFR S768I, L861Q, and/or G719X Mutations

For patients with the less common *EGFR* S768I, L861Q, and/or G719X mutations, treatment recommendations are based on non-randomized studies. Afatinib is a second-generation oral TKI that irreversibly inhibits the ErbB/HER family of receptors including EGFR and HER2.[1043,1044] Afatinib is approved by the FDA for the first-line treatment of metastatic NSCLC whose tumors have some *EFGR* mutations.[1045] A post-hoc analysis of several LUX-Lung trials (LUX-Lung 2, 3, and 6) assessed afatinib in patients with advanced NSCLC and the most frequent uncommon *EGFR* mutations (L861Q, G719X, and S768I).[1026] Median OS was 19.4 months. A response to afatinib was reported in 8 patients (100%) with *EGFR* S768I mutations. Among those with *EGFR* G719X mutations, an objective response to afatinib was reported in 14 patients (77.8%), while a response to afatinib was reported in 9 patients (56.3%) of those with *EGFR* L861Q.

Osimertinib has also been studied in patients with less common *EGFR* mutations, including S768I, L861Q, and G719X. KCSG-LU15-09, a phase 2 trial based in Korea, assessed first-line therapy with osimertinib in patients with metastatic or recurrent NSCLC and these mutations.[291] The median PFS was 8.2 months and the objective response rate was 50%. An objective response with osimertinib was observed in 78% (7/9) of those with *EGFR* L861Q, 53% (10/19) of those with *EGFR* G719X, and 38% (3/8) of those with *EGFR* S768I). The median PFS was 15.2 months, 8.2 months, and 12.3 months in the L861Q, G719X and S768I groups, respectively. Manageable AEs included rash, pruritus, decreased appetite, diarrhea, and dyspnea.[291]

Retrospective data suggest that the clinical response to osimertinib versus afatinib may differ, depending on the exact *EGFR* mutation identified; for example, NSCLC with *EGFR* L861Q may be more likely to respond to osimertinib than afatinib.[1026,1046,1047]

NCCN Recommendations: Advanced or Metastatic NSCLC with EGFR S768I, L861Q, and/or G719X Mutations (NSCL-24)

The NCCN NSCLC Panel recommends afatinib or osimertinib as preferred first-line therapy options for patients with advanced or metastatic NSCLC with the less common *EGFR* S768I, L861Q, and/or

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G719X mutations. All are appropriate for patients with performance status 0–4.

Subsequent treatment options for advanced or metastatic NSCLC with *EGFR* S768I, L861Q, and/or G719X alterations that progressed following first-line treatment with afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib are the same as for the more common *EGFR* alterations – refer to NSCL-22 and NSCL-23 and the subsequent therapy treatment recommendations for advanced or metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R detailed above.

Clinical Data: NSCLC with EGFR Exon 20 Insertion Mutation

For patients with NSCLC and *EGFR* exon 20 insertions, treatment with early-generation EGFR TKIs has generally not been associated with disease response.[178,179,257] Patients with *EGFR* exon 20 insertion-positive metastatic NSCLC have frequently been treated with first-line platinum-based chemotherapy.[297,299] The response rates (0%–25%) to immunotherapy regimens vary, depending on the specific *EGFR* exon 20 insertion mutation.[179,302] Mobocertinib, an EGFR TKI developed specifically for patients with *EGFR* exon 20 insertions, was previously granted accelerated approval by the FDA in the United States. However, mobocertinib was withdrawn from the U.S. market in 2023 and is no longer recommended as a subsequent treatment option by the panel based on data from the phase 3 EXCLAIM-2 trial, which compared first-line mobocertinib to platinum-based chemotherapy, as the primary endpoint was not met.[1048,1049]

Single-agent amivantamab-vmjw is FDA-approved for the treatment of adults with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.[1050] CHRYSALIS, a phase 1 study, assessed subsequent therapy with amivantamab-vmjw in 81 patients with *EGFR* exon 20 insertion-positive metastatic NSCLC who had received one or more previous lines of therapy.[178] The overall response rate was 40%, with 3 complete responses. The median PFS was 8.3 months. Common treatment-related AEs included cutaneous reactions, infusion-related reactions, and paronychia. The most common grade 3 to 4 AEs included hypokalemia as well as pulmonary embolism, neutropenia, diarrhea, and rash. Eight deaths were reported in the safety assessment (7%).

Amivantamab-vmjw in combination with carboplatin and pemetrexed is also approved by the FDA for the treatment of adults with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations.[1050] PAPILLON, a phase 3 randomized trial, assessed the efficacy and safety of first-line amivantamab-vmjw plus chemotherapy (pemetrexed and carboplatin) versus chemotherapy alone in 308 patients with advanced NSCLC with *EGFR* exon 20 insertions who had not previously received systemic therapy.[1051] The median PFS was longer in the amivantamab-vmjw plus chemotherapy group than in the chemotherapy alone group (11.4 months vs. 6.7 months; HR, 0.40; $P < .001$). Based on the interim OS analysis, the HR for amivantamab-vmjw plus chemotherapy versus chemotherapy alone was 0.67 ($P = .11$). The most common AEs reported with amivantamab-vmjw plus chemotherapy were hematologic effects and skin-related EGFR-related toxic events (eg, rash, paronychia, dermatitis acneiform).

NCCN Recommendations: Advanced or Metastatic NSCLC with EGFR Exon 20 Insertion Mutation (NSCL-25)

The NCCN NSCLC Panel recommends amivantamab-vmjw in combination with carboplatin and pemetrexed as a category 1 and preferred treatment option for patients with advanced or metastatic nonsquamous *EGFR* exon 20 insertion mutation-positive NSCLC. Other systemic therapy regimens (eg, chemotherapy) listed on NSCL-K 1 of 5 or NSCL-K 2 of 5 in the NCCN Guidelines for NSCLC are also recommended as first-line treatment options. Data indicate that ICI

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monotherapy is associated with low activity in NSCLC with *EGFR* alterations.[184,1052]

The NCCN NSCLC Panel recommends amivantamab-vmjw as a subsequent therapy option for patients with *EGFR* exon 20 insertion mutation-positive advanced or metastatic NSCLC and disease progression who were not previously treated with amivantamab-vmjw. For patients whose disease progressed after first-line treatment with amivantamab-vmjw in combination with chemotherapy, subsequent therapy options listed on NSCL-K 4 of 5 in the NCCN Guidelines for NSCLC are recommended.

NSCLC with *KRAS* G12C Mutation

KRAS is a protein with intrinsic GTPase activity that is commonly mutated in lung cancers; these mutations can result in unregulated signaling through the MAP/ERK pathway.[1053,1054] *KRAS* G12C is an activating mutation that results in increased activation of downstream oncogenic pathways.[317] Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have a *KRAS* mutation, the most common mutation in this population.[118,175,211,307,308] Some, but not all, *KRAS* mutations are associated with cigarette smoking, unlike many of the other actionable mutations (eg, *EGFR* mutations, *ALK* rearrangements).[309,1055]

Clinical Data

Targeted therapies are not recommended as first-line treatment options for advanced or metastatic NSCLC with a *KRAS* G12C mutation, unlike most other actionable alterations. Data indicate that patients with advanced or metastatic NSCLC and *KRAS* mutations are likely to derive benefit from immunotherapy-based regimens in the first-line setting.[1022,1023] Additionally, one study reported a positive association between PFS and PD-L1 expression in patients with advanced NSCLC and *KRAS* mutations who received ICI monotherapy.[184]

Two targeted therapies are available as subsequent therapy options for NSCLC with *KRAS* G12C mutations. Adagrasib and sotorasib are oral small molecules that target KRAS G12C and have both been granted accelerated approval by the FDA for the treatment of adults with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who received at least one prior systemic therapy.[315,1056,1057]

A phase 2 study assessed sotorasib as subsequent therapy in 126 patients with *KRAS* G12C mutation-positive advanced NSCLC who had previously received platinum-based chemotherapy (± PD-1 or PD-L1 immunotherapy).[317] The median OS was 12.5 months and the objective response rate was 37.1%; a complete response was reported in 4 patients. Treatment-related grade 3 AEs occurred in 19.8% of patients, including diarrhea, and increased alanine transaminase (ALT) and aspartate transferase (AST) levels; one treatment-related grade 4 event occurred (dyspnea and pneumonitis).

A phase 2 study evaluated adagrasib as subsequent therapy in 116 patients with *KRAS* G12C mutation-positive advanced NSCLC who had previously received at least one platinum-based chemotherapy and immunotherapy.[315] The median OS was 12.6 months and the objective response rate was 42.9%. The intracranial response rate was 33.3%. Grade 3 or higher AEs occurred in 44.8% of patients, including anemia, pneumonia, dyspnea, acute kidney injury, hyponatremia, fatigue, nausea, and increased ALT and AST levels. There were two deaths (cardiac failure and pulmonary hemorrhage).

A randomized phase 3 trial compared subsequent therapy with sotorasib to treatment with docetaxel in 345 patients with *KRAS* G12C mutation-positive advanced NSCLC who had previously received

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platinum-based chemotherapy plus a PD-1 or PD-L1 inhibitor.[316] Median PFS was 5.6 months in patients receiving sotorasib compared with 4.5 months in those receiving docetaxel (HR, 0.66; *P* = .0017). There was no reported difference in OS.

NCCN Recommendations (NSCL-26)

The NCCN NSCLC Panel recommends using PD-L1 level to determine the appropriate first-line systemic therapy regimen (such as immunotherapy and/or chemotherapy) for patients with advanced or metastatic NSCLC with *KRAS* G12C mutations. See NSCL-37 and NSCL-38 in the full NCCN Guidelines for NSCLC at www.NCCN.org for treatment recommendations based on PD-L1 level.

The panel recommends sotorasib or adagrasib as subsequent therapy options for patients who experience disease progression after treatment with first-line systemic therapy. Sotorasib or adagrasib may also be used as third-line therapy or beyond if the patient has not previously received a KRAS G12C-targeted therapy. The panel notes that switching between agents with a similar mechanism of action at the time of progression is not recommended.

NSCLC with *ALK* Rearrangement

About 5% of patients with NSCLC have *ALK* gene rearrangements leading to gene fusions.[120] These events can result in dysregulation and inappropriate ALK signaling.[1058]

Clinical Data

Initial studies have shown that single-agent ALK inhibitors (crizotinib and ceritinib) are superior to chemotherapy in patients with advanced or metastatic NSCLC with *ALK* rearrangements.[218-220,1059] Both crizotinib and ceritinib are FDA-approved for the treatment of adults with *ALK*-positive metastatic NSCLC.[1060,1061] Subsequent trials have compared newer agents to crizotinib.

Alectinib is an ALK inhibitor that is approved by the FDA for the treatment of patients with *ALK*-positive metastatic NSCLC.[1062,1063] 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.[218] Disease progression or death occurred in a lower proportion of patients receiving alectinib when compared with crizotinib (41% vs. 68%). Investigator-assessed PFS rate was higher with alectinib versus crizotinib (68.4% versus 48.7%; HR, 0.47; *P* < .001). The median PFS was not reached for alectinib when compared with crizotinib at 11.1 months. Fewer patients receiving alectinib had CNS progression (12%) versus crizotinib (45%). Response rates were 82.9% in the alectinib group versus 75.5% in the crizotinib group (*P* = .09). Patients receiving alectinib had fewer grade 3 or higher AEs than those who received crizotinib (41% vs. 50%, 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%) versus crizotinib (4.6%); two treatment-related deaths were reported with crizotinib and none with alectinib. An updated analysis of the trial reported that the five-year OS rate was 62.5% with alectinib and 45.5% with crizotinib.[14]

J-ALEX, a phase 3 open-label randomized trial, assessed first-line therapy with alectinib versus crizotinib in 207 Japanese patients with *ALK*-positive advanced NSCLC who were ALK inhibitor-naive.[1064] Median PFS was not reached with alectinib versus 10.2 months with crizotinib (HR, 0.34; stratified log-rank *P* < .0001). Grade 3 or 4 AEs were less frequent with alectinib (26%) than with crizotinib (52%). Fewer patients stopped taking alectinib (9%) because of an AE when compared with crizotinib (20%).

Brigatinib is an ALK inhibitor that is approved by the FDA for the treatment of adults with *ALK*-positive metastatic NSCLC.[1065,1066]

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ALTA-1L, a phase 3 randomized trial, assessed brigatinib versus crizotinib as first-line therapy in 275 patients with *ALK*-positive metastatic NSCLC.[221] At the first interim analysis, PFS rate was higher in patients receiving brigatinib (67%) than in those receiving crizotinib (43%) (HR, 0.49; $P < .001$). The rate of intracranial response was also higher with brigatinib (78%) versus crizotinib (29%).[221] At the second interim analysis (24.9 months of median follow-up), brigatinib continued to show improved blinded independent review committee (BIRC)-assessed PFS when compared with crizotinib (48% vs. 26%; HR, 0.49; $P < .0001$).[1067] After 3 years, the PFS was 43% for brigatinib versus 19% for crizotinib (HR, 0.48). The median OS was not reached in either arm; however, a post-hoc analysis suggested a survival benefit for patients with intracranial metastasis (HR, 0.43; 95% CI, 0.21-0.89).[1068]

Lorlatinib is an ALK inhibitor that is approved by the FDA for the treatment of adults with *ALK*-positive metastatic NSCLC.[1069] CROWN, a phase 3 randomized trial, assessed lorlatinib versus crizotinib as first-line therapy in 296 patients with *ALK*-positive advanced NSCLC.[217] At 12 months, 78% of patients were alive without disease progression in the lorlatinib group versus 39% in the crizotinib group (HR, 0.28; $P < .001$). The objective response rate was 76% for patients receiving lorlatinib and 58% for those receiving crizotinib. For patients with measurable brain metastases, an intracranial response was reported in 82% of those receiving lorlatinib and 23% of those receiving crizotinib. A complete intracranial response was achieved in 71% of those who received lorlatinib. Hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects were the most common AEs seen with lorlatinib. More grade 3 or 4 AEs (mainly altered lipid levels) occurred with lorlatinib than with crizotinib (72% vs. 56%, respectively). A post hoc analysis of the CROWN study showed that in patients with brain metastases at baseline, the 12-month cumulative incidence of CNS progression was 7% with lorlatinib compared with 72% with crizotinib; the 12-month PFS rates were 78% versus 22%, respectively.[1070] In patients without brain metastases at baseline, the 12-month cumulative incidence of CNS progression was 1% with lorlatinib compared with 18% with crizotinib; the 12-month PFS rates were 78% versus 45%, respectively.[1070] Updated data from the CROWN trial demonstrated that the 3-year PFS rate was 64% with lorlatinib and 19% with crizotinib.[1071] Additionally, the HR for time to intracranial progression for lorlatinib in comparison to crizotinib was 0.10 among those with baseline brain metastases and 0.02 among those without brain metastases at baseline.

Data have suggested that lorlatinib can be used as subsequent therapy in patients with disease progression after treatment with other ALK inhibitors, including those with CNS metastases.[1072,1073] A phase 2 trial assessed lorlatinib in patients with *ALK*-positive or *ROS1*-positive advanced NSCLC and disease progression after ALK inhibitor therapy; many patients had asymptomatic CNS metastases.[1072] In the cohort of *ALK*-positive patients who had received at least one previous ALK inhibitor, objective responses were achieved in 47% of patients; 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. Lorlatinib was effective in patients who had received up to three previous ALK inhibitors. Grade 3 to 4 AEs included hypercholesterolemia and hypertriglyceridemia. Serious treatment-related AEs occurred in 7% of patients including cognitive effects in 1%; the cognitive effects resulted in permanent discontinuation of lorlatinib.

Data from this trial also showed that lorlatinib is effective as subsequent therapy in patients with the resistance mutation *ALK* G1202R, which is often detected after progression on second-generation ALK TKIs such as brigatinib, alectinib, or ceritinib.[1074] The objective response rate with lorlatinib was 62% when using plasma ctDNA (and 69% when using

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tissue) for patients with *ALK* resistance mutations and disease progression on second-generation ALK TKIs compared with 32% (plasma) and 27% (tissue) in patients without *ALK* mutations. However, data from other studies suggest that lorlatinib may not be effective in NSCLC with resistant compound *ALK* mutations (eg, combination of L1196M and G1202R).[1074-1076]

NCCN Recommendations (NSCL-27, NSCL-28, and NSCL-29)

The NCCN NSCLC Panel recommends alectinib, brigatinib, or lorlatinib as preferred first-line therapy options for patients with advanced or metastatic NSCLC and *ALK* rearrangements. Ceritinib is an "other recommended" first-line option, whereas crizotinib is considered useful in certain circumstances. All these options are appropriate for patients with performance status 0–4 and are category 1 recommendations if an *ALK* rearrangement is discovered prior to first-line systemic therapy.

Upon disease progression, the NCCN Panel recommends considering plasma and/or tissue-based testing using broad molecular profiling to determine genomic resistance mechanisms and to guide use of subsequent therapy options.[1074]

After progression on alectinib, brigatinib, or ceritinib, the NCCN Panel recommends a switch in treatment to lorlatinib. Continuing lorlatinib is an option for those who experienced disease progression on or after lorlatinib given in the first-line setting. Lorlatinib can be used for NSCLC with resistant mutations such as *ALK* G1202R or L1196M, but not if compound resistant mutations are detected (ie, both L1196M and G1202R). Continuing the same TKI that was used in the first-line setting is another option, except for those with symptomatic systemic progression and multiple lesions.

Systemic therapy options such as chemotherapy (see NSCL-K 1 of 5 or NSCL-K 2 of 5 in the NCCN Guidelines for NSCLC) are recommended as additional subsequent therapy options for patients with symptomatic systemic progression and multiple lesions. Data suggest that PD-1/PD-L1 inhibitor monotherapy is less effective in *ALK*-positive NSCLC, irrespective of PD-L1 expression.[184,827,1052]

Definitive local therapy has a role in the treatment of metastatic *ALK*-positive NSCLC. For patients with a limited number of initial sites of metastasis (oligometastasis; limited number is not universally defined, but clinical trials have included 3-5 metastases), definitive local therapy (eg, SABR or surgery) should be considered as consolidation after initiating ALK TKI therapy (local consolidative therapy) if not given prior to ALK TKI therapy (see *Principles of Radiation Therapy* [NSCL-C] and NSCL-15 in the NCCN Guidelines for NSCLC). Local therapy may also be an appropriate subsequent therapy option for certain patients who have progressed after initial therapy with an ALK TKI. For those with asymptomatic progression or symptomatic systemic progression that is limited in nature (oligoprogression), definitive local therapy (eg, SABR or surgery) should be considered for limited lesions; IGTA therapy (eg, cryotherapy, microwave ablation, radiofrequency ablation) may also be an option for certain patients (see *Principles of Image-Guided Thermal Ablation Therapy* [NSCL-D] in the NCCN Guidelines for NSCLC). For patients with CNS progression, definitive local therapy (eg, SRS with or without surgical resection) should be considered for symptomatic lesions, and SRS should be considered for asymptomatic lesions at risk of symptomatic progression based on factors including size, location, and edema. See also the NCCN Guidelines for CNS Cancers on www.NCCN.org for additional recommendations.

NSCLC with *ROS1* Rearrangement

It is estimated that *ROS1* gene rearrangements occur in about 1% to 2% of patients with NSCLC.[344-347] *ROS1* rearrangements can result in ROS1 kinase dysregulation and inappropriate signaling.[1077] Although ROS1 is a

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distinct receptor tyrosine kinase, it is similar to ALK and members of the insulin receptor family.[343,344] Several (but not all) targeted therapies recommended for the treatment of *ALK*-positive metastatic NSCLC are also recommended for the treatment of *ROS1*-positive metastatic disease (ie, ceritinib, crizotinib, lorlatinib).

Clinical Data

Crizotinib is a first-generation oral TKI that inhibits ALK, ROS1, and MET.[190,219,318,1078-1082] Crizotinib is approved for the treatment of adults with *ROS1*-positive and *ALK*-positive metastatic NSCLC.[1060] Crizotinib is effective for patients with *ROS1* rearrangements with response rates of about 70% to 80% including complete responses.[190,344,349,1083,1084] A phase 2 single-arm trial assessed crizotinib in 127 East Asian patients with *ROS1*-positive advanced NSCLC who had received 3 or fewer lines of systemic therapy. The objective response rate was 71.7% with 17 complete responses; the median duration of response was 19.7 months. The median PFS was 15.9 months.[1084]

PROFILE 1001, a phase 1 study, assessed crizotinib in 50 patients with advanced NSCLC and *ROS1* rearrangements.[344] Crizotinib yielded an objective response rate of 72%; there were 3 complete responses and 33 partial responses.[344] The median duration of response was 17.6 months, and the median PFS was 19.2 months. Updated results from PROFILE 1001 reported an objective response rate of 72% with crizotinib including 6 confirmed complete responses in 53 patients with *ROS1*-positive advanced NSCLC.[22] The median OS was 51.4 months. No grade 4 or higher treatment-related AEs were reported.

The phase 2 single-arm EUCROSS study reported that crizotinib yielded an objective response rate of 70% and a median PFS of 20 months in 30 patients with *ROS1*-positive advanced NSCLC.[1083] AEs related to treatment occurred in 97% of patients. A retrospective study based on data from Europe in patients (n = 30 evaluable) with stage IV lung adenocarcinoma and *ROS1* rearrangements also assessed crizotinib.[190] 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%; the median PFS was 7.2 months.

Entrectinib is an oral TKI that inhibits several kinases (including ROS1, ALK, and TRK) and is approved by the FDA for the treatment of *ROS1*-positive metastatic NSCLC.[330,1085,1086] Entrectinib has been assessed in several phase 1 and 2 trials in patients with *ROS1*-positive metastatic NSCLC (ie, phase 2 STARTRK-2 trial, phase 1 STARTRK-1 trial, phase 1 ALKA-372-001 trial).[348,1087] Pooled data from these 3 trials in 53 patients with *ROS1*-positive metastatic NSCLC receiving first-line entrectinib showed an objective response rate of 77% (3 complete responses).[348,357] The intracranial overall response rate was 55% (4 complete responses, 7 partial responses) among the 20 patients with baseline CNS metastases.[348,1087] In the larger *ROS1* population (n = 134), grade 3 to 4 AEs were seen in 34% of patients. Fifteen patients had serious AEs such as nervous system disorders and cardiac disorders. Although entrectinib has better CNS penetration than crizotinib, it is more toxic.[357]

Repotrectinib is a next-generation ROS1, TRK, and ALK TKI that is approved by the FDA for the treatment of adults with locally advanced or metastatic *ROS1*-positive NSCLC.[1088,1089] The phase 1 and 2 TRIDENT-1 trial evaluated repotrectinib in 71 patients with *ROS1* fusion-positive NSCLC who had not previously received a ROS1 TKI and 56 patients with *ROS1* fusion-positive NSCLC who had previously received one ROS1 TKI (crizotinib, entrectinib, or ceritinib) and never received chemotherapy.[1090] The confirmed objective response with repotrectinib was 79% among those who had not received a ROS1 TKI and 38%

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among those who had received one ROS1 TKI. Patients who had not received a ROS1 TKI had a median duration of response of 34.1 months and median PFS of 35.7 months. Patients who previously received one ROS1 TKI and no chemotherapy had a median duration of response of 14.8 months and a median PFS of 9 months. For those with measurable brain metastases at baseline, the intracranial objective response with repotrectinib was 89% (8/9) among those who had no previous ROS1 TKI and 38% (5/13) among those who had one previous TKI and no chemotherapy. The most common treatment-related AEs were dizziness, dysgeusia, and paresthesia.

Lorlatinib is an oral TKI that is active against both ALK and ROS1 and can penetrate the blood-brain barrier.[1069,1091] A phase 1 to 2 trial assessed lorlatinib in 69 patients with *ROS1*-positive metastatic NSCLC.[356] Many patients (58%) had previously received crizotinib; some patients were TKI naïve (30%). Objective responses were achieved in 35% (14/40) of patients who previously received crizotinib and 62% (13/21) of those who were TKI-naïve. An intracranial response was observed in 50% (12/24) of patients who previously received crizotinib and 64% (7/11) of those who were TKI-naïve. Serious treatment-related AEs occurred in 7% of patients.

Data suggest that ceritinib, an oral TKI that has activity against both ALK and ROS1, can also be considered as a treatment option for patients with NSCLC and *ROS1* rearrangements.[1061,1091,1092]

NCCN Recommendations (NSCL-30 and NSCL-31)

The NCCN NSCLC Panel recommends entrectinib, crizotinib, or repotrectinib as preferred first-line treatment options for patients with *ROS1*-positive advanced or metastatic NSCLC, while ceritinib is considered an “other recommended” first-line treatment option. All are appropriate for patients with performance status 0–4; however, entrectinib or repotrectinib may be better for patients with brain metastases.

Upon disease progression, plasma or tissue-based testing via broad molecular profiling should be considered to identify genomic resistance mechanisms. If plasma-based testing is negative, the panel strongly recommends tissue-based testing with rebiopsy material.

For asymptomatic progression on entrectinib, crizotinib, repotrectinib, or ceritinib, the NCCN NSCLC Panel recommends repotrectinib (if not previously given) or lorlatinib as subsequent therapy options. For patients with CNS progression, entrectinib (if previously treated with crizotinib or ceritinib), repotrectinib (if previously treated with crizotinib, ceritinib, or entrectinib), or lorlatinib are recommended options. See also the NCCN Guidelines for CNS Cancers on www.NCCN.org for additional recommendations. For symptomatic systemic progression with multiple systemic lesions, repotrectinib (if not previously given) or lorlatinib are recommended targeted therapy options. Systemic therapies (such as chemotherapy with or without immunotherapy) can be considered in this setting as well (see NSCL-K 1 of 5 and NSCL-K 2 of 5 in the NCCN Guidelines for NSCLC). Data indicate that ICI monotherapy is less effective in NSCLC with *ROS1* alterations.[184,1052]

Continuation of entrectinib, crizotinib, repotrectinib, or ceritinib is also an option for certain patients with disease progression; continuation of these therapies is not recommended for those with symptomatic systemic progression and either multiple lesions or brain metastases.

Definitive local therapy has a role in the treatment of metastatic *ROS1*-positive NSCLC. For patients with a limited number of initial sites of metastasis (oligometastasis; limited number is not universally defined, but clinical trials have included 3-5 metastases), definitive local therapy (eg, SABR or surgery) should be considered as consolidation after

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initiating ROS1 TKI therapy (local consolidative therapy) if not given prior to ROS1 TKI therapy (see *Principles of Radiation Therapy* [NSCL-C] and NSCL-15 in the NCCN Guidelines for NSCLC). Local therapy may also be an appropriate subsequent therapy option for certain patients who have progressed after initial therapy with a ROS1 TKI. For patients with asymptomatic or symptomatic systemic progression that is limited in nature (oligoprogression), definitive local therapy (eg, SABR or surgery) should be considered. IGTA therapy, such as cryotherapy, microwave ablation, or radiofrequency ablation, may also be an option for select patients; see *Principles of Image-Guided Thermal Ablation Therapy* (NSCL-D) in the NCCN Guidelines for NSCLC for additional information. For those with CNS progression, definitive local therapy (eg, SRS with or without surgical resection) should be considered for symptomatic lesions, and SRS should be considered for asymptomatic lesions at risk of symptomatic progression based on factors including size, location, and edema. See also the NCCN Guidelines for CNS Cancers on www.NCCN.org for additional recommendations.

NSCLC with *BRAF* V600E Mutation

The *BRAF* V600E mutation occurs in 1% to 2% of patients with lung adenocarcinoma; it is the most common of the *BRAF* point mutations when considered across all tumor types.[188,241] Rare *BRAF* mutations include V600K and V600D. The *BRAF* gene encodes for BRAF, a serine/threonine kinase; activating mutations in *BRAF* result in unregulated signaling through the MAP/ERK pathway.[1093]

Clinical Data

Dabrafenib and encorafenib are both oral BRAF kinase inhibitors.[188,189,1094,1095] Dabrafenib, in combination with MEK1/2 inhibitor trametinib, is approved by the FDA for the treatment of metastatic NSCLC with *BRAF* V600E mutation.[1096] Encorafenib, in combination with MEK1/2 inhibitor binimetinib, is FDA-approved for the treatment of metastatic NSCLC with a *BRAF* V600E mutation.[1097]

A phase 2 trial assessed dabrafenib in combination with trametinib as first-line therapy in 36 patients with metastatic NSCLC and *BRAF* V600E mutations.[15,1098] The overall response rate was 63.9%; there were 2 complete responses.[15] The median PFS was 10.8 months.[15] Many patients (69%) had one or more grade 3 or 4 AEs.[1098] Serious AEs included increased ALT, increased AST, pyrexia, and decreased ejection fraction.[1098] An updated analysis reported that patients receiving dabrafenib plus trametinib had a median OS of 17.3 months.[15] After 5 years, the OS rate was 22%.

The same trial also assessed the dabrafenib plus trametinib regimen as subsequent therapy in 57 patients with advanced NSCLC and *BRAF* V600E mutations and disease progression on chemotherapy.[15,188] The overall response rate was 68.4% and the median PFS was 10.2 months.[15] Serious AEs occurred in 56% of patients, including pyrexia, anemia, confused state, hemoptysis, hypercalcemia, and cutaneous squamous cell carcinoma.[188] Grade 3 to 4 AEs included neutropenia, hyponatremia, and anemia.[188] An updated analysis reported that the median OS was 18.2 months.[15] After 5 years, the OS rate was 19%.

A phase 2, open-label, single-arm study evaluated encorafenib in combination with binimetinib in patients with *BRAF* V600E-positive metastatic NSCLC in both the first-line and subsequent therapy settings.[1095] The objective response rate was 75% in treatment-naïve patients and 46% in previously treated patients. The median PFS was not estimable for the treatment-naïve patients and 9.3 months in those who were previously treated. The most common treatment-related AEs were nausea, diarrhea, and fatigue. One Grade 5 treatment-related AE (intracranial hemorrhage) was reported.

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Data suggest that treatment with a single-agent BRAF inhibitor, such as vemurafenib, can also be used to treat patients with metastatic NSCLC and *BRAF* V600E.[243] Results from retrospective studies indicate that patients with advanced NSCLC and *BRAF* mutations may also derive benefit from PD-1/PD-L1 inhibitors.[184,1099] Therefore, first-line treatment with an ICI-based regimen can be considered, particularly for those with a minimal burden of disease and/or high PD-L1 levels.

NCCN Recommendations (NSCL-32)

The NCCN NSCLC Panel recommends dabrafenib plus trametinib or encorafenib plus binimetinib as preferred first-line therapy options for patients with *BRAF* V600E mutation-positive advanced or metastatic NSCLC. The panel also recommends dabrafenib plus trametinib or encorafenib plus binimetinib as subsequent therapy options if the patient with *BRAF* V600E mutation did not previously receive a BRAF inhibitor. Single-agent therapy with dabrafenib or vemurafenib can be considered for those who do not tolerate dabrafenib plus trametinib. These options are all appropriate for patients with performance status 0–4.

Other first-line therapy options include systemic therapy regimens (such as chemotherapy with or without immunotherapy) listed on NSCL-K 1 of 5 and NSCL-K 2 of 5 in the NCCN Guidelines for NSCLC; these are designated as “other recommended” options. These regimens can also be used as subsequent therapy options for patients whose disease progressed after receiving a first-line therapy that included a BRAF inhibitor.

NSCLC with *NTRK* Gene Fusion

NTRK1/2/3 gene fusions encode TRK fusion proteins that act as oncogenic drivers for various solid tumors, including lung, salivary gland, thyroid, and sarcoma.[328,1100] It is estimated that *NTRK1/2/3* fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers such as *EGFR*, *ALK*, or *ROS1*.[327]

Clinical Data

Entrectinib and larotrectinib are oral TRK inhibitors and both were granted accelerated approval by the FDA for the treatment of patients with solid tumors that have an *NTRK* gene fusion.[1086,1100,1101] Entrectinib is also approved for the treatment of *ROS1*-positive metastatic NSCLC (see above for more information).[1086]

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).[331] 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% (7/10).[331] Updated data in 22 patients with *NTRK*-positive locally advanced or metastatic NSCLC found that the objective response rate was 64.5%; a complete response was observed in 16.1% of patients.[1102] Among the 15 patients with CNS metastases at baseline, the intracranial objective response rate was 60%. Most treatment-related AEs were grade 1 or 2.

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 (by independent review) of 75%.[328] In an analysis of 15 patients with *NTRK* fusion-positive lung cancer, the objective response rate by investigator assessment was 73%; 1 patient had a complete response and 10 had a partial response.[1103] The median OS was 40.7 months, and the median PFS was 35.4 months. Among those with CNS metastases at baseline, the objective response rate was 63%. Most of the reported AEs were grade 1 or 2.

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NCCN Recommendations (NSCL-33)

The NCCN NSCLC Panel recommends larotrectinib or entrectinib as preferred first-line therapy options for patients with *NTRK1/2/3* gene fusion-positive advanced or metastatic NSCLC (performance status 0–4). Either may be used as a subsequent therapy option for *NTRK1/2/3* gene fusion-positive metastatic NSCLC if larotrectinib or entrectinib was not previously given as first-line therapy.

Other systemic therapies (such as chemotherapy with or without immunotherapy) on NSCL-K 1 of 5 and NSCL-K 2 of 5 in the NCCN Guidelines for NSCLC are categorized as first-line treatment options that may be useful in certain circumstances for *NTRK*-positive advanced or metastatic NSCLC; these are also recommended as subsequent therapy options for patients whose disease progressed after treatment with larotrectinib or entrectinib. Data indicate that ICI monotherapy may be less effective in NSCLC with *NTRK* mutations.[184,1052]

NSCLC with *MET* Exon 14 Skipping Mutation

*MET*ex14 skipping mutations occur in 3% to 4% of patients with adenocarcinoma NSCLC and 1% to 2% of patients with other NSCLC histologies.[319,320] *MET*ex14 skipping mutations lead to dysregulation of the MET receptor tyrosine kinase and inappropriate signaling. The presence of this type of mutation is associated with responsiveness to oral MET TKIs. The NCCN Guidelines recommend testing for *MET*ex14 skipping mutations as part of broad molecular profiling, due to the availability of FDA-approved targeted therapies for this biomarker.

In contrast, high-level *MET* amplification is designated as an emerging biomarker in the NCCN Guidelines because there is less evidence for using targeted agents for this biomarker. In addition, no therapies have been approved by the FDA for the treatment of metastatic NSCLC with *MET* amplification.

Clinical Data

Capmatinib and tepotinib are oral TKIs that selectively inhibit MET kinase and are both approved by the FDA for the treatment of adults with metastatic NSCLC whose tumors have a *MET* exon 14 skipping mutation.[1104-1106]

GEOMETRY, a phase 2 study, assessed capmatinib in different cohorts of patients with *MET* genomic alterations, including those with *MET*ex14 skipping mutations; patients had stage IIIB or IV NSCLC and were wild-type for *EGFR* and *ALK* genomic alterations.[170,324] Updated data from GEOMETRY showed that first-line therapy with capmatinib resulted in an overall response rate of 68% in 28 patients with *MET*ex14 skipping mutations; the median PFS was 12.4 months for first-line therapy.[170] Subsequent therapy with capmatinib yielded an overall response rate of 41% in 69 patients with *MET*ex14 skipping mutations; the median PFS was 5.4 months for subsequent therapy.[170] The data from GEOMETRY also suggest that capmatinib is effective for patients with brain metastases.[170,1107] Among patients with brain metastases, a response to capmatinib was reported in 54%; 4 patients had a complete response in the brain. However, 43% of patients whose disease responded had previously received RT.[170] Common AEs for patients with *MET*ex14 skipping mutations across all cohorts included peripheral edema, nausea, and vomiting, but most of these events were grades 1 to 2.[170] One treatment-related death occurred.

VISION, a phase 2 study, assessed tepotinib in patients with *MET*ex14 skipping mutations; patients mainly had stage IV NSCLC and were wild-type (negative) for *EGFR* and *ALK* genomic alteration.[167,1108,1109] The response rate to tepotinib was 46%; PFS was 8.5 months in the combined biopsy group (tissue biopsy plus plasma ctDNA).[1109] Grade 3 or higher AEs occurred in 28% of patients receiving tepotinib, such as peripheral edema; 11% of patients had to permanently discontinue

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tepotinib because of peripheral edema, pleural effusion, or dyspnea.[1109] One treatment-related death occurred.[1109] The 18-month follow-up analysis of VISION confirmed the efficacy of tepotinib in patients with *MET*ex14-positive advanced/metastatic NSCLC.[1110] Among treatment-naïve patients, the objective response rate with tepotinib was 57.3% and the median duration of response was 46.6 months. Among previously treated patients, the objective response rate was 45% and the median duration of response was 12.6 months.

Data suggest that crizotinib, an oral TKI that inhibits multiple kinases, including ALK, ROS1, and MET, is also a viable option for patients with advanced NSCLC and *MET*ex14 skipping mutations.[325]

NCCN Recommendations (NSCL-34)

The NCCN NSCLC Panel recommends capmatinib, tepotinib, or crizotinib as first-line treatment options for patients with advanced or metastatic NSCLC and *MET*ex14 skipping mutation. These are also recommended as subsequent therapy options, if the patient was not previously treated with capmatinib, tepotinib, or crizotinib. Capmatinib and tepotinib are categorized as preferred, while crizotinib is considered useful in certain circumstances. The panel notes that switching between agents with a similar mechanism of action at the time of progression is not recommended.

Other systemic therapy regimens (such as chemotherapy with or without immunotherapy) listed on NSCL-K 1 of 5 and NSCL-K 2 of 5 in the NCCN Guidelines for NSCLC are recommended as useful in certain circumstances for first-line therapy. These are also recommended as subsequent therapy options in patients whose disease progressed following treatment with capmatinib, tepotinib, or crizotinib. Data indicate that ICI monotherapy may be less effective in NSCLC with *MET* alterations.[184,1052]

NSCLC with *RET* Rearrangement

RET rearrangements occur in about 1% to 2% of patients with NSCLC and are more frequent in patients with adenocarcinoma histology.[332-336] Rearrangements may occur between *RET* and other genes, including *KIF5B* and *CCDC6*, which can lead to overexpression and dysregulation of RET kinase and inappropriate signaling.[332,333]

Clinical Data

Selpercatinib and pralsetinib are oral TKIs that inhibit RET and are both approved by the FDA for the treatment of metastatic NSCLC with *RET* gene fusion.[1111-1113]

Libretto-001, a phase 1/2 study, assessed selpercatinib in patients with NSCLC and *RET* rearrangements.[338,1114] Updated results from the trial showed that first-line therapy with selpercatinib yielded an objective response rate of 85%.[338] Second-line therapy with selpercatinib yielded an objective response rate of 64%; the median PFS was 18.4 months. Of patients with brain metastases, a response to selpercatinib was reported in 91% (10/11). Common grade 3 or more AEs with selpercatinib included hypertension, increased liver enzyme levels, hyponatremia, and lymphopenia.

Libretto-431, a randomized phase 3 trial, evaluated selpercatinib versus control (platinum-based chemotherapy with or without pembrolizumab) as first-line therapy in 212 patients with advanced NSCLC and *RET* gene fusion.[1115] Based on the interim analysis, the median PFS was longer with selpercatinib than with the control treatment (24.8 months vs. 11.2 months; HR, 0.46; $P < .001$). The HR for time to CNS progression was 0.28. Among those with brain metastases at baseline, a higher proportion of patients in the selpercatinib group experienced an intracranial response compared with those in the control group (82% versus 58%).

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ARROW, a phase 1/2 study, assessed pralsetinib in 233 patients with metastatic NSCLC and *RET* rearrangements.[337] First-line therapy with pralsetinib resulted in an overall response rate of 70%; 3 patients (11%) had a complete response. Second-line therapy with pralsetinib resulted in an overall response rate of 61% (53/87); 5 patients (6%) had a complete response. Among the nine patients with measurable brain metastases, a response to pralsetinib was reported in 56%; 3 patients had an intracranial complete response. Grade 3 or more AEs with pralsetinib include anemia, neutropenia, and hypertension. Common AEs with pralsetinib included increased AST levels, increased ALT levels, anemia, hypertension, constipation, and neutropenia. Updated data from the ARROW trial showed that the overall response rate with pralsetinib was 72% for those who were treatment-naïve and 59% for those who previously received platinum-based chemotherapy.[1116] Among the 10 patients with intracranial metastases (all who previously received systemic therapy), the intracranial response rate was 70%.

Data suggest that cabozantinib, an oral kinase inhibitor active against multiple receptor tyrosine kinases, including RET, MET, VEGFR2, and others,[1111] is another viable treatment option for patients with *RET*-positive metastatic NSCLC.[339,340,1117]

NCCN Recommendations (NSCL-35)

The NCCN NSCLC Panel recommends selpercatinib or pralsetinib as preferred first-line therapy options for patients with advanced or metastatic NSCLC and *RET* rearrangements. Cabozantinib is recommended by the panel as a first-line therapy option that may be useful in certain circumstances. All are appropriate for performance status 0–4. These agents are also recommended as subsequent therapy options for patients with *RET* rearrangement–positive metastatic NSCLC if selpercatinib, pralsetinib, or cabozantinib were not previously given as first-line therapy. The panel notes that switching between agents with a similar mechanism of action at the time of progression is not recommended.

Other systemic therapies (such as chemotherapy with or without immunotherapy) on NSCL-K 1 of 5 and NSCL-K 2 of 5 in the NCCN Guidelines for NSCLC are categorized as “other recommended” first-line treatment options for *RET*-positive advanced or metastatic NSCLC; these are also recommended as subsequent therapy options in patients whose disease progressed after treatment with selpercatinib, pralsetinib, or cabozantinib. Data indicate that ICI monotherapy may be less effective in NSCLC with *RET* rearrangements.[184,1052]

NSCLC with *ERBB2 (HER2)* Mutation

ERBB2 encodes for HER2, a receptor tyrosine kinase found on the surface of normal epithelial cells that is often overexpressed or mutated in a variety of human malignancies.[1118] Approximately 3% of advanced NSCLC (adenocarcinoma) have a mutation in *ERBB2 (HER2)*.[169] Resources are available to assess whether a specific *ERBB2* (*HER2*) mutation is oncogenic or likely to be oncogenic (such as oncoKB.org).

Clinical Data

Fam-trastuzumab deruxtecan-nxki was granted accelerated approval by the FDA for the treatment of adults with unresectable or metastatic NSCLC tumors that have activating *ERBB2 (HER2)* mutations, and who received a prior systemic therapy.[1119] Fam-trastuzumab deruxtecan-nxki is a humanized monoclonal antibody drug conjugate consisting of trastuzumab, an antibody targeting HER2, linked to deruxtecan, a topoisomerase I inhibitor; the agent remains stable until it is cleaved by peptides in cancer cells.[169]

DESTINY-Lung01, a phase 2 study, assessed fam-trastuzumab deruxtecan-nxki in 91 patients with metastatic nonsquamous NSCLC and *ERBB2* mutations (not *ERBB2* amplification).[169,1120,1121] Most patients had

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ERBB2 (*HER2*) exon 20 insertion mutations (86%); 66% were female, 57% had never smoked cigarettes, 36% had CNS metastases at baseline, and all had nonsquamous NSCLC.[169] The objective response rate with fam-trastuzumab deruxtecan-nxki was 55%; most patients had received prior treatment.[169] Median OS was 17.8 months.[169] Grade 3 or higher AEs occurred in 46% of patients including neutropenia (19%). Two patients died from drug-related interstitial lung disease.

Data have shown that ado-trastuzumab emtansine (also known as T-DM1), a humanized antibody-drug conjugate consisting of trastuzumab and microtubule inhibitor emtansine, also has efficacy in patients with metastatic or recurrent NSCLC and *ERBB2* (*HER2*) mutations.[168,1122]

NCCN Recommendations (NSCL-36)

The NCCN NSCLC Panel recommends the systemic therapy regimens (such as chemotherapy with or without immunotherapy) listed on NSCL-K 1 of 5 or NSCL-K 2 of 5 in the NCCN Guidelines for NSCLC for the first-line treatment of advanced or metastatic NSCLC with *ERBB2 (HER2)* mutations. Data indicate that ICI monotherapy may be less effective in NSCLC with *ERBB2 (HER2)* mutations.[184,1052]

After disease progression, fam-trastuzumab deruxtecan-nxki is recommended as a preferred subsequent therapy option, while ado-trastuzumab emtansine is categorized as an “other recommended” option. The panel notes that switching between agents with a similar mechanism of action at the time of progression is not recommended.

NSCLC with HER2 protein overexpression

This section is under development.

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Systemic Therapy for Advanced or Metastatic NSCLC: Other Options and Additional Information

For patients with metastatic NSCLC and contraindications to pembrolizumab or other ICIs, chemotherapy options are recommended (such as carboplatin plus 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).[962,1123] Chemotherapy with or without bevacizumab is an option if eligibility criteria are met for patients with nonsquamous NSCLC and negative test results for actionable driver mutations, and with PD-L1 expression less than 1%.[1124] Chemotherapy with or without bevacizumab regimens may be used as first-line or subsequent therapy options in eligible patients with actionable driver mutations as shown in the algorithm, although they are generally not preferred options. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations. 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.[1125] A phase 3 randomized trial in older 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).[1126] Systemic therapy for older patients with advanced NSCLC needs to be carefully selected to avoid adverse reactions.[1127] The NCCN NSCLC Panel does not recommend carboplatin plus vinorelbine, cisplatin plus vinorelbine, etoposide, irinotecan, and vinorelbine for patients with metastatic nonsquamous NSCLC or NSCLC NOS and negative test results for actionable driver mutations, because these regimens are rarely used in the United States.

For patients with metastatic squamous cell NSCLC and negative test results for actionable driver mutations, chemotherapy plus immunotherapy regimens—such as pembrolizumab plus carboplatin with either paclitaxel or albumin-bound paclitaxel—are recommended options (category 1; preferred). For patients with metastatic squamous cell NSCLC who have contraindications to ICIs, recommended options include cisplatin plus gemcitabine (category 1).[790] Carboplatin plus paclitaxel, carboplatin plus gemcitabine (category 1 for both), and other regimens listed in the NSCLC algorithm are also recommended options (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). Data supporting the combination platinum-based chemotherapy options are described in the following sections (see *Clinical Trial Data* in this Discussion). These chemotherapy with or without immunotherapy regimens may be used as first-line or subsequent therapy options in eligible patients with actionable driver mutations as shown in the algorithm, although they are generally not preferred options. Targeted therapy is a preferred first-line therapy option for patients with actionable driver mutations, except for *EGFR* exon 20 mutations or *KRAS* mutations. The NCCN NSCLC Panel does not recommend carboplatin plus etoposide, carboplatin plus vinorelbine, cisplatin plus vinorelbine, cisplatin plus gemcitabine plus necitumumab, etoposide, irinotecan, and vinorelbine for patients with metastatic squamous cell NSCLC and negative test results for actionable driver mutations, because these regimens are rarely used in the United States although they may be used in other countries. 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.

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Clinical 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), and pemetrexed (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).[738,743,788-790,797,798,818] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.[1128] Non-platinum regimens (eg, gemcitabine plus docetaxel, gemcitabine plus vinorelbine) are reasonable alternatives, because data show they are active and less toxic than platinum-based regimens.[800-803,1129]

ECOG 4599, a phase 2/3 trial, randomly assigned 878 patients to either 1) bevacizumab in combination with paclitaxel plus carboplatin; or 2) paclitaxel plus carboplatin alone.[806,1130] Both regimens were well tolerated with selected toxicities. Patients receiving bevacizumab plus paclitaxel plus carboplatin showed an improved median survival (12.3 vs. 10.3 months, $P = .003$) when compared to patients receiving paclitaxel plus carboplatin alone.[806] The overall 1-year survival was 51% versus 44%; 2-year survival was 23% versus 15%, respectively, in favor of the bevacizumab plus paclitaxel plus carboplatin arm.[806] More significant toxicities were observed with bevacizumab plus paclitaxel plus carboplatin compared to paclitaxel plus 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 plus paclitaxel plus carboplatin (15 patients) than with paclitaxel plus carboplatin (2 patients) ($P = .001$). An analysis of ECOG 4599 found that patients with adenocarcinoma histology receiving bevacizumab plus paclitaxel plus carboplatin had improved survival compared with chemotherapy alone (14.2 vs. 10.3 months).[1124] AVAiL, a phase 3 randomized trial, compared cisplatin plus gemcitabine with (or without) bevacizumab; survival was not increased with the addition of bevacizumab.[1131,1132] 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.[833,846-849]

A noninferiority trial in 1725 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) assessed cisplatin plus gemcitabine compared with cisplatin plus pemetrexed.[790] Patients with either adenocarcinoma or large cell carcinoma (ie, nonsquamous NSCLC) had improved survival with cisplatin plus pemetrexed (adenocarcinoma: 12.6 vs. 10.9 months). Patients with squamous cell carcinoma had improved survival with the cisplatin plus gemcitabine regimen (10.8 vs. 9.4 months). When compared with the cisplatin plus gemcitabine regimen, the cisplatin plus 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 plus pemetrexed, 9 patients [1.0%]; cisplatin plus 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.[1133]

Number of Cycles of First-Line Systemic Therapy

Data from the PARAMOUNT trial suggest that 4 cycles of platinum-based therapy is not optimal;[881] 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.[810] A meta-analysis suggests that continuing the initial regimen beyond 4 to 6 cycles is associated with increased PFS;

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however, patients have more adverse events.[1134] 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.[807,808] In this phase 3 trial, taxane-based regimens were used and patients had increasing neurotoxicity as more cycles were used.[807]

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.[810] 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.[807,883]

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 of initial therapy and then every 2 to 4 cycles using CT of known or high-risk sites of disease (with or without contrast) or when clinically indicated.[263,1135-1137] Patients with responsive or stable disease can continue to receive a total of 4 to 6 cycles of systemic therapy.[714,807,1138] 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 plus pemetrexed plus pembrolizumab for nonsquamous NSCLC) before starting maintenance therapy. However, if patients are tolerating the therapy, then 6 cycles of systemic therapy can be considered. 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).

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 with or without chemotherapy (see the NCCN Guidelines for NSCLC).

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 whose tumors had not progressed.[891] 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; $P < .0001$).

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.[893] Overall survival and PFS were not improved in patients receiving erlotinib when compared with placebo. The NCCN NSCLC Panel does not recommend 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 clinical trial data and a revised indication by the FDA.[893]

For patients with squamous cell NSCLC, pembrolizumab was used as continuation maintenance therapy if patients received either pembrolizumab plus carboplatin plus either paclitaxel or albumin-bound paclitaxel or they received pembrolizumab alone (see *Immune Checkpoint Inhibitors* in this Discussion). IFCT-GFPC 0502, a phase 3 randomized trial, compared maintenance therapy with either gemcitabine

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or erlotinib after initial cytotoxic therapy with cisplatin plus gemcitabine in patients with advanced NSCLC.[742,887] 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).[742,887] A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression in patients with advanced NSCLC.[895] Many patients in the delayed chemotherapy arm did not receive docetaxel.[896]

Depending on first-line therapy, the NCCN NSCLC Panel recommends continuation maintenance therapy options for patients with nonsquamous NSCLC with atezolizumab, atezolizumab plus bevacizumab (category 1), bevacizumab (category 1), bevacizumab plus pemetrexed, cemiplimab-rwlc with or without pemetrexed (category 1), durvalumab with or without pemetrexed (category 1), gemcitabine (category 2B), nivolumab plus ipilimumab, pembrolizumab (category 1), pembrolizumab plus pemetrexed (category 1), or pemetrexed (category 1) (see the NCCN Guidelines for NSCLC).[742,806,812,881,885,887,1139] Switch maintenance therapy with pemetrexed is a recommended option for patients with nonsquamous NSCLC.[742,887,890,891] The benefits of continuation maintenance therapy with gemcitabine were very slight; therefore, the recommendation is only category 2B.[742] For patients with squamous cell NSCLC and depending on first-line therapy, the panel recommends continuation maintenance therapy with atezolizumab, cemiplimab-rwlc (category 1), durvalumab, gemcitabine (category 2B), nivolumab plus ipilimumab, or pembrolizumab. Previously, the NCCN Panel deleted the recommendation for docetaxel (category 2B) as switch maintenance therapy for patients with squamous cell NSCLC because there are better options.[896]

Second-Line and Beyond (Subsequent) Systemic Therapy

The phrase *subsequent* therapy is substituted for the terms *second-line, third-line, and beyond* systemic therapy in the NCCN Guidelines, because the line of therapy may vary depending on previous treatment with targeted agents. Subsequent systemic therapy options for patients with disease progression during or after first-line therapy are described in the NSCLC algorithm and depend on the specific genetic variant, the histologic subtype, whether the patient has symptoms, and PS (see the NCCN Guidelines for NSCLC).[1140-1149] The NCCN NSCLC Panel recommends response assessment of known or high-risk sites of disease with CT with or without contrast every 6 to 12 weeks in patients receiving subsequent therapy or maintenance 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.[263,1135,1137,1150-1152] If patients have received and completed first-line systemic therapy (such as carboplatin plus paclitaxel), including maintenance therapy, before receiving targeted therapy for an actionable mutation, but have disease progression on targeted therapy, then certain subsequent therapy options are recommended, such as docetaxel.

If patients have not previously received an ICI, the NCCN NSCLC Panel recommends (category 1) atezolizumab, nivolumab, or pembrolizumab as preferred subsequent therapy options in eligible patients with metastatic NSCLC based on clinical trial data and FDA approvals (see *Immune Checkpoint Inhibitors* in this Discussion).[358,362,834,835,851,858] 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.[358-360]

Most patients with NSCLC do not have actionable driver mutations [eg, *ALK*, *BRAF* p.V600E, *EGFR, ERBB2 (HER2)*, *KRAS*, *MET*ex14 skipping,

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NTRK1/2/3, RET, ROS1]. Platinum-based doublet therapy is recommended (eg, carboplatin plus paclitaxel) as subsequent systemic therapy options for patients with metastatic NSCLC (but without these genetic variants), positive PD-L1 levels (≥50%), and disease progression after first-line therapy with single-agent ICIs. For patients with metastatic NSCLC and disease progression after first-line therapy with ICIs plus chemotherapy, subsequent systemic therapy options include docetaxel (± ramucirumab), gemcitabine, albumin-bound paclitaxel, or pemetrexed (for nonsquamous only), depending on which agent was not previously given. For patients with all histologic subtypes and PS of 0 to 2, but without these genetic variants, who have disease progression during or after first-line platinum-based combination therapy, recommended subsequent systemic therapy options include single-agent ICIs or chemotherapy. If ICIs have not previously been given, the panel recommends (category 1) atezolizumab, nivolumab, or pembrolizumab as preferred subsequent therapy options for all histologic subtypes based on improved survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy (see *Immune Checkpoint Inhibitors* in this Discussion).[358,362,834,835,851,858]

Data show that overall survival is improved with subsequent therapy with atezolizumab, nivolumab, or pembrolizumab compared with docetaxel.[834,835,858] However, some patients cannot tolerate immunotherapy or have had disease progression on immunotherapy. A phase 3 randomized trial assessed ramucirumab plus docetaxel versus docetaxel as subsequent therapy options for all histologic subtypes.[1153] Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.[1146,1147] When compared with docetaxel, pemetrexed has similar median survival but less toxicity.[1148,1154] Pemetrexed is a recommended subsequent therapy option for eligible patients with metastatic nonsquamous NSCLC.[891] Docetaxel is recommended for patients with wild-type *EGFR* tumors based on two randomized trials comparing erlotinib versus docetaxel.[1155,1156] Patients often have a limited response to subsequent therapy other than ICIs, although chemotherapy may serve a useful palliative role.[1157]

ABOUND, a phase 2 trial, assessed albumin-bound paclitaxel with or without oral 5-azacitidine as subsequent therapy in 161 patients with advanced nonsquamous NSCLC.[1158] Median overall survival was 8.1 months with combination therapy and 17 months with single-agent albumin-bound paclitaxel (HR, 1.7; 95% CI, 1.08–2.57). Grade 3 or greater adverse events were reported in 41% of patients receiving combination therapy and 32% of single-agent albumin-bound paclitaxel.

The NSCLC Panel recommends the following subsequent therapy options for patients with metastatic NSCLC, depending on which agents have not previously been given: 1) atezolizumab, nivolumab, or pembrolizumab if none has been previously given (all are category 1, preferred); 2) docetaxel (± ramucirumab); 3) gemcitabine; 4) albumin-bound paclitaxel; or 5) pemetrexed (nonsquamous only). In patients with PS of 3 to 4, best supportive care is recommended (see the NCCN Guidelines for NSCLC).[664,721,722] After second disease progression, subsequent therapy is recommended for certain patients if the following agents have not already been given: 1) atezolizumab, nivolumab, or pembrolizumab if none has been previously given; 2) docetaxel (± ramucirumab; category 2B for both); 3) gemcitabine (category 2B); 4) albumin-bound paclitaxel (category 2B); or 5) pemetrexed (nonsquamous only) (category 2B).[1141,1156,1159,1160] These patients include those with advanced NSCLC and a PS of 0 to 2.

UNO, a randomized trial, showed that overall survival and PFS were not improved in patients receiving erlotinib as a subsequent therapy option when compared with placebo.[893] The NCCN NSCLC Panel does not recommend erlotinib as a subsequent therapy option (or as switch maintenance therapy) for patients with nonsquamous NSCLC and PS of 0 to 2 but without *EGFR* mutations based on clinical trial data and a revised

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indication by the FDA.[893] A phase 3 randomized trial compared afatinib with erlotinib as subsequent therapy options for patients with squamous cell NSCLC .[1161] 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). 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.[362] In addition, only 7% of patients receiving nivolumab had grade 3 or higher adverse events. The NCCN NSCLC Panel does not recommend erlotinib as a subsequent therapy option for patients with squamous cell NSCLC based on this study comparing afatinib with erlotinib; this study was statistically significant but not clinically significant.[1161] Erlotinib or afatinib are not recommended as subsequent therapy options for patients with squamous cell NSCLC; they are less efficacious and safe compared to other available options.[1161]

Summary

Management of NSCLC is described in the NCCN Guidelines for NSCLC, which include the algorithm and this supporting Discussion text. Revisions for the 2023 update of the NCCN Guidelines for NSCLC are described in this Discussion and outlined in the algorithm (see *Summary of the Guidelines Updates* in the algorithm). Most lung cancer (approximately 85%) is due to NSCLC; SCLC accounts for about 15% of lung cancer. Recommendations for SCLC are provided in a different guideline (see the NCCN Guidelines for Small Cell Lung Cancer, available at www.NCCN.org). The NCCN Guidelines for NSCLC are updated at least once a year by the NCCN NSCLC Panel; there were 6 updates to the 2022 guidelines.

For the 2023 update (Version 1), the NCCN NSCLC Panel revised the *Principles of Molecular and Biomarker Analysis*. For example, the NCCN Panel added testing recommendations for *ERBB2 (HER2)* mutations. NGS-based approaches are best able to detect the broad spectrum of genomic *ERBB2 (HER2)* alterations that may occur, although Sanger sequencing and targeted PCR approaches may also be used. The NCCN Panel also revised the *Principles of Diagnostic Evaluation* in the NCCN Guidelines for NSCLC. For example, the NCCN Panel clarified that a preoperative biopsy may be useful for patients with early-stage NSCLC (ie, clinical stage IB or more) who may be candidates for systemic therapy before surgery (also known as neoadjuvant, induction, or preoperative therapy).[107] The NCCN Panel added a recommendation that patients should be evaluated for perioperative (neoadjuvant or adjuvant) therapy before surgery. Neoadjuvant therapy should not be used to attempt to induce resectability in patients who do not already meet criteria for resectability on initial evaluation.

For the 2023 update (Version 2), the NCCN Panel added a recommendation for adjuvant pembrolizumab for eligible patients with completely resected (R0) stage IIB to IIIA, stage IIIB (only T3,N2), or high-risk stage IIA NSCLC who are negative for *EGFR* exon 19 deletions, *EGFR* exon 21 L858R mutations, or *ALK* fusions and who have previously received adjuvant chemotherapy.[751] The panel added a caveat that the benefit of adjuvant pembrolizumab is unclear for patients with PD-L1 levels less than 1%. The NCCN Panel also expanded the molecular testing criteria to include *ALK* rearrangements because patients with completely resected (R0) NSCLC who have *ALK* rearrangements, *EGFR* exon 19 deletions, or *EGFR* exon 21 L858R mutations have less benefit from ICIs.[184] Single-agent therapy with osimertinib is recommended for eligible patients with completely resected (R0) stage IB–IIIA or stage IIIB (T3, N2) NSCLC if patients have *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations, regardless of PD-L1 levels. The NCCN Panel clarified that adjuvant chemotherapy followed by single-agent therapy with osimertinib is recommended for eligible patients with completely resected (R0) early-stage NSCLC if patients have both *EGFR* mutations and PD-L1

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levels of 1% or more; the panel does not recommend using atezolizumab or pembrolizumab, or combined therapy with osimertinib and either atezolizumab or pembrolizumab in this setting.

For the 2023 update (Version 1), the NCCN NSCLC Panel expanded the criteria for using adjuvant osimertinib, atezolizumab, or pembrolizumab for eligible patients with completely resected (R0) early-stage NSCLC to include certain patients with stage IIIB (only T3,N2) disease based on differences between the AJCC staging systems for the 7th and 8th editions.[159] Although the 8th edition of the AJCC staging manual is currently being used, the clinical trials used the 7th edition.

For the 2023 update (Version 1), the NCCN NSCLC Panel recommends adagrasib as a subsequent therapy option for select patients with metastatic NSCLC and *KRAS* p.G12C mutations who have disease progression after treatment with platinum-based chemotherapy (± immunotherapy) based on clinical trial data and FDA approval.[315] Responsiveness to adagrasib has not been assessed for mutations other than *KRAS* p.G12C. The NCCN Panel clarified that adagrasib is recommended as third-line or beyond therapy if the patient has not previously received targeted therapy for *KRAS* p.G12C mutations. The NCCN Panel also recommends lorlatinib as a subsequent therapy option, if not previously given, for patients with *ROS1*-positive metastatic NSCLC and symptomatic brain metastases.[1162,1163]

For the 2023 update (Version 1), the NCCN Panel clarified that postoperative RT may be considered for select patients with high-risk N2 disease such as extracapsular extension, multistation involvement, inadequate lymph node dissection or sampling, and/or refusal or intolerance of adjuvant systemic therapy.[450,453,767] The Panel revised the algorithm for multiple lung cancers. For example, the NCCN Panel added an initial recommendation for multidisciplinary evaluation for patients suspected of or confirmed with having multiple lung cancers. One of the goals during multidisciplinary evaluation for multiple lung cancers is to assess whether patients have lung nodules that can be observed instead of erroneously assuming that patients have stage IV NSCLC. The panel also added the following caveats: lesions at low risk of becoming symptomatic can be observed, such as small subsolid nodules with slow growth. However, treatment should be considered if the lesion(s) show accelerating growth, increasing solid component, or increasing FDG uptake, even if the lesions are small.

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