National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 1.2024 — December 21, 2023

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Þ Internal medicine	ф Diagnostic/Interventional
† Medical oncology	radiology
≠ Pathology	£ Pulmonary medicine
¥ Patient advocacy	* Discussion Section Writing
§ Radiation oncology/Radiotherapy	Committee

National Comprehensive Cancer Network®

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

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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.

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

DIAG-2
- Footnote i modified
  ‣ First sentence modified: FDG-PET/CT performed skull base to *mid-thigh* ~~knees or whole body~~. (also applies to DIAG-3, footnote k on NSCL-3, NSCL-5, NSCL-8, NSCL-11, NSCL-13 through NSCL-15)
  ‣ Third sentence modified: 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). (also applies to DIAG-3)
  ‣ Last sentence added: 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. (also applies to DIAG-3)
- Footnote j modified: ~~If empiric therapy is contemplated without tissue confirmation~~*Prior to treatment,* multidisciplinary evaluation that ~~at least~~ 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* ~~and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)~~ (also applies to DIAG-3, footnote o on NSCL-2, NSCL-3)

DIAG-A 1 of 3
- Bullet 1, including sub-bullets replaced with the following
  ‣ 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.
      – To establish the diagnosis prior to stereotactic ablative radiotherapy (SABR)
- Footnote 2 added: 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 treatment is warranted.

DIAG-A 2 of 3
- Bullet 4; sub-bullet 1
  ‣ Last diamond added: Left anterior mediastinotomy/Chamberlain

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

DIAG-A 3 of 3
• Bullet 1; sub-bullet 2
‣ Diamond 2 modified: Patients with ~~peripheral (outer one-third)~~ *pulmonary* nodules may benefit from navigational bronchoscopy *(including robotic)*, radial EBUS, or transthoracic needle aspiration (TTNA).
‣ Diamond 3; entry 3 modified with the addition of the 3P nodal station
‣ Diamond 6 modified: Patients with lung cancer with an associated pleural effusion should undergo thoracentesis and cytology. A negative *pleural* cytology result ~~on initial thoracentesis~~ does not exclude pleural involvement. ~~An additional thoracentesis and/or~~ Thoracoscopic evaluation of the pleura should be considered before starting curative intent therapy *if pleural fluid is a lymphocytic exudate with negative pleural fluid cytology.*

NSCL-2
• Medically inoperable category modified (also applies to NSCL-3)
‣ Medically inoperable, *high surgical risk as determined by thoracic surgeon, and those who decline surgery after thoracic surgical consultation*
• Footnote n modified: Image-guided thermal ablation (IGTA) therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients ~~not receiving SABR or definitive RT~~. (also applies to NSCL-12, NSCL-16, NSCL-18, NSCL-22, NSCL-23, NSCL-28, NSCL-29, NSCL-31)

NSCL-3
• Following Pretreatment Evaluation
‣ Negative mediastinal nodes changed to No nodal disease
  ◊ Consider adjuvant chemotherapy for high-risk stage~~s IB,~~ II
  ◊ Treatment row for N1 removed, as the category changed to no nodal disease
‣ Positive mediastinal nodes changed to N1 or N2 disease
  ◊ Stage IIB added with a link to NSCL-8
• Footnote r modified: Examples of high-risk factors 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. (also applies to NSCL-9)

NSCL-4
• Footnote l added to Adjuvant Treatment with a link to the Principles of Surgical Therapy.

NSCL-5
• Proximal airway or mediastinum changed to Trachea/carina or mediastinum

NSCL-6
• Footnote v added: For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy. (also applies to NSCL-7, NSCL-9, NSCL-13, NSCL-14)

NSCL-7
• Initial Treatment options modified
‣ Surgery (preferred) ~~after preoperative systemic therapy, if planned~~
‣ *Systemic therapy* or concurrent chemoradiation ~~or chemotherapy~~
  ◊ Margins negative after surgery; Following reresection after Margins positive
    – Adjuvant Systemic Therapy (NSCL-E) added
• Footnote x added: Resectability should be determined by thoracic surgery evaluation prior to initiation of any therapy.

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

NSCL-9
- Mediastinal biopsy categories modified and NSCL-9 now covers 2 pages (NSCL-9 and NSCL-10)
  - ▸ T1–3, N0–1 (including T3 with multiple nodules in same lobe) changed to 3 categories
    - ◊ T1, N0
      Categories of operable and medically inoperable added
      - ‒ Operable
        - ▪ Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling ~~after preoperative systemic therapy, if planned~~
        - ▪ Adjuvant Treatment (NSCL-4) added
      - ‒ Medically inoperable, high surgical risk as determined by thoracic surgeon, and those who decline surgery after thoracic surgical consultation
        - ▪ Definitive RT, preferably SABR added
    - ◊ T2a–3, N0
      Categories of operable and medically inoperable added
      - ‒ Operable
        - ▪ Adjuvant Treatment (NSCL-4) changed to Adjuvant Systemic Therapy (NSCL-E)
      - ‒ Medically inoperable changed as noted above
        - ▪ Definitive RT, preferably SABR added
        - ▪ Consider adjuvant chemotherapy for high-risk stage II added

NSCL-10
- Mediastinal biopsy categories modified and cover 2 pages (NSCL-9 and NSCL-10)
  - ▸ T1-3, N1 nodes positive, M0
    - ◊ Categories of operable and medically inoperable added, as per NSCL-9
      - ‒ Operable
        - ▪ Surgical resection + mediastinal lymph node dissection or systematic lymph node sampling after preoperative systemic therapy, if planned
        - ▪ Adjuvant Treatment (NSCL-E) added
      - ‒ Medically inoperable, high surgical risk as determined by thoracic surgeon, and those who decline surgery after thoracic surgical consultation
        - ▪ Definitive concurrent chemoradiation (category 1) added
        - ▪ Durvalumab (category 1 stage III; category 2A stage II) added
- T3 (invasion), N2 nodes positive, M0 combined with T1–2, T3 (other than invasive), N2 nodes positive, M0
  New category is T1–3, N2 nodes positive, M0
  - ▸ ~~Induction~~ Systemic therapy followed by surgery ± RT
    - ◊ Adjuvant Systemic Therapy (NSCL-E) added
- Footnote y added: Selected patients with N2 disease (fit, single station non-bulky N2, requiring only lobectomy) may be considered for systemic therapy followed by surgery.

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

NSCL-11
- Separate pulmonary nodule(s), same lobe (T3, N0–1), or ipsilateral non-primary lobe (T4, N0–1)
  ‣ Margins negative after surgery
    ◇ Adjuvant Treatment modified: ~~Chemotherapy (category 1)~~ *Adjuvant Systemic Therapy (NSCL-E)* or Sequential chemotherapy + *Consider* RT

NSCL-19
- Footnote ll modified: ~~If there is insufficient tissue to allow testing for all of~~ *Complete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET,* and *ERBB2 (HER2) via* ~~repeat~~ biopsy and/or plasma testing ~~should be done~~. *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. If a clinically actionable marker is found, it is reasonable to start therapy based on the identified marker.* ~~If these are not feasible,~~ Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes. (also applies to NSCL-20)

NSCL-21
- First-line therapy, Other recommended
  ‣ Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous) (category 1) added
- Footnote tt modified: If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when 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.* (also applies NSCL-24)

NSCL-22
- Subsequent therapy
  ‣ Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous) (category 1) (preferred) added
- Footnote ww modified: Consider a biopsy at time of progression to rule out SCLC transformation (approximately 6%) and *biopsy or plasma testing to* evaluate mechanisms of resistance. (also applies to NSCL-23)

NSCL-25
- First-line therapy
  ‣ Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous) (category 1) (preferred) added

NSCL-26
- First-line therapy
  ‣ Systemic therapy as per NSCL-K changed to Systemic therapy based on PD-L1 status (NSCL-37, NSCL-38)
- Footnote removed: Adagrasib and sotorasib have a similar mechanism of action and it is not recommended to switch between these agents at the time of progression (reworded and added to NSCL-J 1 of 6)

NSCL-28
- Lorlatinib
  ‣ Qualifier if ALK G1202R removed from the algorithm
  ‣ Footnote ggg added: Lorlatinib is an option for resistant mutations, such as *ALK* G1202R and L1196M (except compound L1196M/G1202R)

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

NSCL-30
• Repotrectinib added as a preferred first-line therapy option. (continues on to NSCL-31)
• Footnote iii modified: Entrectinib *or repotrectinib* may be better for patients with brain metastases.
NSCL-31
• Brain: Entrectinib *or repotrectinib* (if previously treated with crizotinib or ceritinib)
NSCL-37
• Footnote nnn added: Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status. (also applies to NSCL-38, footnote f on NSCL-J 2 of 6, NSCL-J 3 of 6, footnote j on NSCL-K 1 of 5, NSCL-K 2 of 5)
NSCL-B 2 of 6
• Bullet 2 modified: Sublobar resection - Segmentectomy and wedge resection *should be strongly considered for peripheral T1ab, N0 tumors*
• Bullet 5 modified: Segmentectomy (preferred) or wedge resection is appropriate in selected patients ~~for the following reasons:~~ *with poor pulmonary reserve or other major comorbidity that contraindicates lobectomy*
• The following content was removed
  ▸ Poor pulmonary reserve or other major comorbidity that contraindicates lobectomy
  ▸ Peripheral nodule ≤2 cm with at least one of the following:
    ◊ Pure AIS histology
    ◊ Nodule has ≥50% ground-glass appearance on CT
    ◊ Radiologic surveillance confirms a long doubling time (≥400 days)
• Bullet 6 modified: *Minimally invasive surgery (*VATS or ~~minimally invasive surgery (including~~ robotic-assisted approaches) should be strongly considered for patients with no anatomic or surgical contraindications, as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery. *Robotic surgery should only be initiated by surgeons who have completed and maintained proficiency in the technique*.
• Bullet 8 added: Studies of robotic-assisted pulmonary resection show non-inferiority to traditional VATS approaches when performed by experienced robotic surgeons.
NSCL-B 3 of 6
• Margins and Nodal Assessment
  ▸ Bullet 2 modified: 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.
  ▸ Bullet 3 modified: Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for ~~stage IIIA (N2)~~ disease.
  ▸ Bullet 6 modified: Consider referral to a radiation oncologist for ~~resected stage IIIA~~ N2 disease.
• The Role of Surgery in Patients with ~~Stage IIIA (N2)~~ NSCLC
NSCL-B 6 of 6
• References added:
  1 Altorki N, Wang X, Kozono D, et al. Lobar or sublobar resection for peripheral stage IA non-small-cell lung cancer. N Engl J Med 2023;388:489-498
  2 Lampridis S, Maraschi A, Le Reun C, et al. Robotic versus video-assisted thoracic surgery for lung cancer: short-term outcomes of a propensity matched analysis. Cancer (Basel) 2023;15:2391.
  3 Ma J, Li X, Zhao S, et al. Robot-assisted thoracic surgery versus video-assisted thoracic surgery for lung lobectomy or segmentectomy in patients with non-small cell lung cancer: a meta-analysis. BMC Cancer 2021;21:498.

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

NSCL-C 1 of 11
• General Principles
▸ Bullet 4, sentence 2 modified: More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT ~~and/or FDG-PET/CT simulation~~, *FDG-PET/CT and/or MRI simulation*, IMRT/VMAT, IGRT, motion management, and proton therapy (https://www.astro.org/Daily-Practice/Reimbursement/Model-Policies/Model-Policies).
▸ Bullet 4, last sentence added: 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.

NSCL-C 2 of 11
• Radiation Therapy Simulation, Planning, and Delivery
▸ Bullet 6 modified: IGRT—including (but not limited to) orthogonal pair planar imaging and/or volumetric imaging (such as 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 OARs are in close proximity to high-dose regions, and when using complex motion management techniques.

NSCL-C 3 of 11
• Early-Stage NSCLC (Stage I, selected node-negative Stage IIA)
▸ Bullet 1 modified: SABR (also known as SBRT) has achieved good primary tumor control rates and overall survival, higher than conventionally fractionated radiotherapy. Although SABR is not proven equivalent to lobectomy, some prospective series have demonstrated similar overall and cancer-specific survival *with reduced acute toxicity*.
▸ Bullet 2 modified: SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years, poor lung *or cardiac* function]).
▸ Bullet 3 modified: More modestly hypofractionated or dose-intensified conventionally fractionated ~~3D-CRT regimens~~ *highly conformal radiation (IMRT with IGRT preferred)* are less preferred alternatives and may be considered if referral for SABR is not feasible.
• SABR for Node-Negative Early-Stage NSCLC
▸ Bullet 2, sub-bullet 1, sentence 3 modified: 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, while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.

NSCL-C 4 of 11
• Locally Advanced NSCLC (Stage II–III)
▸ Bullets 4 and 5 modified: stage IIIA changed to N2.
▸ Last bullet added: 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.

NSCL-C 5 of 11
• Palliative RT for Advanced/Metastatic NSCLC
▸ Bullet 2, last sentence added: 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.

Continued
UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

NSCL-C 7 of 11
• Table 2. Commonly Used Doses for SABR
▸ Row 4: Example Indications modified: Central ~~or peripheral~~ tumors
▸ Row 5 added: Total dose = 50–60 Gy; # of Fractions = 5; Example Indications = Peripheral tumors

NSCL-C 9 of 11 through **NSCL-C 11 of 11**
• References added
▸ 31 Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol 2019;20:494-503.
▸ 112 Sahgal A, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicenter, randomised, controlled, phase 2/3 trial. Lancet Oncol 2021;22:1023-1033.

NSCL-E 1 of 5
• Neoadjuvant Systemic Therapy
▸ Bullet 2 modified: Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB-IIIA, IIIB [T3,N2]). *PD-L1 status can be incorporated with other clinical factors to determine patients who may benefit from induction chemotherapy and immunotherapy.*
▸ Bullet 3 added: Clinical trials for neoadjuvant nivolumab + chemotherapy excluded patients harboring EGFR mutations and ALK rearrangements. Thus, exclusion of these biomarkers, at a minimum, is recommended prior to consideration for neoadjuvant nivolumab + chemotherapy.

NSCL-E 3 of 5
• Adjuvant Chemotherapy
▸ Bullet 1 modified: Stage IB (T2a, N0) removed.
▸ Bullet 3 modified: Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages ~~IB~~*II*–IIIA, IIIB [T3,N2]).

NSCL-E 4 of 5
• Pembrolizumab
▸ Sub-bullet 2 modified: For patients with completely resected stage ~~IB~~*II*–IIIA or stage IIIB (T3, N2) NSCLC who received previous neoadjuvant pembrolizumab + chemotherapy (category 1).
• Footnote c added: In general, perioperative therapy should be given as a single regimen and change of immunotherapy is not recommended.

NSCL-F 1 of 2
• Additional cycles of pemetrexed removed from bullet and added to a footnote.
• Additional cycles of paclitaxel and carboplatin removed from bullets and added to a footnote.
• Footnote e modified into 2 new footnotes
▸ Footnote e: If using durvalumab, additional chemotherapy after radiation is not recommended. *If not using durvalumab, an additional 4 cycles of pemetrexed 500 mg/m² may be used.*
▸ Footnote f: If using durvalumab, additional chemotherapy after radiation is not recommended. *If not using durvalumab, an additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6 may be used.*
• Footnote g added: 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 IO therapy.
• Footnote h added: For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy.

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

NSCL-H
• Terminology modified to use circulating tumor DNA (ctDNA) and remove cell-free DNA (cf DNA)
NSCL-H 1 of 8
• Molecular Diagnostic Studies in NSCLC
   ‣ Bullet 3, sub-bullet 6 added: 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.
• Testing Methodologies
   ‣ Sub-bullet 1, diamond 1, entry 1, sentence 2 modified: 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 with greater than* 50 genes ~~for panels larger than 50 genes, it~~ may be practical to follow these recommendations.
   ‣ Sub-bullet 1, diamond 1, entry 2 added: 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.
NSCL-H 2 of 8
• Specimen Selection
   ‣ Sub-bullet 2, diamond 2 modified: If an assay has a technical failure related to an insufficient quantity, consideration of an alternate testing modality *or procurement of additional tissue* ~~may be warranted~~ *is recommended to achieve broad molecular profiling*.
NSCL-H 6 of 8
• PD-L1
   ‣ Sub-bullet 2, diamond 1, entry 2 modified: While some clones for PD-L1 IHC are FDA-approved for specific indications, use of multiple IHC tests is not ~~necessary~~ *routinely recommended*, provided any individual IHC test has been internally validated for comparability for categorical results against the FDA-approved clone.

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

NSCL-H 8 of 8
• ~~Plasma Cell-Free/~~Circulating Tumor DNA (ctDNA) Testing
 ‣ Sub-bullet 2 added: 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.
 ‣ Sub-bullet 3 modified: Some laboratories offer testing for molecular alterations examining nucleic acids in peripheral circulation, most commonly in processed plasma ~~(sometimes referred to as "liquid biopsy")~~.
 ‣ Sub-bullet 4 added:
 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
• Bullets removed:
 ‣ Published guidelines elaborating standards for analytical performance characteristics of ctDNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.
 ‣ Cell-free tumor DNA testing can identify alterations that are unrelated to a lesion of interest, for example, clonal hematopoiesis of indeterminate potential (CHIP)
 ‣ Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to a 30% false-negative rate; however, data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection.
 ‣ The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably:
  ◊ If a patient is medically unfit for invasive tissue sampling
  ◊ In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA can be used; however, follow-up tissue-based analysis for all patients in which an oncogenic driver is not identified should be planned (see NSCL-18 for oncogenic drivers with available targeted therapy options).
  ◊ In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available, consider repeat biopsy and/or cell-free/circulating tumor DNA testing.
  ◊ In the initial diagnostic setting, if the feasibility of timely tissue-based testing is uncertain, concurrent cfDNA testing may aid in biomarker evaluation for treatment selection, provided negative results are considered per above limitations.

NSCL-I
• Footnote b added: In patients with *EGFR* mutant NSCLC who develop high-level *MET* amplifications, administration of these agents with continuation of osimertinib is acceptable.

UPDATES

Updates in Version 1.2024 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2023 include:

NSCL-J 1 of 6
- *EGFR* Exon 19 Deletion or Exon 21 L858R
  ‣ First-line therapy
    ◊ Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous) added
  ‣ Subsequent therapy
    ◊ Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous) added
- *EGFR* Exon 20 Insertion Mutation
  ‣ First-line therapy
    ◊ Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous) added
- *ROS1* Rearrangement
  ‣ First-line therapy and Subsequent therapy
    ◊ Repotrectinib added
- Footnote d added: For agents with a similar mechanism of action, it is not recommended to switch between these drugs at the time of progression.

NSCL-J 2 of 6
- Adenocarcinoma, Large Cell, NSCLC NOS
  ‣ Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1) moved from other recommended to preferred (also applies to NSCL-J 3 of 6, NSCL-K 1 of 5)
- Squamous Cell Carcinoma
  ‣ Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1) moved from other recommended to preferred (also applies to NSCL-J 3 of 6, NSCL-K 2 of 5)

NSCL-J 5 of 6
- References added:
  7 Planchard D, et al. Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC. N Eng J Med 2023;389:1935-1948.
  11 Passaro A, et al. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. Ann Oncol 2023;S0923-7534:04281-04283.
  14 Zhou C, et al. Amivantamab plus chemotherapy in NSCLC with EGFR Exon 20 insertions. N Engl J Med 2023;389:2039-2051.

NSCL-J 6 of 6
- Reference added:
  32 Cho BC, et al. OA03.06 Repotrectinib in patients with ROS1 fusion-positive (ROS1+) NSCLC: Update from the pivotal phase 1/2 TRIDENT-1 trial. J Thorac Oncol 2023;18:S50-S51.

NSCL-K 1 of 5
- Category designation for tremelimumab-actl-combination regimens changed from category 2A to category 1. (also applies to NSCL-K 2 of 5)

NSCL-K 3 of 5
- Footnote k added: Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision. (also applies to NSCL-K 4 of 5)

NSCL-K 4 of 5
- Footnote d added: Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR* exon 19 deletion or L858R, *ALK* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

UPDATES

LUNG CANCER PREVENTION AND SCREENING

- Lung cancer is a unique disease in that the major etiologic agent is an addictive product that is made and promoted by an industry. Approximately 85% to 90% of cases are caused by voluntary or involuntary (second-hand) cigarette smoking. Reduction of lung cancer mortality will require effective public health policies to prevent initiation of smoking, U.S. Food and Drug Administration (FDA) oversight of tobacco products, and other tobacco control measures.

- Persistent smoking is associated with second primary cancers, treatment complications, drug interactions, other tobacco-related medical conditions, diminished quality of life, and reduced survival.

- Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk for lung cancer from second-hand smoke exposure associated with living with a person who smokes (http://www.ncbi.nlm.nih.gov/books/NBK44324).
  Every person should be informed of the health consequences, addictive nature, and mortal threat posed by tobacco consumption and exposure to tobacco smoke, and effective legislative, executive, administrative, or other measures should be contemplated at the appropriate governmental level to protect all persons from exposure to tobacco smoke.

- Further complicating this problem, the delivery system of lung carcinogens also contains the highly addictive substance, nicotine. Reduction of lung cancer mortality will require widespread implementation of Agency for Healthcare Research and Quality (AHRQ) Guidelines (http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html) to identify, counsel, and treat patients with nicotine habituation.

- Patients who 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.

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

RISK ASSESSMENT[b]

Incidental finding of nodule suspicious for lung cancer →
- **Multidisciplinary evaluation**[a]
- **Smoking cessation counseling**

→

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

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

→

Solid nodules
Follow-up
(DIAG-2)

Subsolid nodules
Follow-up
(DIAG-3)

Lung nodules in asymptomatic, high-risk patients detected during lung cancer screening with LDCT →

NCCN Guidelines for Lung Cancer Screening

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[a] Multidisciplinary evaluation including thoracic surgeons, thoracic radiologists, and pulmonologists to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy.
[b] Risk calculators can be used to quantify individual patient and radiologic factors but do not replace evaluation by a multidisciplinary diagnostic team with substantial experience in the diagnosis of lung cancer.
[c] Principles of Diagnostic Evaluation (DIAG-A 1 of 3).
[d] The most important radiologic factor is change or stability compared with a previous imaging study.

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FINDINGS

FOLLOW-UP[c,d,g,h]

Incidental finding: solid nodule(s) on chest CT

Low risk[e]
- <6 mm → No routine follow-up
- 6–8 mm → CT at 6–12 mo → Stable → Consider CT at 18–24 mo
- >8 mm → Consider CT at 3 mo, FDG-PET/CT,[i] or biopsy[j]

High risk[f]
- <6 mm → CT at 12 mo (optional) → Stable → No routine follow-up
- 6–8 mm → CT at 6–12 mo → Stable → Repeat CT at 18–24 mo
- >8 mm → Consider CT at 3 mo, FDG-PET/CT,[i] or biopsy[j]
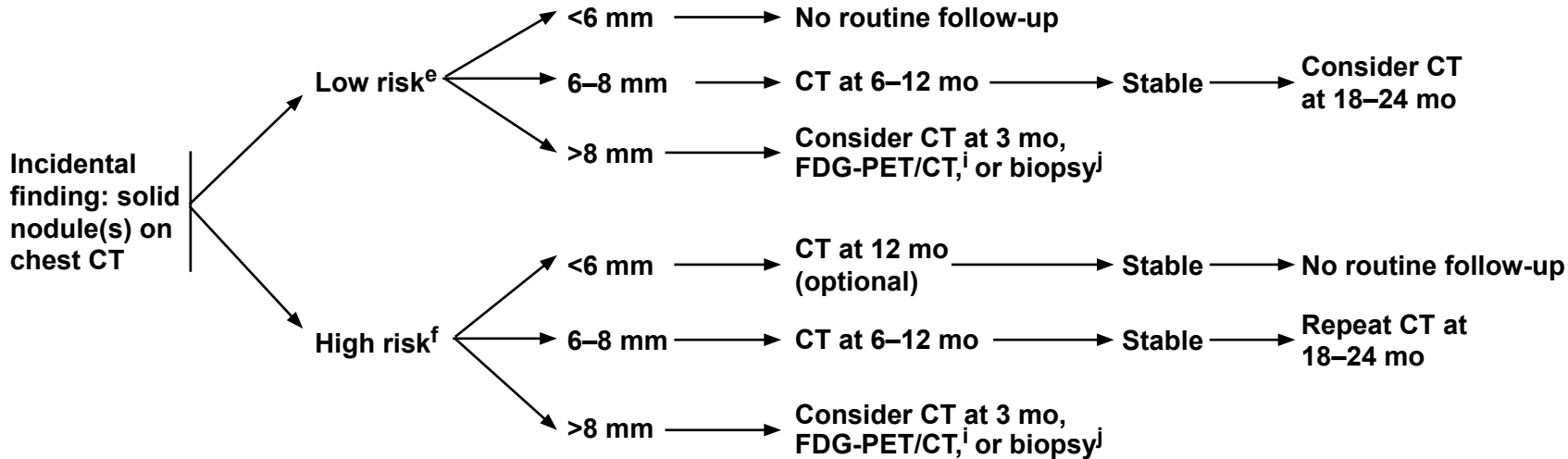
[c] Principles of Diagnostic Evaluation (DIAG-A 1 of 3).
[d] The most important radiologic factor is change or stability compared with a previous imaging study.
[e] Low risk = minimal or absent history of smoking or other known risk factors.
[f] High risk = history of smoking or other known risk factors. 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.
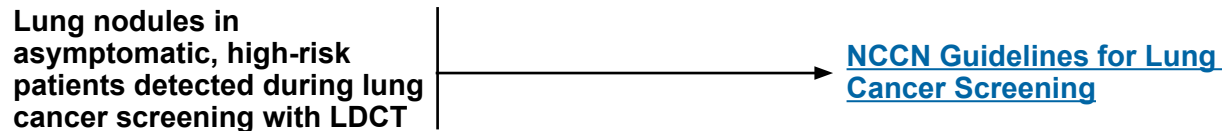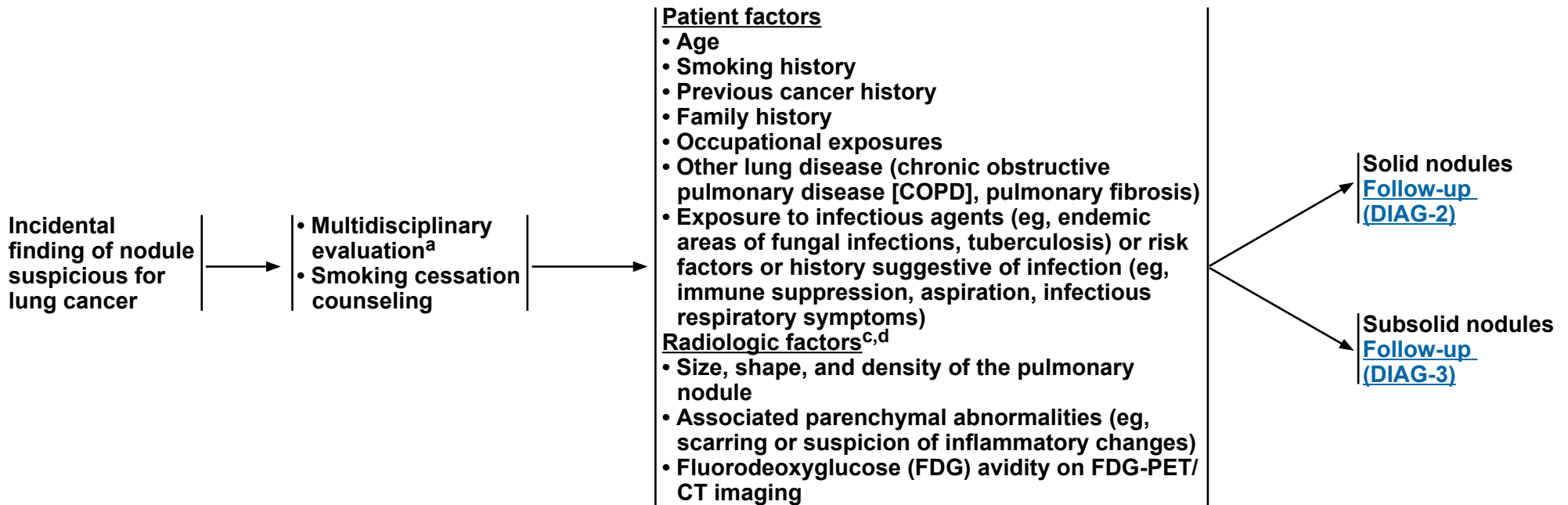
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FINDINGS

FOLLOW-UP[c,d,g,h]

Incidental finding: subsolid nodule(s) on chest CT

Solitary pure ground-glass nodules
- <6 mm → **No routine follow-up**
- ≥6 mm → **CT at 6–12 mo to confirm no growth or development of a solid component, then CT every 2 y until 5 y**

Solitary part-solid nodules
- <6 mm → **No routine follow-up**
- ≥6 mm →
  - **CT at 3–6 mo to confirm no growth or change in solid component, then annual CT for 5 y**
  - **If solid component ≥6 mm, consider PET/CT[i] or biopsy[j]**

Multiple subsolid nodules
- <6 mm →
  - **CT at 3–6 mo**
    - ▸ **If stable, consider CT at 2 and 4 y**
- ≥6 mm →
  - **CT at 3–6 mo**
  - **Subsequent management based on most suspicious nodule(s)**

[c] Principles of Diagnostic Evaluation (DIAG-A 1 of 3).
[d] The most important radiologic factor is change or stability compared with a previous imaging study.
[g] Non-solid (ground-glass) nodules may require longer follow-up to exclude indolent adenocarcinoma.
[h] Adapted from Fleischner Society Guidelines: MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner Society 2017. Radiology 2017;284:228-243. ©Radiological Society of North America. Fleischner Society Guidelines do not direct whether or not contrast is necessary or if an LDCT is appropriate. LDCT is preferred unless there is a reason for contrast enhancement for better diagnostic resolution.
[i] 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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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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). 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

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DIAG-A
2 OF 3

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 5 and 6) lymph nodes if these are clinically suspicious. If TTNA is not possible due to proximity to aorta, VATS biopsy is also an option.**
    - ◊ **EUS also provides reliable access to the left adrenal gland.**
    - ◊ **Rapid on-site evaluation (ROSE), when available, helps to increase diagnostic and molecular yield.**
    - ◊ **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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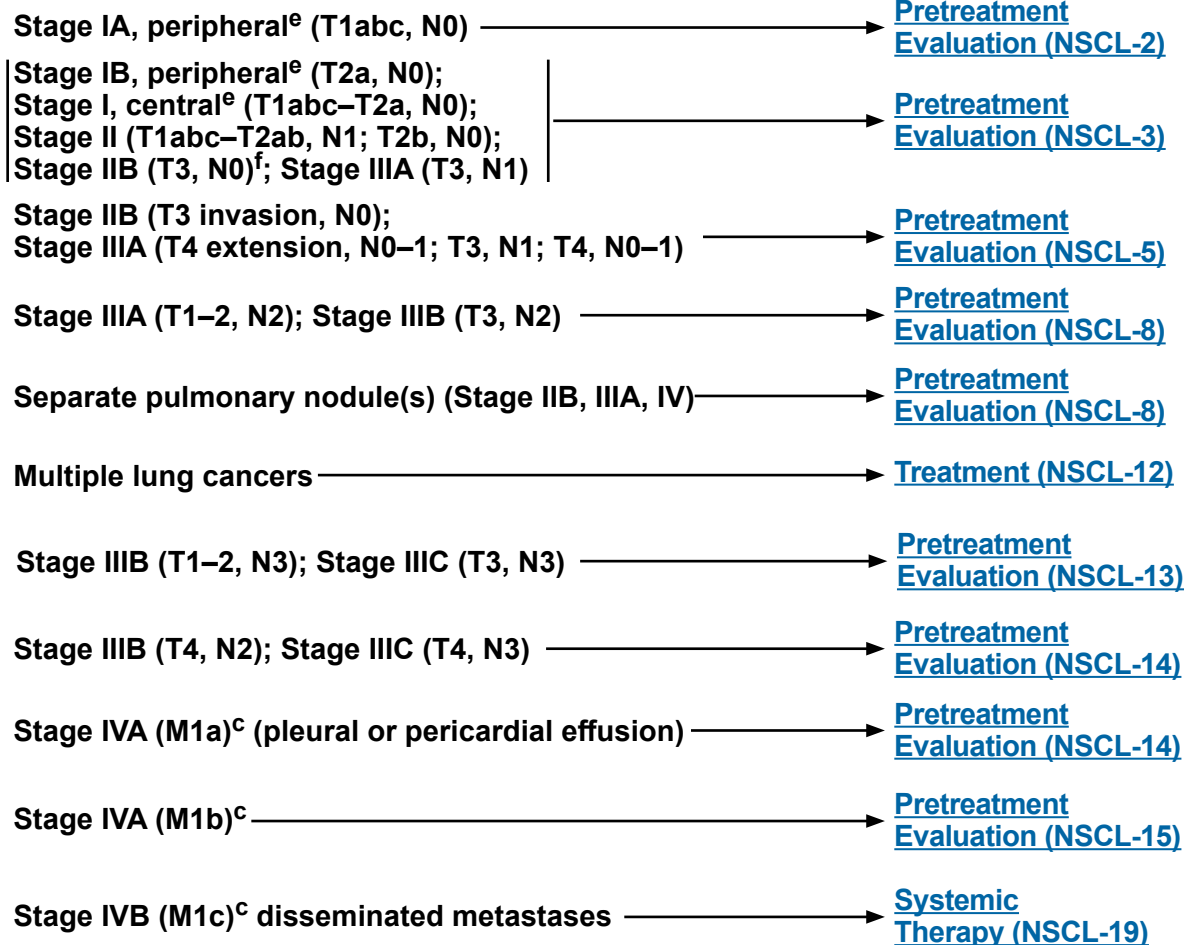
PATHOLOGIC DIAGNOSIS OF NSCLC

INITIAL EVALUATION

CLINICAL STAGE[d]

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**
    http://www.ahrq.gov/clinic/tobacco/5steps.htm
- **Integrate palliative care[c]** NCCN Guidelines for Palliative Care
- **For tools to aid in the optimal assessment and management of NSCLC in older adults, see the NCCN Guidelines for Older Adult Oncology**

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) —→ Pretreatment Evaluation (NSCL-3)

Stage IIB (T3 invasion, N0);
Stage IIIA (T4 extension, 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) —→ Pretreatment Evaluation (NSCL-8)

Multiple lung cancers —→ Treatment (NSCL-12)

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] —→ Pretreatment Evaluation (NSCL-15)

Stage IVB (M1c)[c] disseminated metastases —→ Systemic Therapy (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.
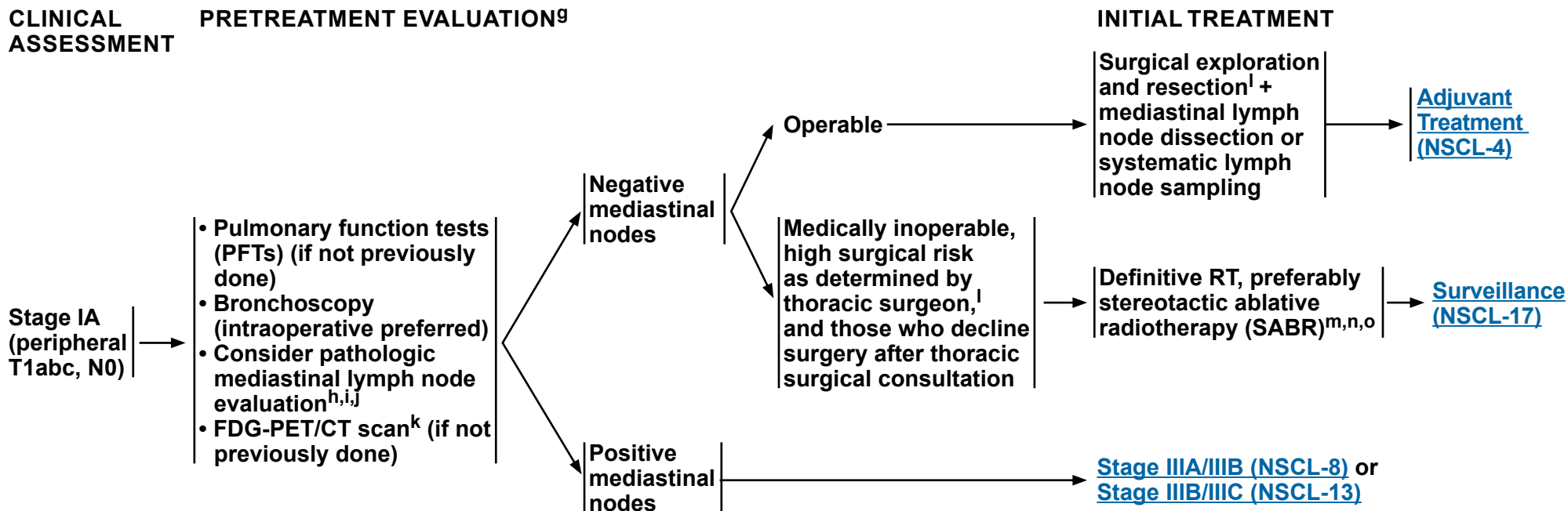[c] Temel JS, et al. N Engl J Med 2010;363:733-742.

[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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CLINICAL ASSESSMENT **PRETREATMENT EVALUATION[g]**   **INITIAL TREATMENT**

Stage IA (peripheral T1abc, N0) →

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

→ **Negative mediastinal nodes**

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

→ **Medically inoperable, high surgical risk as determined by thoracic surgeon,[l] and those who decline surgery after thoracic surgical consultation** → **Definitive RT, preferably stereotactic ablative radiotherapy (SABR)[m,n,o]** → **Surveillance (NSCL-17)**

→ **Positive mediastinal nodes** → **Stage IIIA/IIIB (NSCL-8) or Stage IIIB/IIIC (NSCL-13)**

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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] Principles of Surgical Therapy (NSCL-B).

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

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

[o] 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.
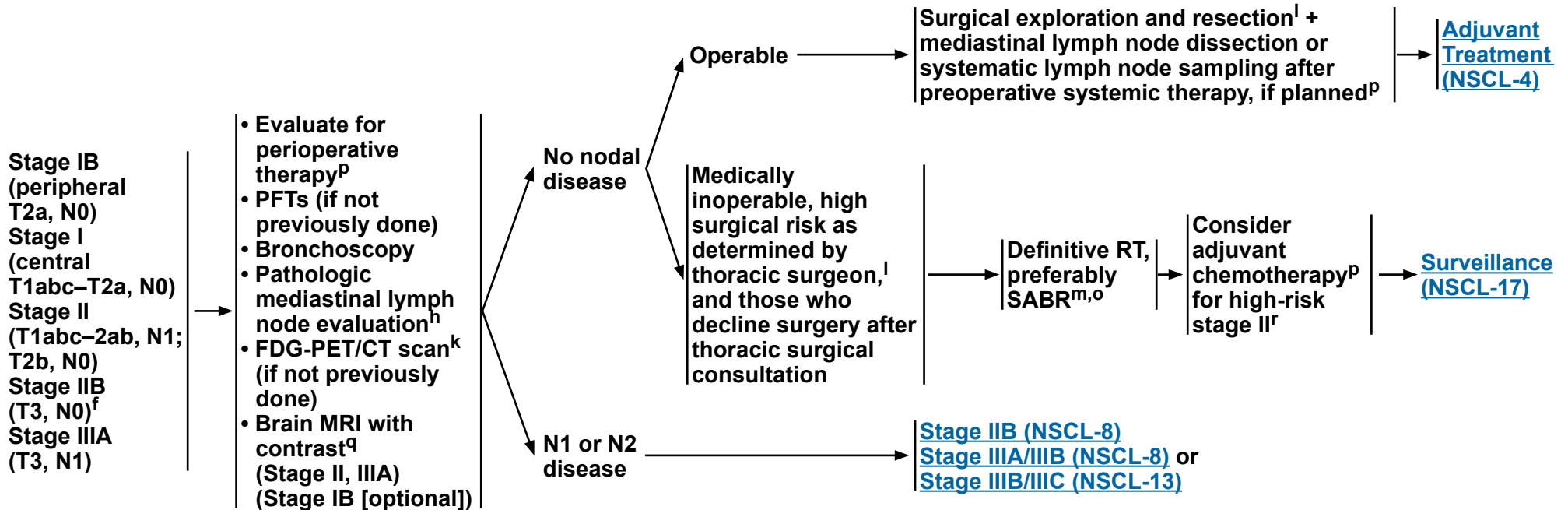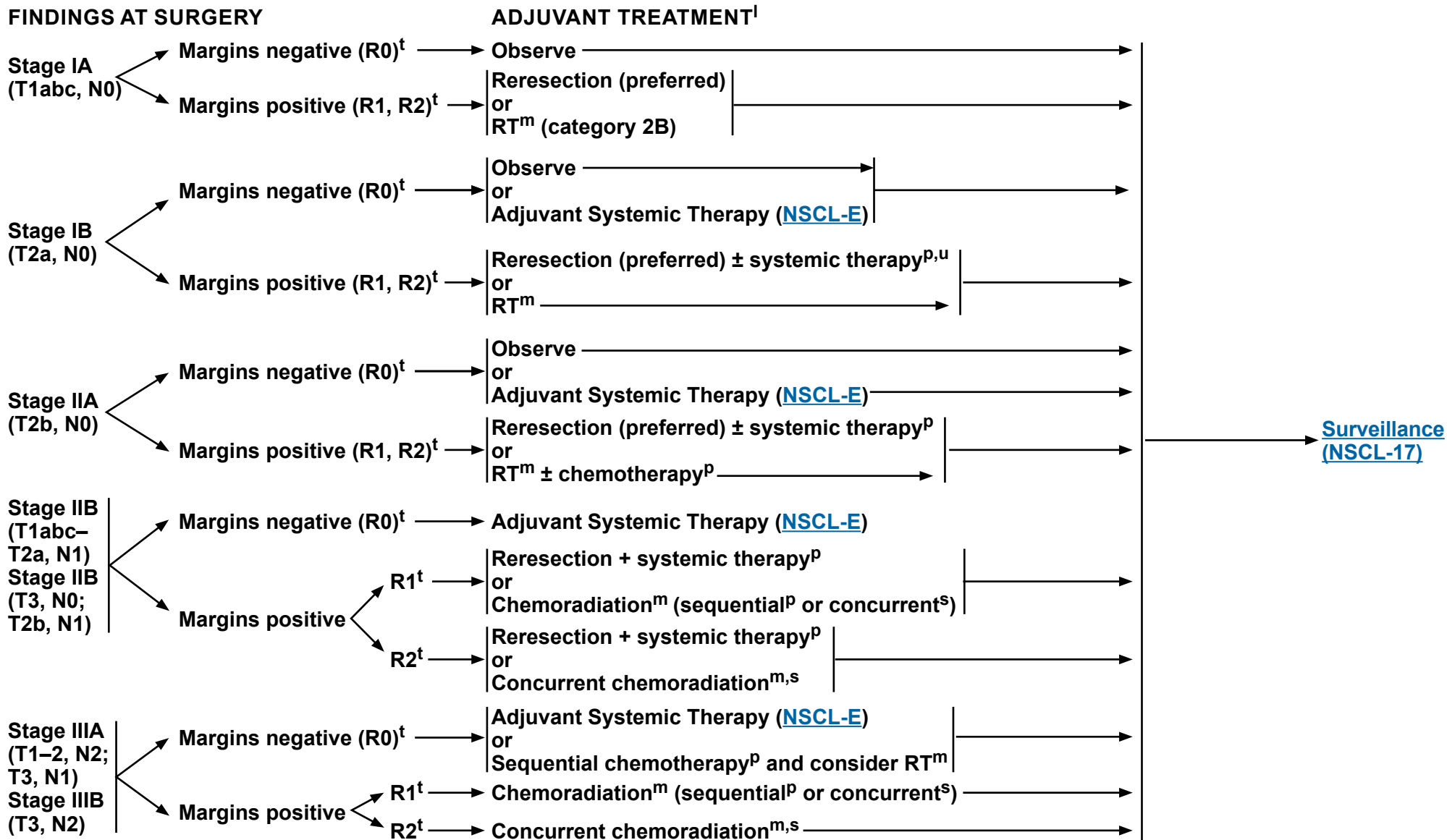
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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION[g]

INITIAL TREATMENT

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

→

- Evaluate for perioperative therapy[p]
- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation[h]
- FDG-PET/CT scan[k] (if not previously done)
- Brain MRI with contrast[q] (Stage II, IIIA) (Stage IB [optional])

No nodal disease

→ **Operable** → Surgical exploration and resection[l] + mediastinal lymph node dissection or systematic lymph node sampling after preoperative systemic therapy, if planned[p] → **Adjuvant Treatment (NSCL-4)**

Medically inoperable, high surgical risk as determined by thoracic surgeon,[l] and those who decline surgery after thoracic surgical consultation → Definitive RT, preferably SABR[m,o] → Consider adjuvant chemotherapy[p] for high-risk stage II[r] → **Surveillance (NSCL-17)**

N1 or N2 disease → **Stage IIB (NSCL-8) Stage IIIA/IIIB (NSCL-8)** or **Stage IIIB/IIIC (NSCL-13)**

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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.

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

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

[o] 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.

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

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

[r] Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
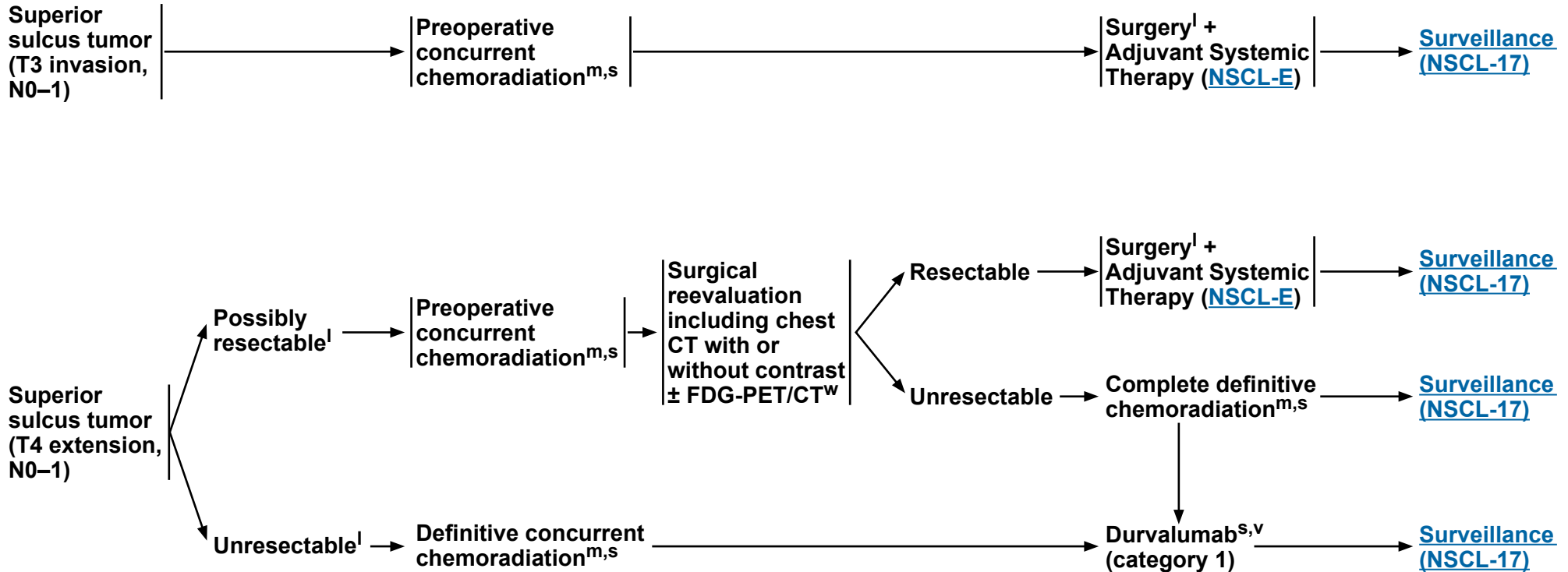
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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

FINDINGS AT SURGERY

ADJUVANT TREATMENT[l]

Stage IA (T1abc, N0)
- Margins negative (R0)[t] → Observe
- Margins positive (R1, R2)[t] → Reresection (preferred) or RT[m] (category 2B)

Stage IB (T2a, N0)
- Margins negative (R0)[t] → Observe or Adjuvant Systemic Therapy (NSCL-E)
- Margins positive (R1, R2)[t] → Reresection (preferred) ± systemic therapy[p,u] or RT[m]

Stage IIA (T2b, N0)
- Margins negative (R0)[t] → Observe or Adjuvant Systemic Therapy (NSCL-E)
- Margins positive (R1, R2)[t] → Reresection (preferred) ± systemic therapy[p] or RT[m] ± chemotherapy[p]

Stage IIB (T1abc–T2a, N1)
Stage IIB (T3, N0; T2b, N1)
- Margins negative (R0)[t] → Adjuvant Systemic Therapy (NSCL-E)
- Margins positive
  - R1[t] → Reresection + systemic therapy[p] or Chemoradiation[m] (sequential[p] or concurrent[s])
  - R2[t] → Reresection + systemic therapy[p] or Concurrent chemoradiation[m,s]

Stage IIIA (T1–2, N2; T3, N1)
Stage IIIB (T3, N2)
- Margins negative (R0)[t] → Adjuvant Systemic Therapy (NSCL-E) or Sequential chemotherapy[p] and consider RT[m]
- Margins positive
  - R1[t] → Chemoradiation[m] (sequential[p] or concurrent[s])
  - R2[t] → Concurrent chemoradiation[m,s]

→ Surveillance (NSCL-17)

Footnotes, NSCL-4A

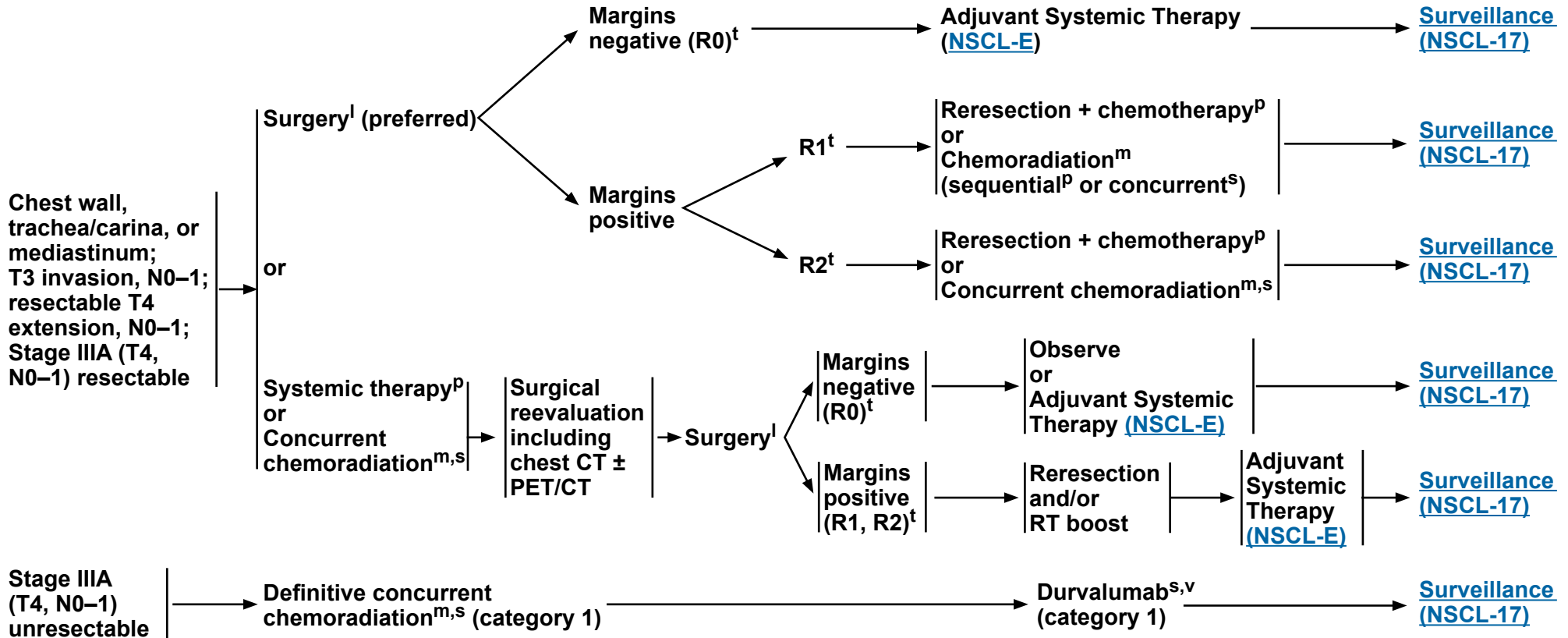**Note:** All recommendations are category 2A unless otherwise indicated.
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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

FOOTNOTES

l Principles of Surgical Therapy (NSCL-B).
m Principles of Radiation Therapy (NSCL-C).
p Perioperative Systemic Therapy (NSCL-E).
s Concurrent Chemoradiation Regimens (NSCL-F).
t R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
u Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

CLINICAL EVALUATION

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

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

Superior sulcus tumor → **Treatment (NSCL-6)**

Chest wall → **Treatment (NSCL-7)**

Trachea/carina or mediastinum → **Treatment (NSCL-7)**

Stage IIIA (T4, N0–1) → **Treatment (NSCL-7)**

Unresectable disease → **Treatment (NSCL-7)**

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

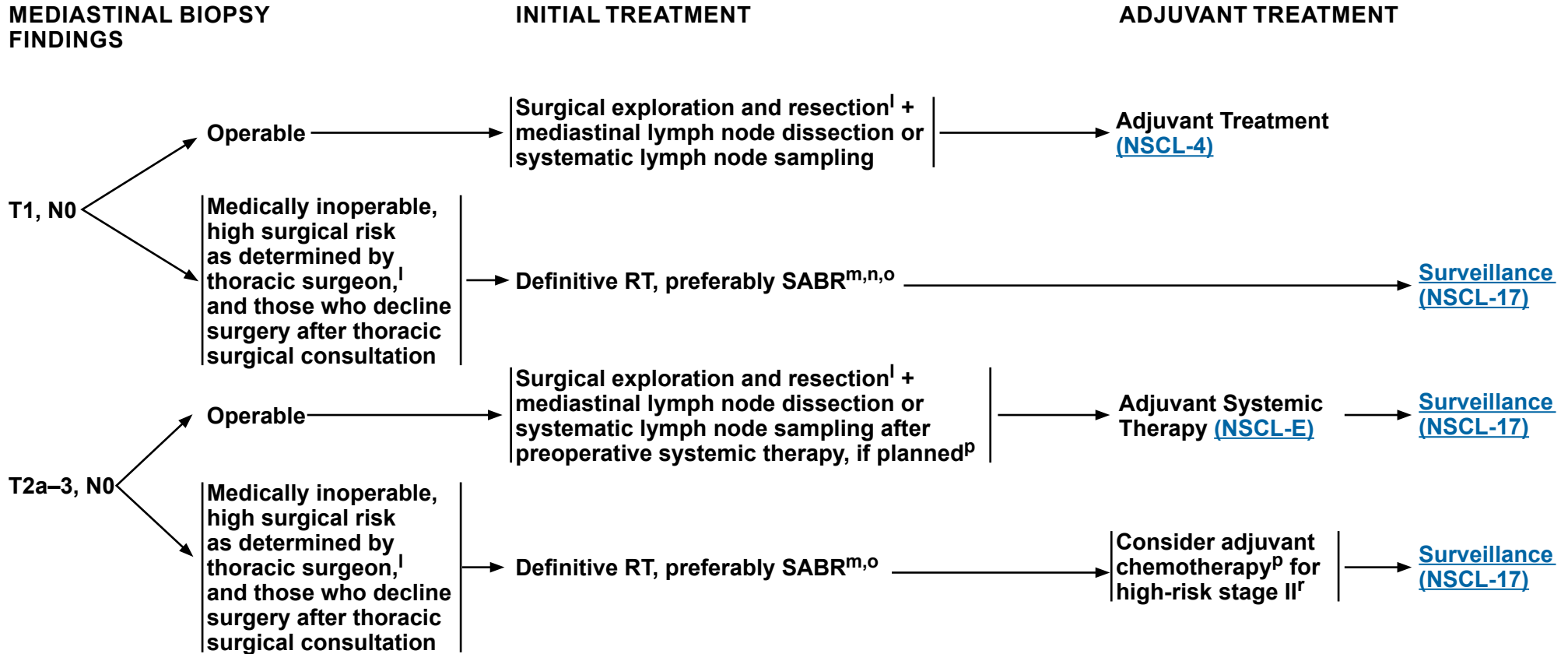**Metastatic disease** → **Treatment for Metastasis limited sites (NSCL-15) or distant disease (NSCL-18)**

[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (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.
[p] Perioperative Systemic Therapy (NSCL-E).
[q] If MRI is not possible, CT of head with contrast.

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CLINICAL PRESENTATION

INITIAL TREATMENT

ADJUVANT TREATMENT

Superior sulcus tumor (T3 invasion, N0–1) → **Preoperative concurrent chemoradiation[m,s]** → **Surgery[l] + Adjuvant Systemic Therapy (NSCL-E)** → **Surveillance (NSCL-17)**

Superior sulcus tumor (T4 extension, N0–1)

- **Possibly resectable[l]** → **Preoperative concurrent chemoradiation[m,s]** → **Surgical reevaluation including chest CT with or without contrast ± FDG-PET/CT[w]**
  - **Resectable** → **Surgery[l] + Adjuvant Systemic Therapy (NSCL-E)** → **Surveillance (NSCL-17)**
  - **Unresectable** → **Complete definitive chemoradiation[m,s]** → **Surveillance (NSCL-17)**
    - → **Durvalumab[s,v] (category 1)** → **Surveillance (NSCL-17)**

- **Unresectable[l]** → **Definitive concurrent chemoradiation[m,s]** → **Durvalumab[s,v] (category 1)** → **Surveillance (NSCL-17)**

[l] Principles of Surgical Therapy (NSCL-B).
[m] Principles of Radiation Therapy (NSCL-C).
[s] Concurrent Chemoradiation Regimens (NSCL-F).
[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy.
[w] MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine, subclavian vessels, or brachial plexus.

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CLINICAL PRESENTATION[x]   **INITIAL TREATMENT**   **ADJUVANT TREATMENT**

Chest wall, trachea/carina, or mediastinum; T3 invasion, N0–1; resectable T4 extension, N0–1; Stage IIIA (T4, N0–1) resectable

Surgery[l] (preferred)

→ **Margins negative (R0)[t]** → **Adjuvant Systemic Therapy (NSCL-E)** → Surveillance (NSCL-17)

→ **Margins positive**
- → **R1[t]** → Reresection + chemotherapy[p] or Chemoradiation[m] (sequential[p] or concurrent[s]) → Surveillance (NSCL-17)
- → **R2[t]** → Reresection + chemotherapy[p] or Concurrent chemoradiation[m,s] → Surveillance (NSCL-17)

or

Systemic therapy[p] or Concurrent chemoradiation[m,s] → **Surgical reevaluation including chest CT ± PET/CT** → **Surgery[l]**
- → **Margins negative (R0)[t]** → Observe or Adjuvant Systemic Therapy (NSCL-E) → Surveillance (NSCL-17)
- → **Margins positive (R1, R2)[t]** → Reresection and/or RT boost → Adjuvant Systemic Therapy (NSCL-E) → Surveillance (NSCL-17)

Stage IIIA (T4, N0–1) unresectable → **Definitive concurrent chemoradiation[m,s] (category 1)** → **Durvalumab[s,v] (category 1)** → Surveillance (NSCL-17)

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[l] Principles of Surgical Therapy (NSCL-B).
[m] Principles of Radiation Therapy (NSCL-C).
[p] Perioperative Systemic Therapy (NSCL-E).
[s] Concurrent Chemoradiation Regimens (NSCL-F).
[t] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy.
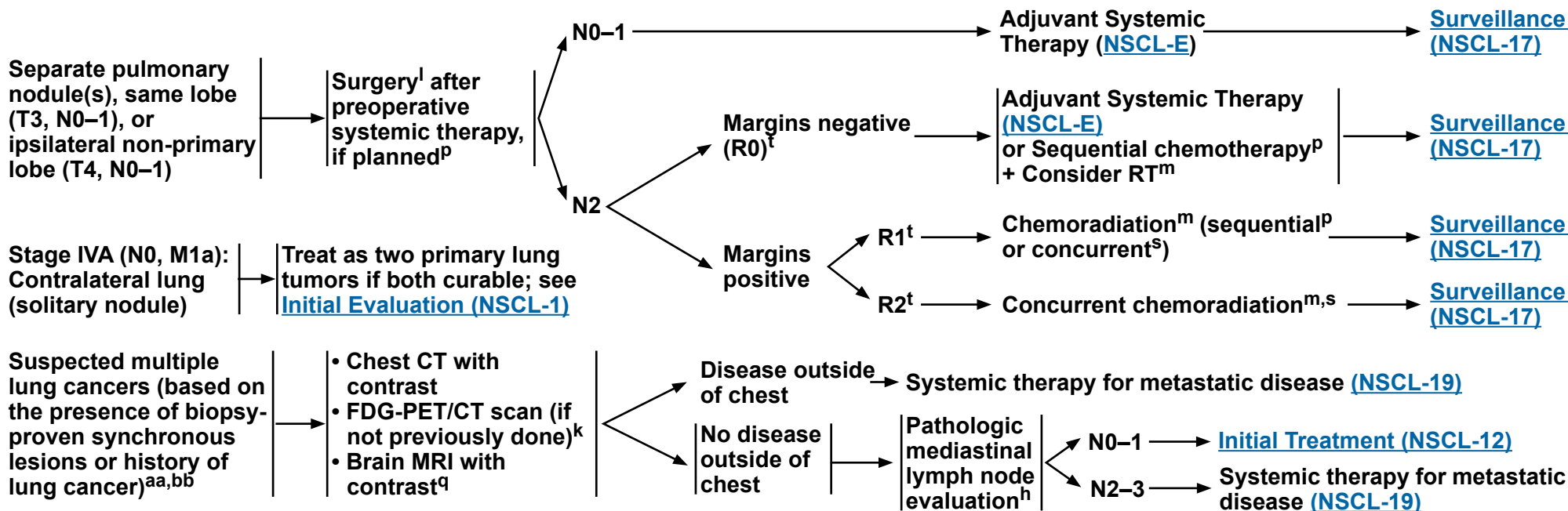[x] Resectability should be determined by thoracic surgery evaluation prior to initiation of any therapy.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

MEDIASTINAL BIOPSY FINDINGS AND RESECTABILITY

Stage IIIA (T1–2, N2)
Stage IIIB (T3, N2) →

- **Evaluate for perioperative therapy[p]**
- **PFTs (if not previously done)**
- **Bronchoscopy**
- **Pathologic mediastinal lymph node evaluation[h]**
- **FDG-PET/CT scan[k] (if not previously done)**
- **Brain MRI with contrast[q]**

→ **Nodes negative** → **Treatment (NSCL-9)**

→ **N1 or N2 nodes positive, M0** → **Treatment (NSCL-10)**

→ **N3 nodes positive, M0** → **Stage IIIB (NSCL-13)**

→ **Metastatic disease** → **Treatment for Metastasis limited sites (NSCL-15) or distant disease (NSCL-18)**

Separate pulmonary nodule(s) (Stage IIB, IIIA, IV) →

- **Evaluate for perioperative therapy[p]**
- **PFTs (if not previously done)**
- **Bronchoscopy**
- **Pathologic mediastinal lymph node evaluation[h]**
- **Brain MRI with contrast[q]**
- **FDG-PET/CT scan[k] (if not previously done)**

→ **Separate pulmonary nodule(s), same lobe (T3, N0–1) or ipsilateral non-primary lobe (T4, N0–1)** → **Treatment (NSCL-11)**

→ **Stage IVA (N0, M1a): Contralateral lung (solitary nodule)** → **Treatment (NSCL-11)**

→ **Extrathoracic metastatic disease** → **Treatment for Metastasis limited sites (NSCL-15) or distant disease (NSCL-18)**

[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (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.
[p] Perioperative Systemic Therapy (NSCL-E).
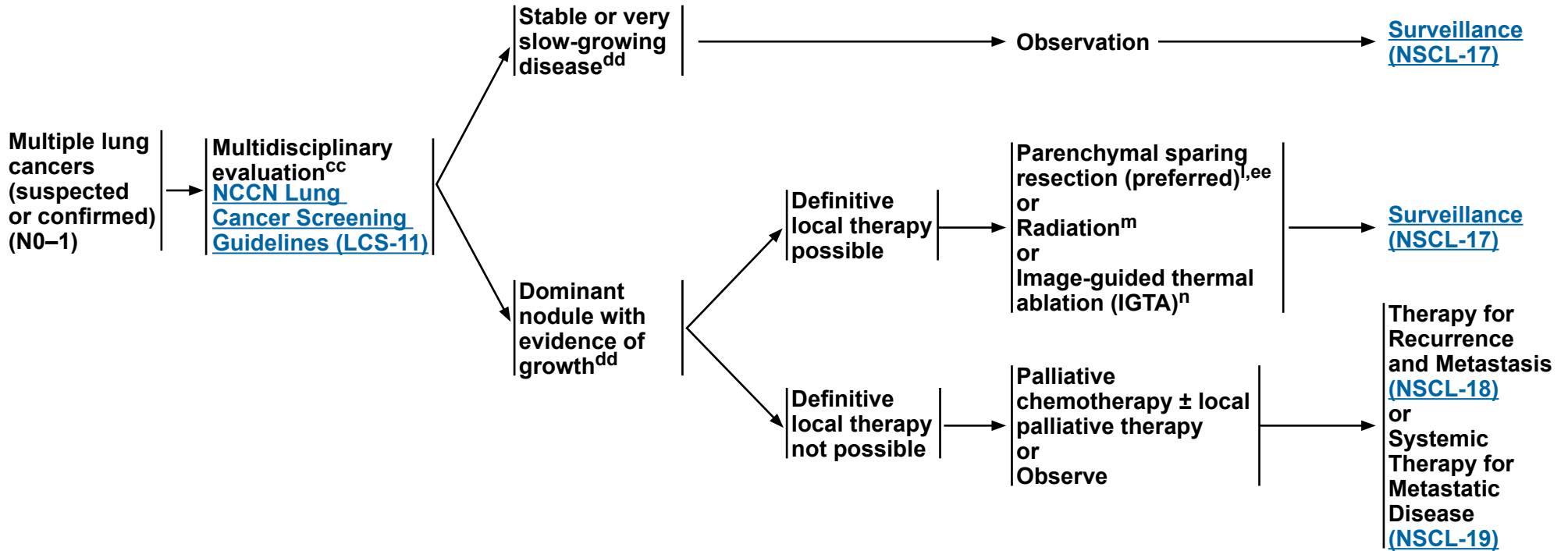[q] If MRI is not possible, CT of head with contrast.

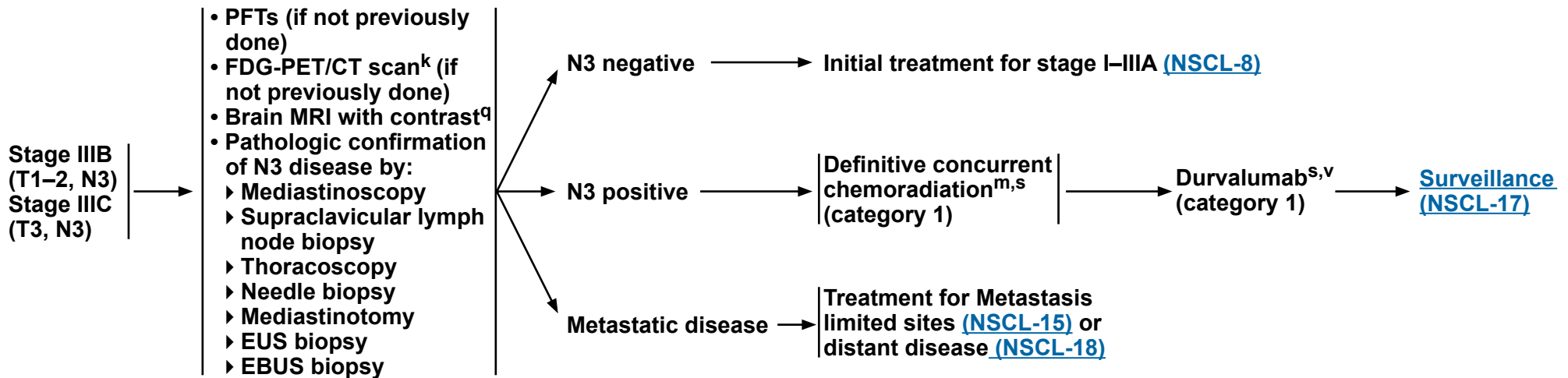**Note: All recommendations are category 2A unless otherwise indicated.**
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MEDIASTINAL BIOPSY FINDINGS **INITIAL TREATMENT** **ADJUVANT TREATMENT**

T1, N0

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

- Medically inoperable, high surgical risk as determined by thoracic surgeon,[l] and those who decline surgery after thoracic surgical consultation → Definitive RT, preferably SABR[m,n,o] → **Surveillance (NSCL-17)**

T2a–3, N0

- Operable → Surgical exploration and resection[l] + mediastinal lymph node dissection or systematic lymph node sampling after preoperative systemic therapy, if planned[p] → **Adjuvant Systemic Therapy (NSCL-E)** → **Surveillance (NSCL-17)**

- Medically inoperable, high surgical risk as determined by thoracic surgeon,[l] and those who decline surgery after thoracic surgical consultation → Definitive RT, preferably SABR[m,o] → Consider adjuvant chemotherapy[p] for high-risk stage II[r] → **Surveillance (NSCL-17)**

[l] Principles of Surgical Therapy (NSCL-B).
[m] Principles of Radiation Therapy (NSCL-C).
[n] Image-guided thermal ablation (IGTA) therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients.
   Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[o] 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.
[p] Perioperative Systemic Therapy (NSCL-E).
[r] Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.
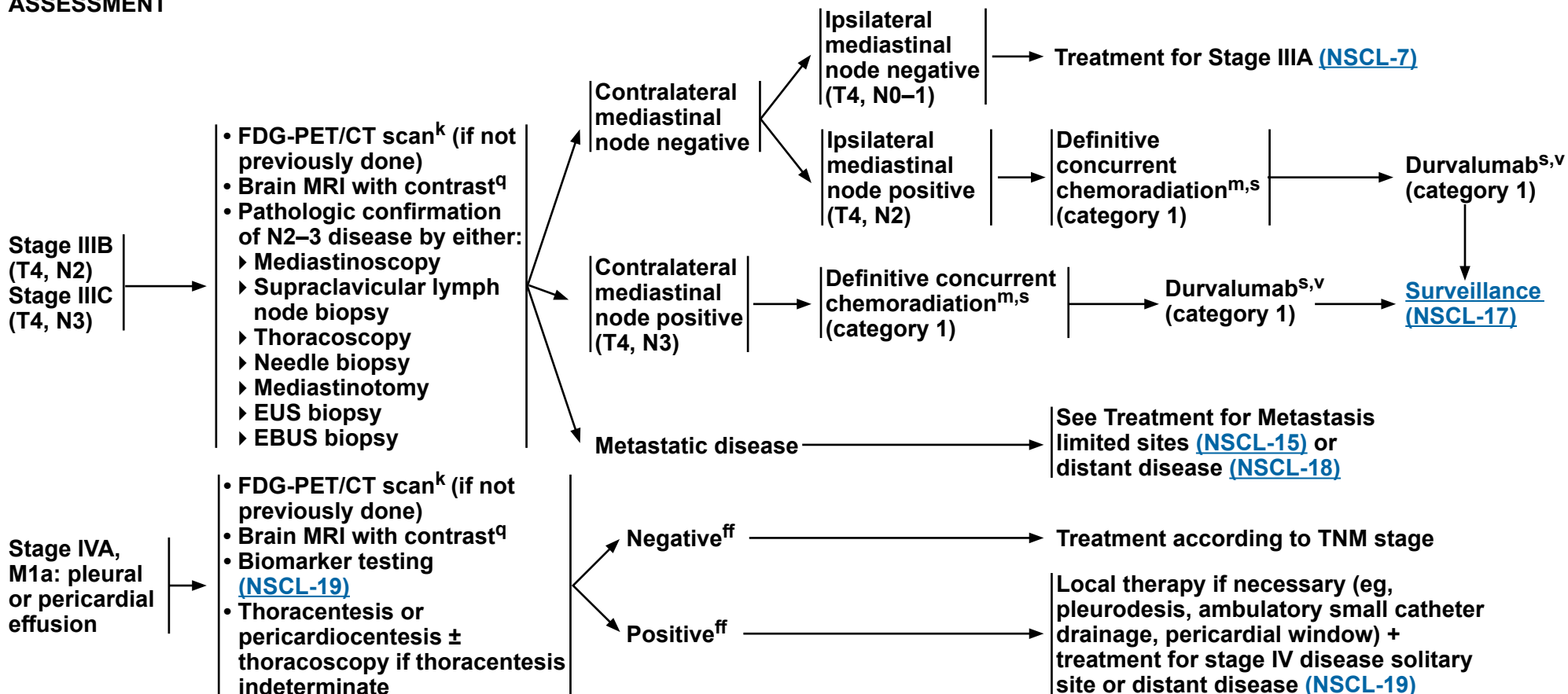
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MEDIASTINAL BIOPSY FINDINGS

INITIAL TREATMENT

ADJUVANT TREATMENT

T1–3, N1 nodes positive, M0

Operable → Surgical resection[l] + mediastinal lymph node dissection or systematic lymph node sampling after preoperative systemic therapy, if planned[p] → Adjuvant Systemic Therapy **(NSCL-E)** → **Surveillance (NSCL-17)**

Medically inoperable, high surgical risk as determined by thoracic surgeon,[l] and those who decline surgery after thoracic surgical consultation → Definitive concurrent chemoradiation[m,s] (category 1) → Durvalumab[s,v] (category 1 stage III; category 2A stage II) → **Surveillance (NSCL-17)**

T1–3, N2 nodes positive, M0 → Definitive concurrent chemoradiation[m,s] (category 1) **or** Systemic therapy[p,y] ± RT[m]

- Definitive concurrent chemoradiation[m,s] (category 1) → Durvalumab[s,v] (category 1) → **Surveillance (NSCL-17)**

- Systemic therapy[p,y] ± RT[m]:
  - **No apparent progression[z]** → • Surgery[l] → Adjuvant Systemic Therapy **(NSCL-E)** → **Surveillance (NSCL-17)**
    - • Consider RT[m] → **Surveillance (NSCL-17)**
  - **Progression[z]**:
    - **Local** → RT[m] (if feasible) ± chemotherapy[p]
    - **Systemic** → Treatment for Metastasis limited sites **(NSCL-15)** or distant disease **(NSCL-18)**

[l] Principles of Surgical Therapy (NSCL-B).
[m] Principles of Radiation Therapy (NSCL-C).
[p] Perioperative Systemic Therapy (NSCL-E).
[s] Concurrent Chemoradiation Regimens (NSCL-F).
[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy.
[y] Selected patients with N2 disease (fit, single station non-bulky N2, requiring only lobectomy) may be considered for systemic therapy followed by surgery.
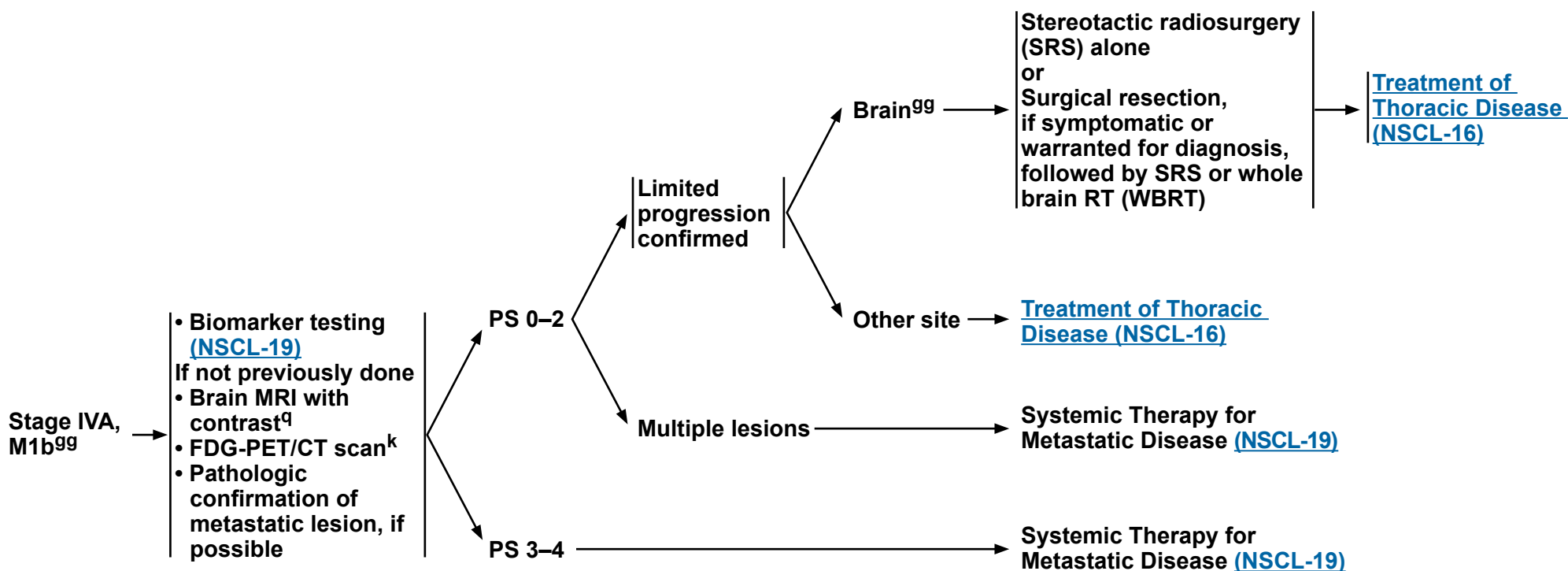[z] Chest CT with contrast and/or FDG-PET/CT to evaluate progression.

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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[l] after preoperative systemic therapy, if planned[p]**

- N0–1 → **Adjuvant Systemic Therapy (NSCL-E)** → Surveillance (NSCL-17)
- N2
  - → **Margins negative (R0)[t]** → **Adjuvant Systemic Therapy (NSCL-E) or Sequential chemotherapy[p] + Consider RT[m]** → Surveillance (NSCL-17)
  - → **Margins positive**
    - R1[t] → **Chemoradiation[m] (sequential[p] or concurrent[s])** → Surveillance (NSCL-17)
    - R2[t] → **Concurrent chemoradiation[m,s]** → Surveillance (NSCL-17)

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[q]

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

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

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

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

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

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

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

[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-11). Multiple studies suggest that next-generation sequencing (NGS) testing with broad gene coverage may allow for unambiguous determination of clonal relatedness among separate lung nodules.

[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).
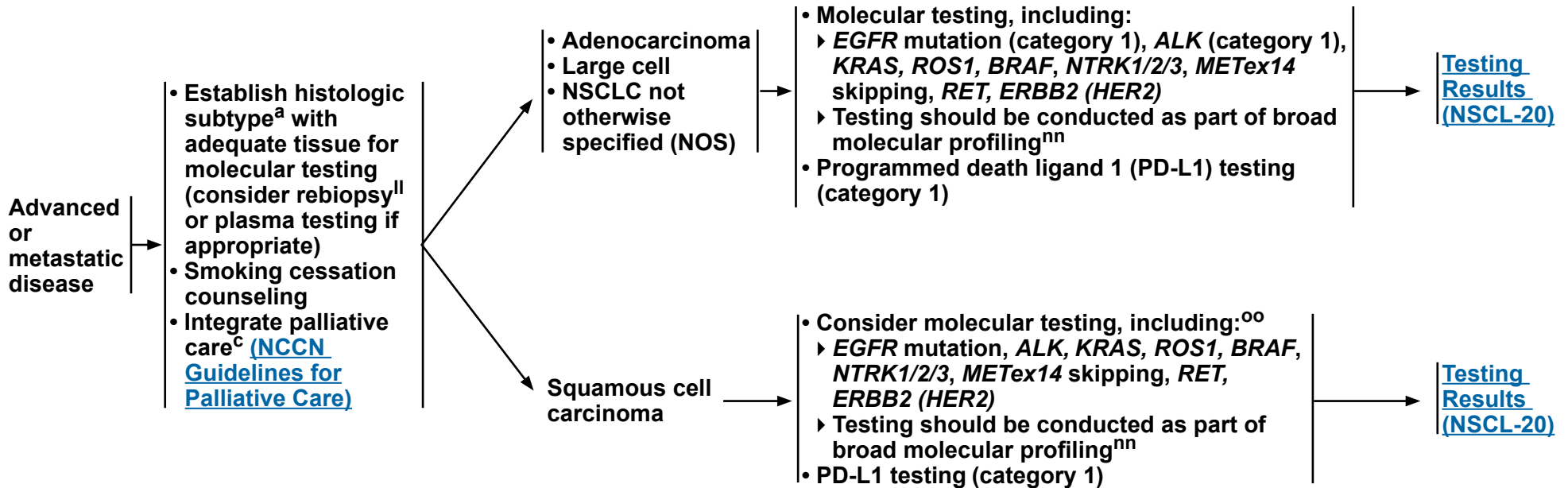
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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL PRESENTATION

INITIAL TREATMENT

Multiple lung cancers (suspected or confirmed) (N0–1) → **Multidisciplinary evaluation[cc] NCCN Lung Cancer Screening Guidelines (LCS-11)**

→ **Stable or very slow-growing disease[dd]** → **Observation** → **Surveillance (NSCL-17)**

→ **Dominant nodule with evidence of growth[dd]**

→ **Definitive local therapy possible** → **Parenchymal sparing resection (preferred)[l,ee] or Radiation[m] or Image-guided thermal ablation (IGTA)[n]** → **Surveillance (NSCL-17)**

→ **Definitive local therapy not possible** → **Palliative chemotherapy ± local palliative therapy or Observe** → **Therapy for Recurrence and Metastasis (NSCL-18) or Systemic Therapy for Metastatic Disease (NSCL-19)**

[l] Principles of Surgical Therapy (NSCL-B).
[m] Principles of Radiation Therapy (NSCL-C).
[n] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. 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 oncology).

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT

Stage IIIB (T1–2, N3)
Stage IIIC (T3, N3)

→

- **PFTs (if not previously done)**
- **FDG-PET/CT scan[k] (if not previously done)**
- **Brain MRI with contrast[q]**
- **Pathologic confirmation of N3 disease by:**
  - ‣ **Mediastinoscopy**
  - ‣ **Supraclavicular lymph node biopsy**
  - ‣ **Thoracoscopy**
  - ‣ **Needle biopsy**
  - ‣ **Mediastinotomy**
  - ‣ **EUS biopsy**
  - ‣ **EBUS biopsy**

N3 negative ⟶ **Initial treatment for stage I–IIIA (NSCL-8)**

N3 positive ⟶ **Definitive concurrent chemoradiation[m,s] (category 1)** → **Durvalumab[s,v] (category 1)** → **Surveillance (NSCL-17)**

Metastatic disease ⟶ **Treatment for Metastasis limited sites (NSCL-15) or distant disease (NSCL-18)**

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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.

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

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

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

[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

Stage IIIB (T4, N2) Stage IIIC (T4, N3)

- FDG-PET/CT scan[k] (if not previously done)
- Brain MRI with contrast[q]
- Pathologic confirmation of N2–3 disease by either:
  ‣ Mediastinoscopy
  ‣ Supraclavicular lymph node biopsy
  ‣ Thoracoscopy
  ‣ Needle biopsy
  ‣ Mediastinotomy
  ‣ EUS biopsy
  ‣ EBUS biopsy

Contralateral mediastinal node negative
→ **Ipsilateral mediastinal node negative (T4, N0–1)** → **Treatment for Stage IIIA (NSCL-7)**
→ **Ipsilateral mediastinal node positive (T4, N2)** → **Definitive concurrent chemoradiation[m,s] (category 1)** → **Durvalumab[s,v] (category 1)**

Contralateral mediastinal node positive (T4, N3) → **Definitive concurrent chemoradiation[m,s] (category 1)** → **Durvalumab[s,v] (category 1)** → **Surveillance (NSCL-17)**

Metastatic disease → **See Treatment for Metastasis limited sites (NSCL-15) or distant disease (NSCL-18)**

Stage IVA, M1a: pleural or pericardial effusion

- FDG-PET/CT scan[k] (if not previously done)
- Brain MRI with contrast[q]
- Biomarker testing (NSCL-19)
- Thoracentesis or pericardiocentesis ± thoracoscopy if thoracentesis indeterminate

Negative[ff] → **Treatment according to TNM stage**

Positive[ff] → **Local therapy if necessary (eg, pleurodesis, ambulatory small catheter drainage, pericardial window) + treatment for stage IV disease solitary site or distant disease (NSCL-19)**

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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.

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

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

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

[v] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy.

[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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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

Stage IVA, M1b[gg] →

- **Biomarker testing (NSCL-19)**
  If not previously done
- **Brain MRI with contrast**[q]
- **FDG-PET/CT scan**[k]
- **Pathologic confirmation of metastatic lesion, if possible**

PS 0–2

Limited progression confirmed

Brain[gg] → **Stereotactic radiosurgery (SRS) alone or Surgical resection, if symptomatic or warranted for diagnosis, followed by SRS or whole brain RT (WBRT)** → **Treatment of Thoracic Disease (NSCL-16)**

Other site → **Treatment of Thoracic Disease (NSCL-16)**

Multiple lesions → **Systemic Therapy for Metastatic Disease (NSCL-19)**

PS 3–4 → **Systemic Therapy for Metastatic Disease (NSCL-19)**

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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.

[q] 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 progressing sites.

[hh] NCCN Guidelines for Central Nervous System Cancers.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

TREATMENT OF THORACIC DISEASE

Definitive therapy for thoracic disease feasible
→
Consider systemic therapy (NSCL-19) and restaging[z] to confirm non-progression or Proceed to definitive therapy

T1–3, N0 →
- Pathologic mediastinal nodal evaluation[h] and
- Surgical resection[l] or SABR[m,n]

T1–3, N1 →
- Pathologic mediastinal nodal evaluation[h] and
- Chemoradiation[s] (preferred) or Surgical resection[l] or Definitive RT[m]

Definitive local therapy for metastatic site,[n,ii] if not already given → **Consider systemic therapy, if not already given (NSCL-19)**

T1–3, N2
T4, N0–2 →
Definitive chemoradiation[s]

Definitive therapy for thoracic disease not feasible →
Systemic Therapy for Metastatic Disease (NSCL-19)

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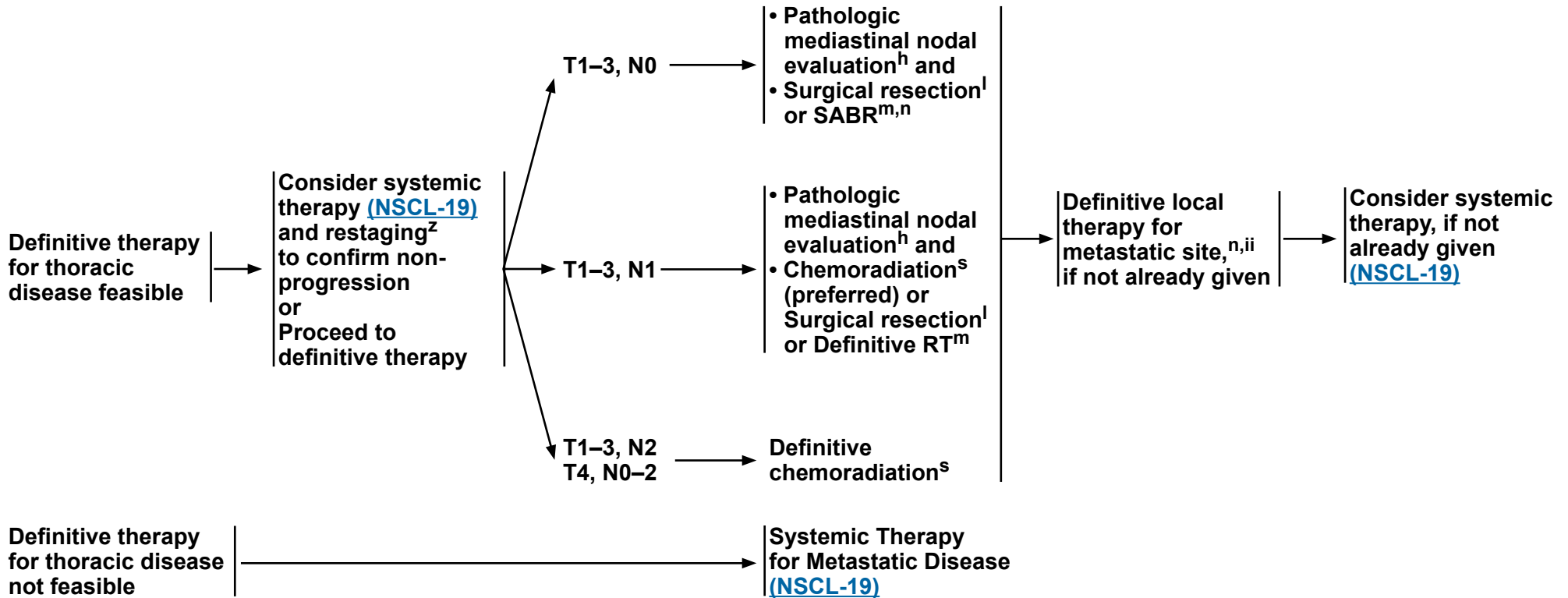
[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.
[l] Principles of Surgical Therapy (NSCL-B).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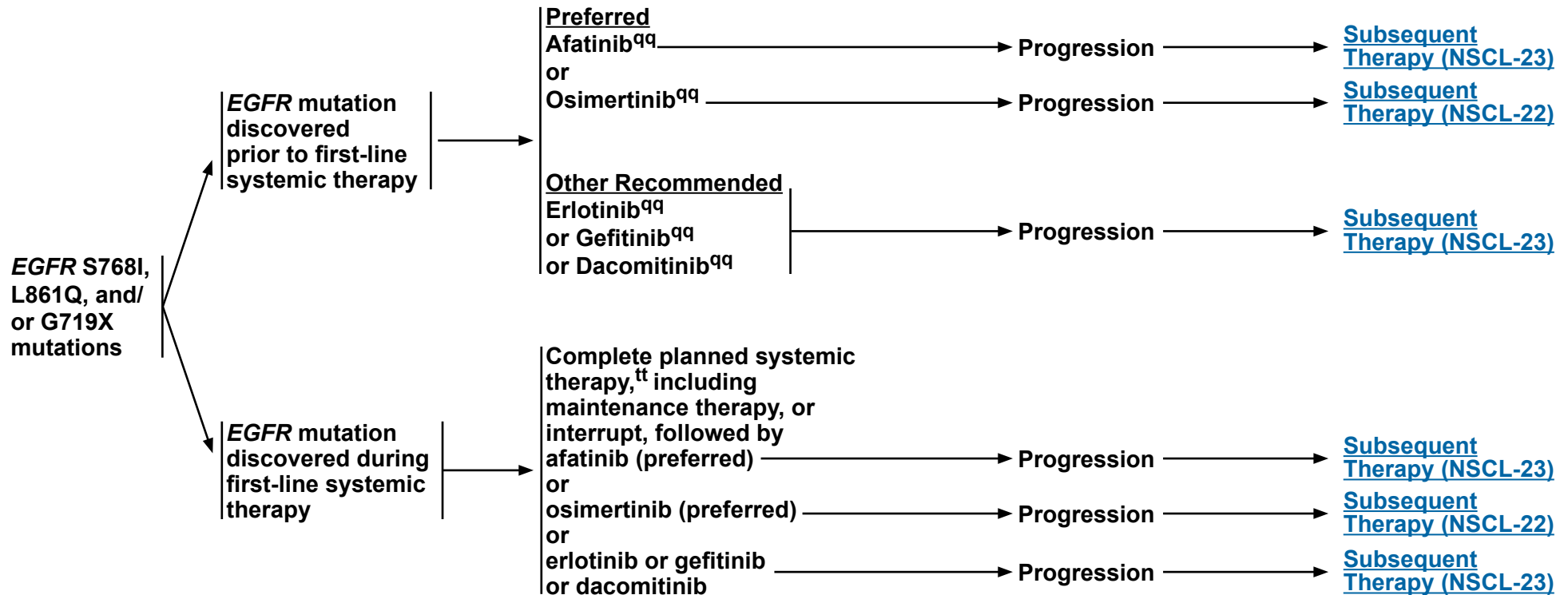[ii] Typically, RT (including SABR) or surgical resection.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

→ **Recurrence** →
- **FDG-PET/CT**
- **Brain MRI with contrast[q]**

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

↘ **Distant metastases** → **Therapy for Recurrence and Metastasis (NSCL-18)**
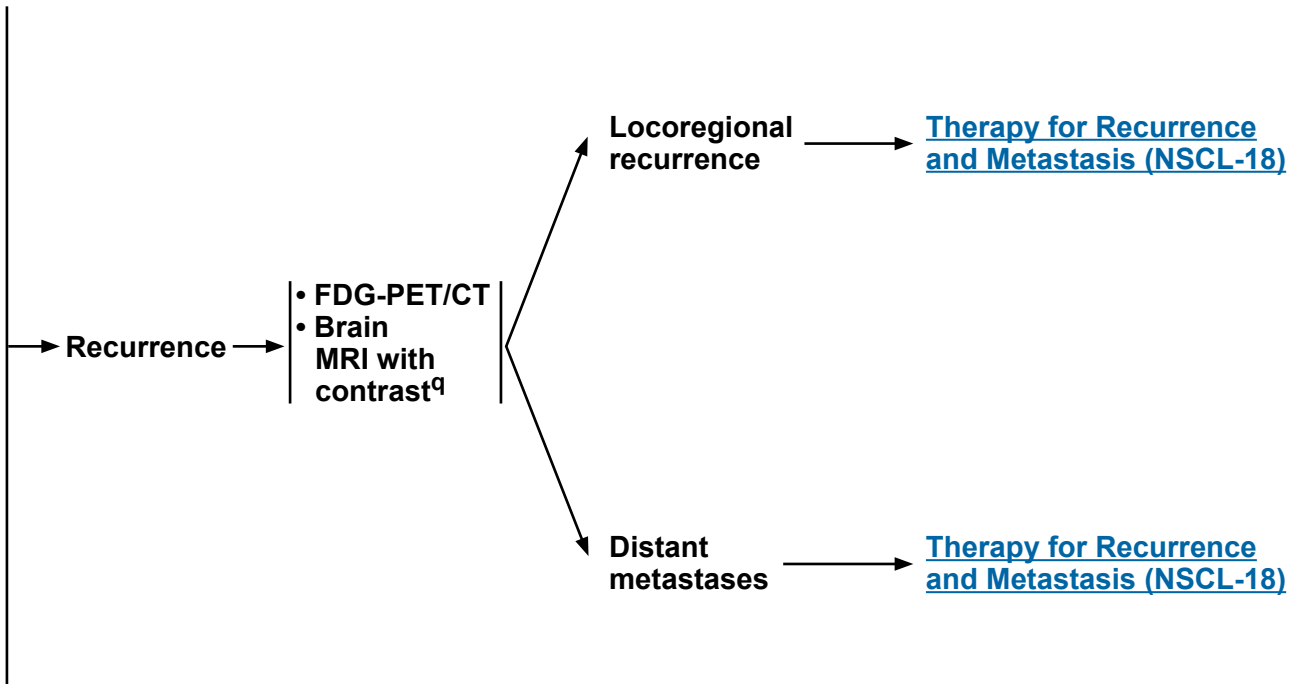
[q] If MRI is not possible, CT of head with contrast.
[jj] Timing of CT scans within Guidelines parameters is a clinical decision.
[kk] FDG-PET/CT is currently not warranted in the routine surveillance and follow-up of patients with NSCLC. However, many benign conditions (such as atelectasis, consolidation, 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.
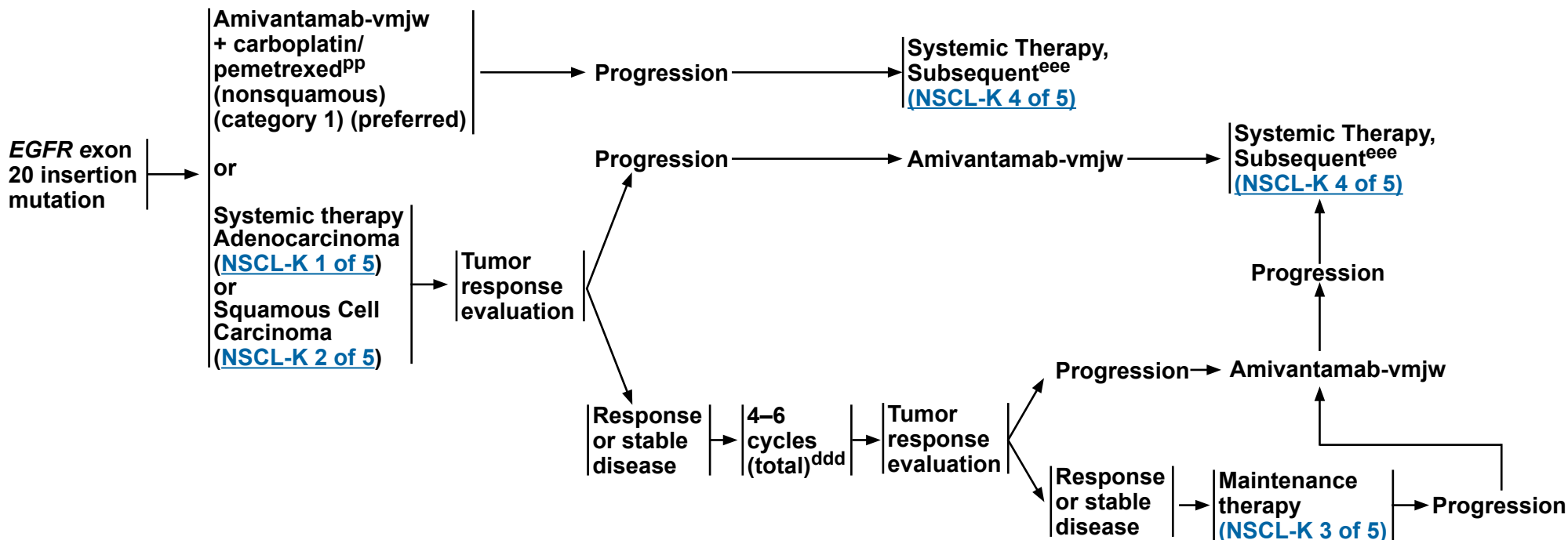
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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

THERAPY FOR RECURRENCE AND METASTASIS

Locoregional recurrence or symptomatic local disease

Endobronchial obstruction →

Any combination of the following:
- Laser/stent/other surgery[l]
- External-beam RT or brachytherapy[m]
- Photodynamic therapy

Resectable recurrence →
- Reresection (preferred)[l]
- External-beam RT or SABR[m,n]

Mediastinal lymph node recurrence →
- No prior RT → Concurrent chemoradiation[m,s] →
- Prior RT → Systemic therapy (NSCL-19) →

Superior vena cava (SVC) obstruction →
- Concurrent chemoradiation[m,s] (if not previously given) ± SVC stent
- External-beam RT[m] ± SVC stent
- SVC stent

Severe hemoptysis →

Any combination of the following:
- External-beam RT or brachytherapy[m]
- Laser or photodynamic therapy or embolization
- Surgery

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

→ **No evidence of disseminated disease** → **Observation or Systemic therapy (NSCL-19) (category 2B)**

→ **Evidence of disseminated disease** → **Systemic therapy (NSCL-19)**

Distant metastases

Localized symptoms → Palliative external-beam RT[m] →

Diffuse brain metastases → Palliative external-beam RT[m,hh] →

Bone metastasis →
- If risk of fracture, orthopedic stabilization + palliative external-beam RT[m]
- Consider bisphosphonate therapy or denosumab

→ **Systemic therapy (NSCL-19)**

Limited metastasis → Stage IV, M1b (NSCL-15)

Disseminated metastases → Systemic therapy (NSCL-19)

---

[l] Principles of Surgical Therapy (NSCL-B).
[m] Principles of Radiation Therapy (NSCL-C).
[n] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[q] If MRI is not possible, CT of head with contrast.
[s] Concurrent Chemoradiation Regimens (NSCL-F).
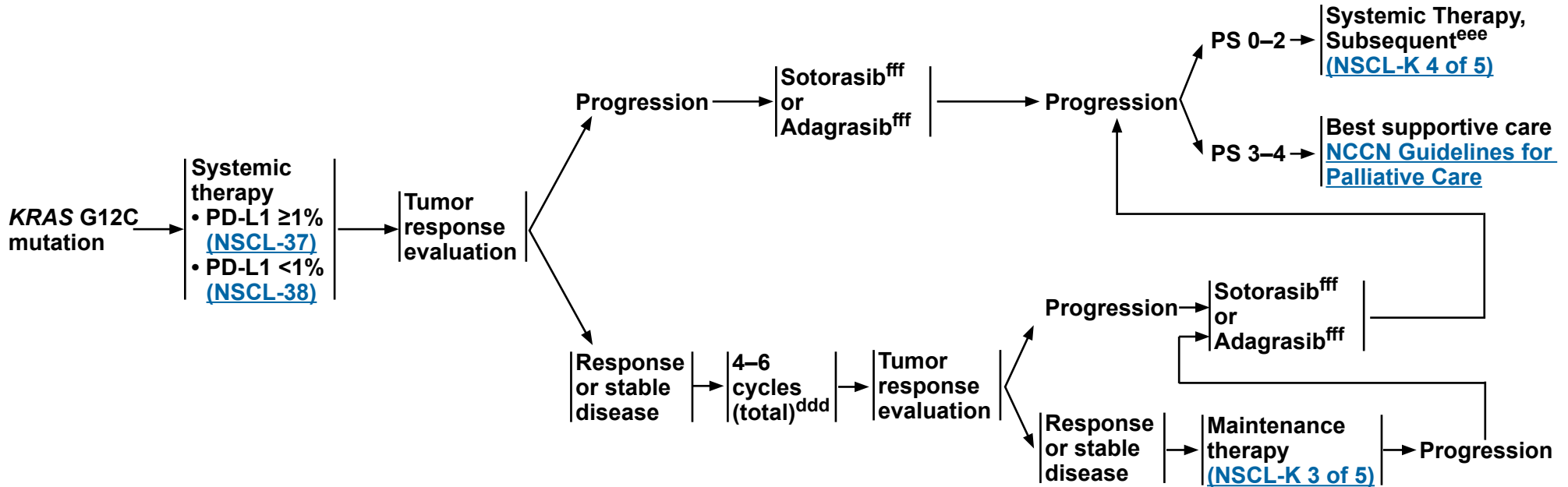[hh] NCCN Guidelines for Central Nervous System Cancers.

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CLINICAL PRESENTATION

Advanced or metastatic disease

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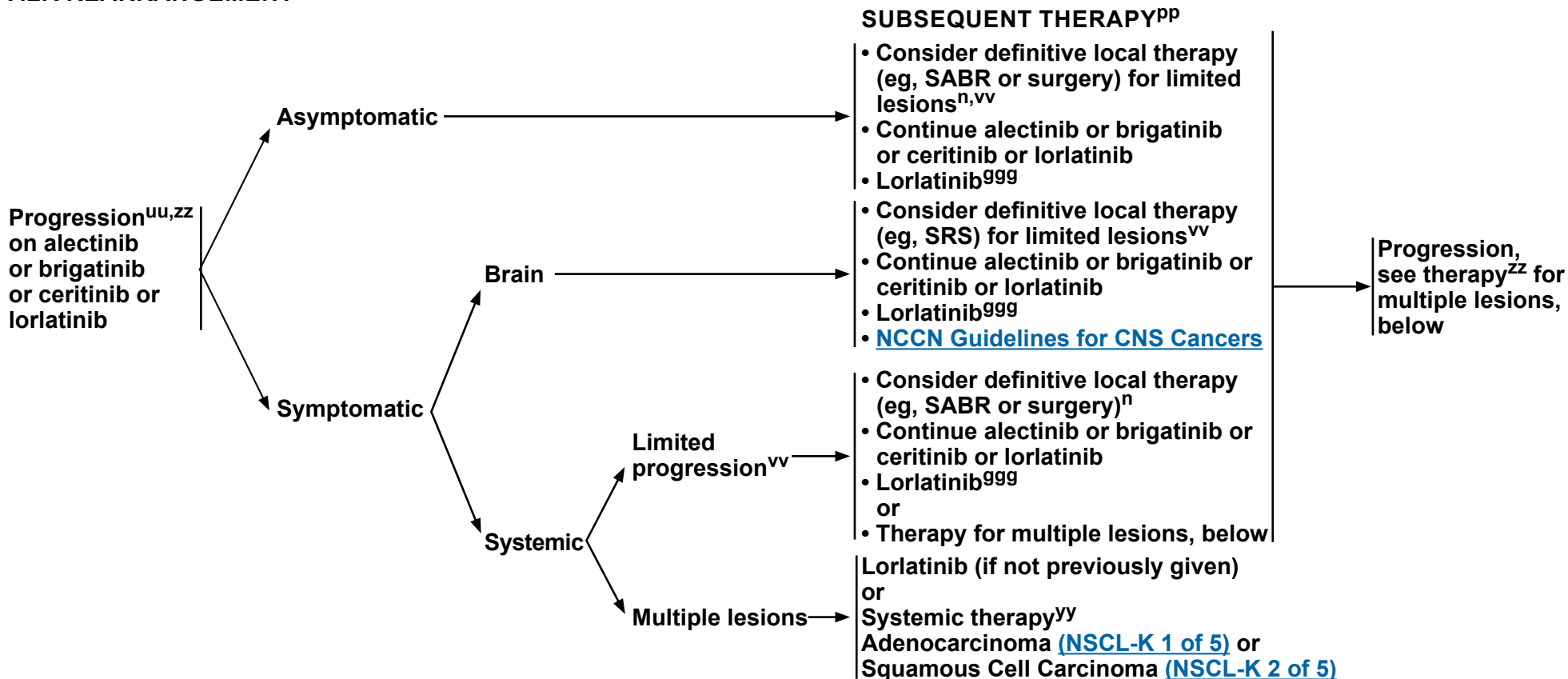- **Smoking cessation counseling**
- **Integrate palliative care[c] (NCCN Guidelines for Palliative Care)**

HISTOLOGIC SUBTYPE[a]

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

Squamous cell carcinoma

BIOMARKER TESTING[mm]

- **Molecular testing, including:**
  - *EGFR* **mutation (category 1),** *ALK* **(category 1),** *KRAS, ROS1, BRAF, NTRK1/2/3, METex14* **skipping,** *RET, ERBB2 (HER2)*
  - **Testing should be conducted as part of broad molecular profiling[nn]**
- **Programmed death ligand 1 (PD-L1) testing (category 1)**

- **Consider molecular testing, including:[oo]**
  - *EGFR* **mutation,** *ALK, KRAS, ROS1, BRAF, NTRK1/2/3, METex14* **skipping,** *RET, ERBB2 (HER2)*
  - **Testing should be conducted as part of broad molecular profiling[nn]**
- **PD-L1 testing (category 1)**

Testing Results (NSCL-20)

Testing Results (NSCL-20)

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

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

[ll] Complete genotyping for *EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET,* and *ERBB2 (HER2)* 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. If a clinically actionable marker is found, it is reasonable to start therapy based on the identified marker. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

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

[nn] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-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. Emerging Biomarkers to Identify Patients for Therapies (NSCL-I).

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

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

TESTING RESULTS[ll,mm]

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**
PD-L1 ≥1% and negative for actionable molecular biomarkers above	**NSCL-37**
PD-L1 <1% and negative for actionable molecular biomarkers above	**NSCL-38**

[ll] Complete genotyping for *EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET,* and *ERBB2 (HER2)* 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. If a clinically actionable marker is found, it is reasonable to start therapy based on the identified marker. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

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

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

FIRST-LINE THERAPY[pp]

EGFR exon 19 deletion or exon 21 L858R mutations

EGFR mutation discovered prior to first-line systemic therapy

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

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

or Erlotinib[qq] (category 1)
or Afatinib[qq] (category 1)
or Gefitinib[qq] (category 1)
or Dacomitinib[qq] (category 1) → **Progression** → **Subsequent Therapy (NSCL-23)**
or Erlotinib + ramucirumab
or Erlotinib + bevacizumab[rr,ss]

EGFR mutation discovered during first-line systemic therapy

Complete planned systemic therapy,[tt] including maintenance therapy, or interrupt, followed by osimertinib (preferred) → **Progression** → **Subsequent Therapy (NSCL-22)**

or

erlotinib or afatinib or gefitinib or dacomitinib or erlotinib + ramucirumab or erlotinib + bevacizumab[rr,ss] → **Progression** → **Subsequent Therapy (NSCL-23)**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
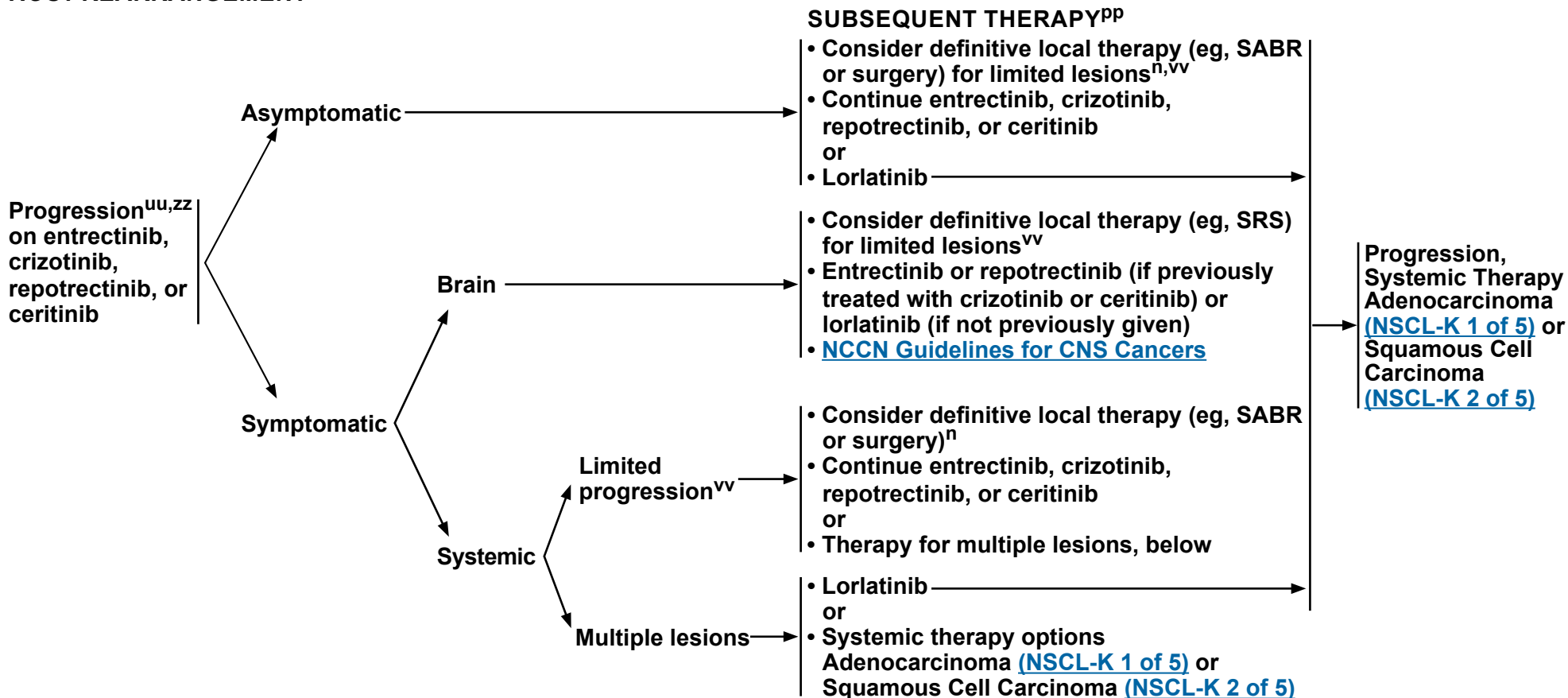[qq] For performance status 0–4.
[rr] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[tt] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. 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.

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EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS[mm]   SUBSEQUENT THERAPY[pp]

Progression on osimertinib[uu]

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

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

  → **Systemic**
    → **Limited progression[vv]** →
    - Consider definitive local therapy (eg, SABR or surgery)[n]
    - Continue osimertinib
    or
    - Therapy for multiple lesions, below

    → **Multiple lesions[ww]** →
    Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous) (category 1) (preferred)
    or
    Systemic therapy[xx,yy]
    Adenocarcinoma (NSCL-K 1 of 5)
    or
    Squamous Cell Carcinoma
    (NSCL-K 2 of 5)

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

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

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[n] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
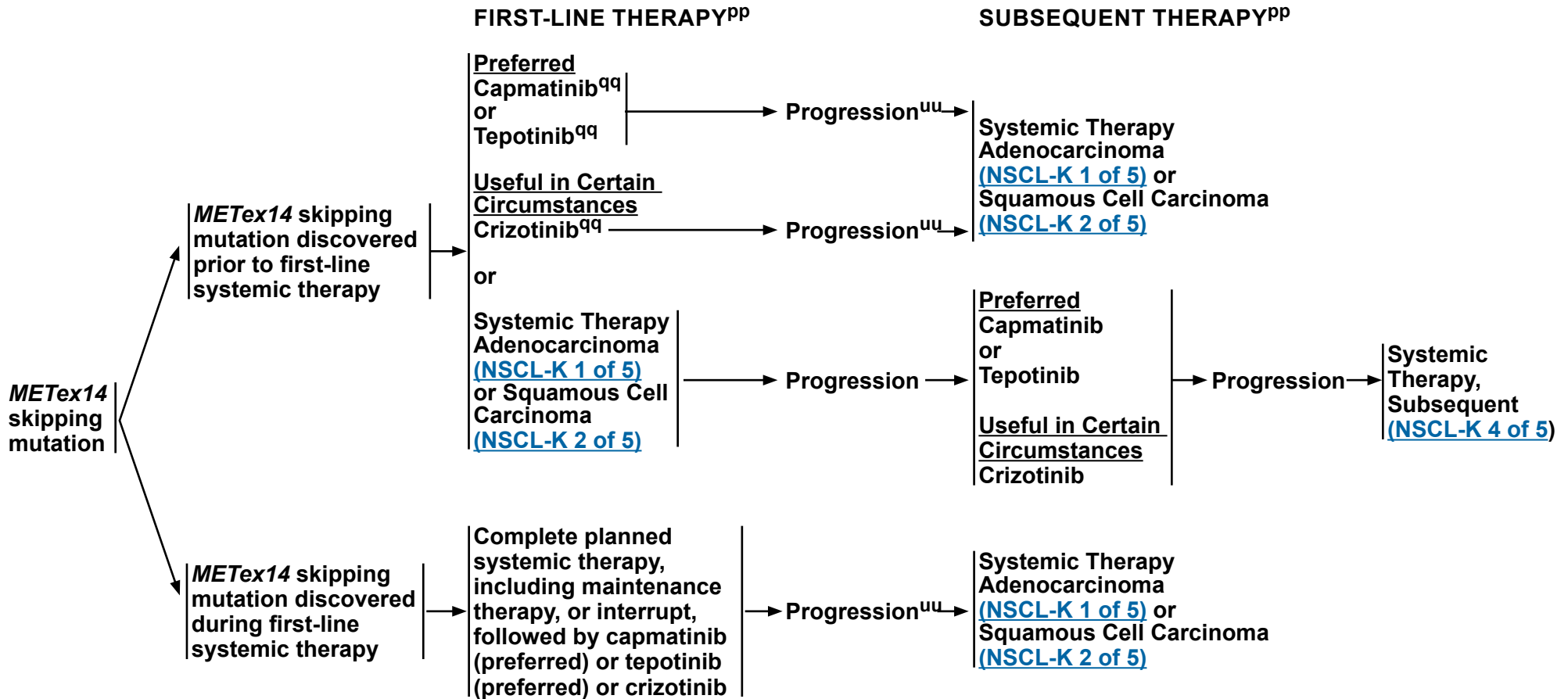[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Moleculer or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[uu] Beware of flare phenomenon in subset of patients who discontinue tyrosine kinase inhibitor (TKI). If disease flare occurs, restart TKI.
[vv] Clinical trials have included up to 3 to 5 progressing sites.
[ww] 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. Principles of Molecular and Biomarker Analysis (NSCL-H) and NCCN Guidelines for Small Cell Lung Cancer.
[xx] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
[yy] The data in the second-line setting suggest that programmed death cell 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[mm]　　SUBSEQUENT THERAPY[pp]

Progression[uu,zz] on erlotinib (± ramucirumab or bevacizumab), afatinib, gefitinib, or dacomitinib

→ *T790M* testing (category 1)

Asymptomatic →
- Consider definitive local therapy (eg, SABR or surgery) for limited lesions[n,vv]
- Osimertinib[qq] (if *T790M+*) (category 1) ———→ **Progression (NSCL-22)**
  or
  Continue erlotinib (± ramucirumab or bevacizumab[rr]) or afatinib or gefitinib or dacomitinib (if *T790M-*)
  → Progression, see therapy[xx,yy] for multiple lesions, below

Brain[aaa] →
- Consider definitive local therapy (eg, SRS) for limited lesions[vv]
- Osimertinib[qq] (if *T790M+*) (category 1) ———→ **Progression (NSCL-22)**
  or
  Continue erlotinib (± ramucirumab or bevacizumab[rr]) or afatinib or gefitinib or dacomitinib[bbb] (if *T790M-*)
  → Progression, see therapy[xx,yy] for multiple lesions, below
- **NCCN Guidelines for CNS Cancers**

Symptomatic

Systemic

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

Multiple lesions[ww,aaa]
- *T790M+* ——→ Osimertinib[qq] (category 1) (if not previously given) ———→ **Progression (NSCL-22)**
- *T790M-* ——→ Systemic therapy[xx,yy] Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)

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

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

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

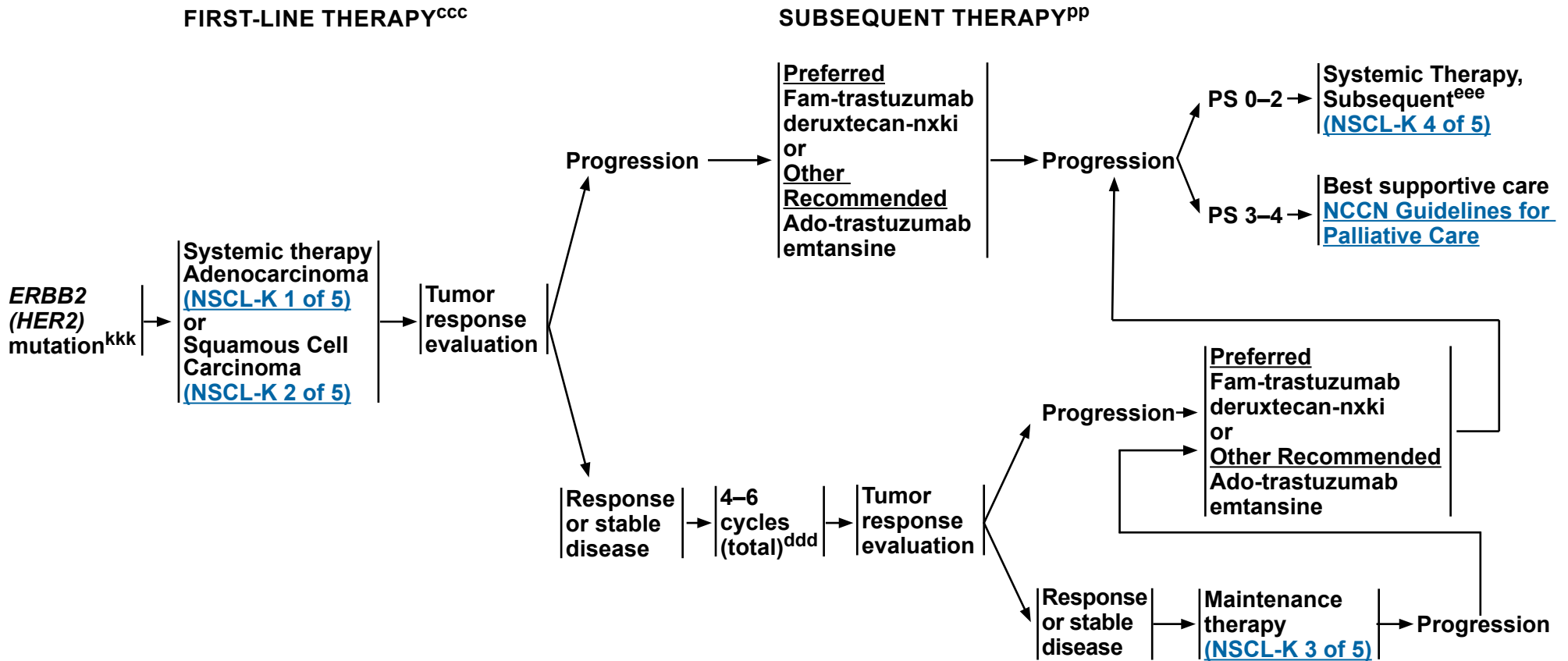[qq] For performance status 0–4.

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

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

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

[ww] Consider a biopsy at time of progression to rule out SCLC transformation (approximately 6%) and biopsy or plasma testing to evaluate mechanisms of resistance. NCCN Guidelines for Small Cell Lung Cancer.

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

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

[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression, for the T790M mutation and other genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

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

[bbb] In the randomized phase III trial of dacomitinib, patients with brain metastases were not eligible for enrollment. In the setting of brain metastases, consider other options.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

FIRST-LINE THERAPY[pp]

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

EGFR **mutation discovered prior to first-line systemic therapy**

Preferred
Afatinib[qq] ⟶ Progression ⟶ **Subsequent Therapy (NSCL-23)**
or
Osimertinib[qq] ⟶ Progression ⟶ **Subsequent Therapy (NSCL-22)**

Other Recommended
Erlotinib[qq]
or Gefitinib[qq]
or Dacomitinib[qq] ⟶ Progression ⟶ **Subsequent Therapy (NSCL-23)**

EGFR **mutation discovered during first-line systemic therapy**

Complete planned systemic therapy,[tt] including maintenance therapy, or interrupt, followed by afatinib (preferred) ⟶ Progression ⟶ **Subsequent Therapy (NSCL-23)**
or
osimertinib (preferred) ⟶ Progression ⟶ **Subsequent Therapy (NSCL-22)**
or
erlotinib or gefitinib or dacomitinib ⟶ Progression ⟶ **Subsequent Therapy (NSCL-23)**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[tt] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. 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.

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EGFR EXON 20 INSERTION MUTATION[mm]

FIRST-LINE THERAPY[ccc]

SUBSEQUENT THERAPY[pp]

EGFR exon 20 insertion mutation

Amivantamab-vmjw + carboplatin/ pemetrexed[pp] (nonsquamous) (category 1) (preferred)

or

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

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

Tumor response evaluation

→ Progression → **Amivantamab-vmjw** → **Systemic Therapy, Subsequent[eee] (NSCL-K 4 of 5)**

→ **Response or stable disease** → **4–6 cycles (total)[ddd]** → **Tumor response evaluation**

→ Progression → **Amivantamab-vmjw** → Progression → **Systemic Therapy, Subsequent[eee] (NSCL-K 4 of 5)**

→ **Response or stable disease** → **Maintenance therapy (NSCL-K 3 of 5)** → Progression → **Amivantamab-vmjw**

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

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

***KRAS* G12C MUTATION**^{mm}

FIRST-LINE THERAPY^{ccc}

SUBSEQUENT THERAPY^{pp}

KRAS G12C mutation →

Systemic therapy
• PD-L1 ≥1% (NSCL-37)
• PD-L1 <1% (NSCL-38)

→ **Tumor response evaluation**

Progression → **Sotorasib**^{fff} **or Adagrasib**^{fff} → **Progression**

→ PS 0–2 → **Systemic Therapy, Subsequent**^{eee} (NSCL-K 4 of 5)

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

Response or stable disease → **4–6 cycles (total)**^{ddd} → **Tumor response evaluation**

Progression → **Sotorasib**^{fff} **or Adagrasib**^{fff}

Response or stable disease → **Maintenance therapy** (NSCL-K 3 of 5) → **Progression**

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^{mm} Principles of Molecular and Biomarker Analysis (NSCL-H).
^{pp} Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
^{ccc} Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
^{ddd} In general, 4 cycles of initial systemic therapy (ie, with carboplatin or cisplatin) are administered prior to maintenance therapy. However, if patient is tolerating therapy well, consideration can be given to continue to 6 cycles.
^{eee} Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
^{fff} 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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> **Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

ALK REARRANGEMENT[mm]

FIRST-LINE THERAPY[pp]

ALK rearrangement

ALK rearrangement discovered prior to first-line systemic therapy
→
Preferred
Alectinib[qq] (category 1)
or
Brigatinib[qq] (category 1)
or
Lorlatinib[qq] (category 1)

Other Recommended
Ceritinib[qq] (category 1)
→ **Progression** → **Subsequent Therapy (NSCL-28)**

Useful in Certain Circumstances
Crizotinib[qq] (category 1)
→ **Progression** → **Subsequent Therapy (NSCL-29)**

ALK rearrangement discovered during first-line systemic therapy
→
Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by alectinib (preferred) or brigatinib (preferred) or lorlatinib (preferred) or ceritinib
→ **Progression** → **Subsequent Therapy (NSCL-28)**

or crizotinib → **Progression** → **Subsequent Therapy (NSCL-29)**

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

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ALK REARRANGEMENT[mm]

SUBSEQUENT THERAPY[pp]

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

Asymptomatic
- **Consider definitive local therapy (eg, SABR or surgery) for limited lesions[n,vv]**
- **Continue alectinib or brigatinib or ceritinib or lorlatinib**
- **Lorlatinib[ggg]**

Symptomatic

Brain
- **Consider definitive local therapy (eg, SRS) for limited lesions[vv]**
- **Continue alectinib or brigatinib or ceritinib or lorlatinib**
- **Lorlatinib[ggg]**
- **NCCN Guidelines for CNS Cancers**

Systemic

Limited progression[vv]
- **Consider definitive local therapy (eg, SABR or surgery)[n]**
- **Continue alectinib or brigatinib or ceritinib or lorlatinib**
- **Lorlatinib[ggg]**
  or
- **Therapy for multiple lesions, below**

Multiple lesions
**Lorlatinib (if not previously given)
or
Systemic therapy[yy]
Adenocarcinoma (NSCL-K 1 of 5) or
Squamous Cell Carcinoma (NSCL-K 2 of 5)**

Progression, see therapy[zz] for multiple lesions, below

[n] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[vv] Clinical trials have included up to 3 to 5 progressing sites.
[yy] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR* exon 19 deletion or exon 21 L858R, *ALK*+ NSCLC.
[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.
[ggg] Lorlatinib is an option for resistant mutations, such as *ALK* G1202R and L1196M (except compound L1196M/G1202R).

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ALK REARRANGEMENT[mm]

SUBSEQUENT THERAPY[pp]

Progression on crizotinib[uu,zz,hhh]

Asymptomatic
- Consider definitive local therapy (eg, SABR or surgery) for limited lesions[n,vv]
- Continue crizotinib
or
Alectinib[qq] or brigatinib[qq] or ceritinib[qq] or lorlatinib[qq]

Symptomatic

Brain
- Consider definitive local therapy (eg, SRS) for limited lesions[vv]
- Alectinib[qq] or brigatinib[qq] or ceritinib[qq] or lorlatinib[qq]
- NCCN Guidelines for CNS Cancers

Systemic

Limited progression[vv]
- Consider definitive local therapy (eg, SABR or surgery)[n]
- Continue crizotinib
or
- Therapy for multiple lesions, below

Multiple lesions
- Alectinib[qq] or brigatinib[qq] or ceritinib[qq] or lorlatinib[qq]
or
- Systemic Therapy[yy] Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)

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

---

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

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

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

[qq] For performance status 0–4.

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

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

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

[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

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

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

ROS1 REARRANGEMENT[mm]

FIRST-LINE THERAPY[pp]   **SUBSEQUENT THERAPY**[pp]

ROS1 rearrangement

↗ *ROS1* rearrangement discovered prior to first-line systemic therapy →

Preferred
Entrectinib[qq,iii]
or
Crizotinib[qq]
or
Repotrectinib[qq,iii]
or
Other Recommended
Ceritinib[qq]

→ **Progression**[uu] → **Subsequent Therapy (NSCL-31)**

↘ *ROS1* **rearrangement discovered during first-line systemic therapy** →

Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by entrectinib[iii] **(preferred), crizotinib (preferred), repotrectinib**[iii] **(preferred), or ceritinib**

→ **Progression**[uu] → **Subsequent Therapy (NSCL-31)**
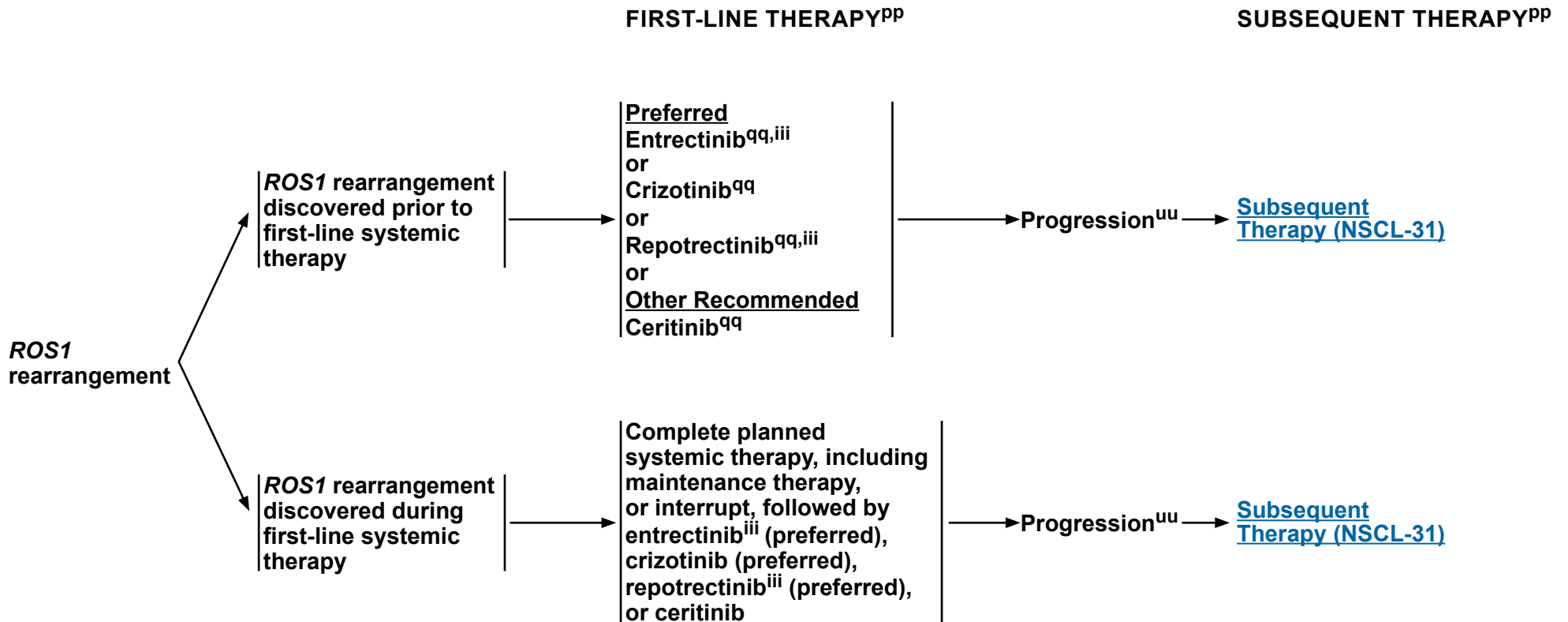
[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[iii] Entrectinib or repotrectinib may be better for patients with brain metastases.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

ROS1 REARRANGEMENT[mm]

SUBSEQUENT THERAPY[pp]

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

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

Symptomatic

Brain
- Consider definitive local therapy (eg, SRS) for limited lesions[vv]
- Entrectinib or repotrectinib (if previously treated with crizotinib or ceritinib) or lorlatinib (if not previously given)
- NCCN Guidelines for CNS Cancers

Systemic

Limited progression[vv]
- Consider definitive local therapy (eg, SABR or surgery)[n]
- Continue entrectinib, crizotinib, repotrectinib, or ceritinib
or
- Therapy for multiple lesions, below

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

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

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[n] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[vv] Clinical trials have included up to 3 to 5 progressing sites.
[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

Note: All recommendations are category 2A unless otherwise indicated.
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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

BRAF V600E MUTATION[mm]

FIRST-LINE THERAPY[pp]   **SUBSEQUENT THERAPY[pp]**

BRAF V600E mutation

→ *BRAF* V600E mutation discovered prior to first-line systemic therapy →

Preferred
Dabrafenib + trametinib[qq]
or
Encorafenib + binimetinib[qq] → **Progression** →

Useful in Certain Circumstances
Vemurafenib[qq,jjj] or **dabrafenib[qq,jjj]** → **Progression** →

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

Other Recommended
Systemic Therapy for Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5) → **Progression** →
Dabrafenib + trametinib[jjj] or **Encorafenib + binimetinib** →

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

→ *BRAF* V600E mutation discovered during first-line systemic therapy →

Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by dabrafenib + trametinib[jjj] (preferred) or encorafenib + binimetinib (preferred) → **Progression** →

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

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[jjj] Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

NTRK GENE FUSION[mm]

FIRST-LINE THERAPY[pp]

SUBSEQUENT THERAPY[pp]

NTRK1/2/3 gene fusion

NTRK1/2/3 gene fusion discovered prior to first-line systemic therapy

Preferred
Larotrectinib[qq]
or
Entrectinib[qq]

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

Useful in Certain Circumstances
Systemic Therapy
Adenocarcinoma
(NSCL-K 1 of 5) or
Squamous Cell Carcinoma
(NSCL-K 2 of 5)

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

NTRK1/2/3 gene fusion discovered during first-line systemic therapy

Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by larotrectinib or entrectinib

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

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

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

METex14 SKIPPING MUTATION[mm]

FIRST-LINE THERAPY[pp]   **SUBSEQUENT THERAPY[pp]**

METex14 skipping mutation

METex14 skipping mutation discovered prior to first-line systemic therapy

Preferred
Capmatinib[qq]
or
Tepotinib[qq]
→ **Progression[uu]** →

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

or

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

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

Preferred
Capmatinib
or
Tepotinib

Useful in Certain Circumstances
Crizotinib
→ **Progression** →

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

METex14 skipping mutation discovered during first-line systemic therapy

Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by capmatinib (preferred) or tepotinib (preferred) or crizotinib
→ **Progression[uu]** →

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

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

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RET REARRANGEMENT[mm]

FIRST-LINE THERAPY[pp]   **SUBSEQUENT THERAPY[pp]**

RET rearrangement

RET rearrangement discovered prior to first-line systemic therapy

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

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

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

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

Preferred
Selpercatinib
or
Pralsetinib

Useful in Certain Circumstances
Cabozantinib → Progression → Systemic Therapy, Subsequent **(NSCL-K 4 of 5)**

RET rearrangement discovered during first-line systemic therapy

Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by selpercatinib (preferred), pralsetinib (preferred), cabozantinib → Progression[uu] →

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

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

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ERBB2 (HER2) MUTATION[mm]

FIRST-LINE THERAPY[ccc]

SUBSEQUENT THERAPY[pp]

ERBB2 (HER2) mutation[kkk] →

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

→ **Progression** →
Preferred
Fam-trastuzumab deruxtecan-nxki
or
Other Recommended
Ado-trastuzumab emtansine
→ **Progression** →

- PS 0–2 → Systemic Therapy, Subsequent[eee] (NSCL-K 4 of 5)
- PS 3–4 → Best supportive care NCCN Guidelines for Palliative Care

→ Response or stable disease → 4–6 cycles (total)[ddd] → Tumor response evaluation

→ **Progression** →
Preferred
Fam-trastuzumab deruxtecan-nxki
or
Other Recommended
Ado-trastuzumab emtansine

→ Response or stable disease → Maintenance therapy (NSCL-K 3 of 5) → **Progression**

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

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

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

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

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

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

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PD-L1 POSITIVE (≥1%)[mm,lll]

FIRST-LINE THERAPY[pp,mmm]
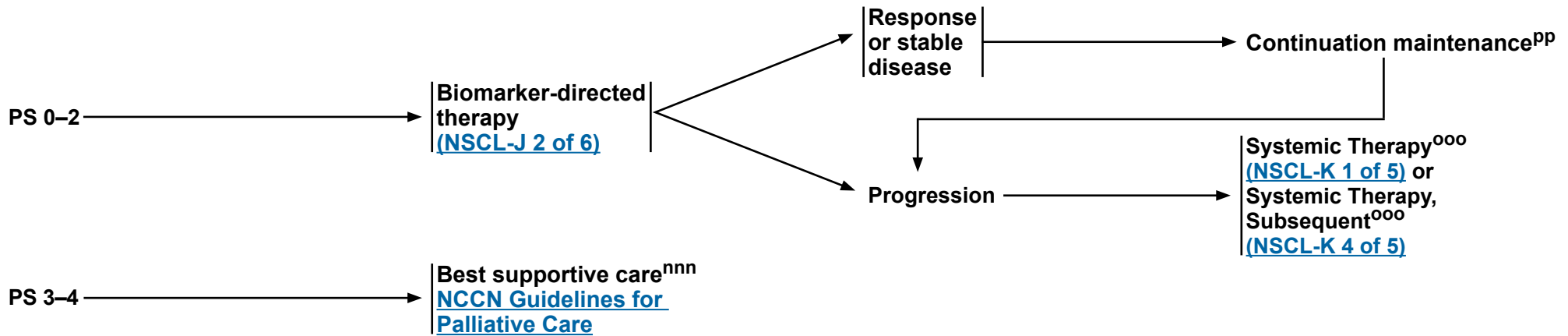
PS 0–2 ⟶ **Biomarker-directed therapy (NSCL-J 2 of 6)**

→ **Response or stable disease** ⟶ **Continuation maintenance**[pp]

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

PS 3–4 ⟶ **Best supportive care**[nnn] **NCCN Guidelines for Palliative Care**

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Molecular or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[lll] 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* 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).
[mmm] 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.
[nnn] Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status.
[ooo] 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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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PD-L1 <1%

INITIAL SYSTEMIC THERAPY^ccc

SUBSEQUENT THERAPY^eee

PS 0–2 →

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

→ **Tumor response evaluation**

Progression

PS 0–2 → **Systemic therapy, Subsequent (NSCL-K 4 of 5)** → **Systemic therapy, Progression (NSCL-K 4 of 5)**

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

Response or stable disease → **4–6 cycles (total)^ddd** → **Tumor response evaluation**

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

↑ **Progression**

Response or stable disease → **Maintenance therapy (NSCL-K 3 of 5)** → **Progression** → **Systemic therapy, Progression (NSCL-K 4 of 5)**

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

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

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

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

^nnn Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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 immunohistochemical testing is uninformative or ambiguous (see section on *Immunohistochemistry*).
    - ◊ Preservation of material for molecular testing is critical. Efforts should be undertaken to minimize block reorientation and the number of immunohistochemistry (IHC) stains for cases that cannot be classified on histologic examination alone (see section on *Immunohistochemistry*).
  - ▸ In resection specimens, the primary purpose is a) to classify the histologic type; and b) to determine all staging parameters, as recommended by the American Joint Committee on Cancer (AJCC), including tumor size, extent of invasion, adequacy of surgical margins, and presence or absence of lymph node metastases.
    - ◊ The number of involved lymph node stations should be documented since it has prognostic significance (AJCC 8th ed). Direct extension of the primary tumor into an adjacent lymph node is considered as nodal involvement.
    - ◊ All lobectomy specimens should be extensively dissected to search for involved lymph nodes.
  - ▸ In small biopsies or cytology specimens—obtained for molecular testing in the context of an established diagnosis after progression on targeted therapies—the primary purpose is a) to confirm the original pathologic type with minimal use of tissue for IHC only in suspected small cell carcinoma transformation or a different histology; and b) to preserve material for molecular analysis.
- **Formalin-fixed paraffin-embedded (FFPE) material is suitable for most molecular analyses, except bone biopsies that were previously treated with acid decalcifying solutions. Non-acid decalcification approaches may be successful for subsequent molecular testing. While many molecular pathology laboratories currently also accept cytopathology specimens such as cell blocks, direct smears, or touch preparations, laboratories that do not currently do so are strongly encouraged to identify approaches to testing on non-FFPE cytopathology specimens.**

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[1] Non-small cell carcinomas (NSCC, without the L for lung) that show no clear adenocarcinoma or squamous cell carcinoma morphology or immunohistochemical markers are regarded as NSCC-NOS. In this setting, it is recommended that pathologists use the term NSCC rather than NSCLC, because the lack of pneumocyte marker expression in small biopsies or cytology leaves open the possibility of a metastatic carcinoma and the determination of a lung primary must be established clinically after excluding other primary sites.

Continue

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NSCL-A
1 OF 4

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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF PATHOLOGIC REVIEW

NSCLC Classification

- The types of NSCLC are: adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma, and sarcomatoid carcinoma.
  - ▸ Squamous cell carcinoma: A malignant epithelial tumor that either shows keratinization and/or intercellular bridges, or a morphologically undifferentiated NSCC that expresses immunohistochemical markers of squamous cell differentiation.
  - ▸ Adenocarcinoma:
    - ◊ For small (<3 cm), resected lesions, determining extent of invasion is critical.
      - – Adenocarcinoma in situ (AIS; formerly BAC): A small (≤3 cm) localized nodule with lepidic growth, mostly non-mucinous, although mucinous types can occur. Multiple synchronous AIS tumors can also occur.
      - – Minimally invasive adenocarcinoma (MIA): A small (≤3 cm) solitary adenocarcinoma with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension. MIA is usually non-mucinous, but rarely may be mucinous. MIA is, by definition, solitary and discrete.
      - – Invasive adenocarcinoma: A malignant epithelial tumor with glandular differentiation, mucin production, or pneumocyte marker expression. The tumors show an acinar, papillary, micropapillary, lepidic, or solid growth pattern, with either mucin or pneumocyte marker expression. The invasive adenocarcinoma component should be present in at least one focus measuring >5 mm in greatest dimension.
      - – Invasive adenocarcinoma variants: invasive mucinous adenocarcinoma, colloid adenocarcinoma, fetal adenocarcinoma, and enteric adenocarcinoma.
      - – Refer to College of American Pathologists Protocols for additional information.
  - ▸ Adenosquamous carcinoma: A carcinoma showing components of both squamous cell carcinoma and adenocarcinoma, with each component constituting at least 10% of the tumor. Definitive diagnosis requires a resection specimen, although it may be suggested based on findings in small biopsies, cytology, or excisional biopsies. Presence of any adenocarcinoma component in a biopsy specimen that is otherwise squamous should trigger molecular testing.
  - ▸ Large cell carcinoma: Undifferentiated NSCC that lacks the cytologic, architectural, and histochemical features of small cell carcinoma, adenocarcinoma, or squamous cell carcinoma. The diagnosis requires a thoroughly sampled resected tumor with immunohistochemical 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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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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 immunohistochemical 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.**

Continue

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PRINCIPLES OF PATHOLOGIC REVIEW

<u>Immunohistochemistry</u>
- IHC should be used to confirm neuroendocrine differentiation when there is morphologic evidence of neuroendocrine morphology (eg, speckled chromatin pattern, nuclear molding, peripheral palisading):
  ‣ NCAM (CD56), chromogranin, synaptophysin, and INSM1 are used to identify neuroendocrine tumors in cases in which morphologic suspicion of neuroendocrine differentiation exists.
  ‣ A panel of markers is useful, but one positive marker is enough if the staining is unambiguous in more than 10% of the tumor cells.
- 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 high-risk or borderline operable patients, a multidisciplinary evaluation including a radiation oncologist is recommended.
- The overall plan of treatment as well as needed imaging studies should be determined before any non-emergency treatment is initiated.
- Thoracic surgeons should actively participate in multidisciplinary discussions and meetings regarding 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)

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

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**NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

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]**
- **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.**
- **Studies of robotic-assisted pulmonary resection show non-inferiority to traditional VATS approaches when performed by experienced robotic surgeons.[2,3]**
- **Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and margin-negative resection is achieved.**
- **T3 (invasion) and T4 local extension tumors require en-bloc resection of the involved structure with negative margins. If a surgeon or center is uncertain about potential complete resection, consider obtaining an additional surgical opinion from a high-volume specialized center.**

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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.
- 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.[4] Two randomized trials evaluated the role of surgery in this population, but neither showed an overall survival benefit with the use of surgery.[5,6] However, this population is heterogeneous and the panel believes that these trials did not sufficiently evaluate the nuances present with the heterogeneity of N2 disease and the likely oncologic benefit of surgery in specific clinical situations.
- The presence or absence of N2 disease should be vigorously determined by both radiologic and invasive staging prior to the initiation of therapy since the presence of mediastinal nodal disease has a profound impact on prognosis and treatment decisions. (NSCL-1, NSCL-2, and NSCL-6)
- Patients with occult-positive N2 nodes discovered at the time of pulmonary resection should continue with the planned resection along with formal mediastinal lymph node dissection. If N2 disease is noted in patients undergoing VATS, the surgeon may consider stopping the procedure so that induction therapy can be administered before surgery; however, continuing the procedure is also an option.
- The determination of the role of surgery in a patient with N2-positive lymph nodes should be made prior to the initiation of any therapy by a multidisciplinary team, including a thoracic surgeon who has a major part of his/her practice dedicated to thoracic oncology.[7]
- 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

References

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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.[8]
- Patients with a single lymph node smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.[4,9,10]
- 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.[10,11]
- 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.[8,12] Neoadjuvant chemoradiotherapy is associated with higher rates of pathologic complete response and negative mediastinal lymph nodes.[13] However, that is achieved at the expense of higher rates of acute toxicity and increased cost.
- When neoadjuvant chemoradiotherapy is used with doses lower than those used for standard definitive therapy, all efforts should be made to minimize any possible breaks in radiotherapy for surgical evaluation. Treatment breaks of more than 1 week are considered unacceptable.
- When timely surgical evaluation is not available, the strategy of neoadjuvant chemoradiotherapy should not be used. Another option in individual cases, and with the agreement of the thoracic surgeon, is to complete definitive chemoradiotherapy prior to re-evaluation and consideration for surgery.[14,15] 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.[5] 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.[16-19] 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.[20]

References

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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 2021 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.**
- **The majority of NCCN Member Institutions prefer EBUS for initial mediastinal staging, reserving mediastinoscopy for possible restaging.**
- **The majority of NCCN Member Institutions do not pathologically restage mediastinal lymph nodes after induction therapy and prior to surgery.**
- **All NCCN Member Institutions consider surgery for single-station non-bulky N2 disease.**
- **Approximately half of the institutions consider surgery for single-station bulky disease, 39% for multi-station non-bulky disease, and 21% for multi-station bulky disease.**
- **Two-thirds of NCCN Member Institutions prefer induction chemotherapy; one-third prefer chemoradiation.**
- **The majority require at least stable disease after induction, but do not require radiologic or pathologic response prior to surgery.**
- **Roughly a half would consider pneumonectomy after induction chemotherapy, but less than a quarter would consider pneumonectomy after chemoradiation.**
- **Approximately three-fourths would give adjuvant RT for positive residual N2 disease, but only approximately one-fourth would give RT for N2 pathologic complete response.**

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The Role of Surgery in Patients with N2 NSCLC – References

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PRINCIPLES OF RADIATION THERAPY

I. General Principles ([Table 1. Commonly Used Abbreviations in Radiation Therapy](#))
- Determination of the appropriateness of radiation therapy (RT) should be made by radiation oncologists who perform lung cancer RT as a prominent part of their practice.
- RT has a potential role in all stages of NSCLC, as either definitive/consolidative or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with stage III NSCLC, with early-stage disease who are medically inoperable, who refuse surgery, or who are high-risk surgical candidates, and with stage IV disease that may benefit from local therapy.
- The critical goals of modern RT are to maximize tumor control and to minimize treatment toxicity. A minimum technologic standard is CT-planned 3D-CRT.[1]
- More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT, FDG-PET/CT and/or MRI simulation, IMRT/VMAT, IGRT, motion management, and proton therapy (https://www.astro.org/Daily-Practice/Reimbursement/Model-Policies/Model-Policies). Nonrandomized comparisons of using advanced technologies demonstrate reduced toxicity and improved survival versus older techniques.[2-4] In a prospective trial of definitive/consolidative 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 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 OARs are in close proximity to high-dose regions, and when using complex motion management techniques.

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

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

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**NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

IV. General Treatment Information

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

- SABR (also known as SBRT)[19] has achieved good primary tumor control rates and overall survival, higher than conventionally fractionated radiotherapy. Although SABR is not proven equivalent to lobectomy, some prospective series have demonstrated similar overall and cancer-specific survival 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 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]
- 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.[10,46,47] All of these must be considered when interpreting or emulating regimens from prior studies.

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PRINCIPLES OF RADIATION THERAPY

Locally Advanced NSCLC (Stage II–III)

- Concurrent chemotherapy/RT is recommended for patients with inoperable stage II (node-positive) and stage III NSCLC.[48-51]
- RT interruptions and dose reductions for manageable acute toxicities should be avoided by employing supportive care.
- Sequential chemotherapy/RT or RT alone is appropriate for frail patients unable to tolerate concurrent therapy.[52,53] Accelerated RT regimens may be beneficial, particularly if concurrent chemotherapy would not be tolerated (ie, in a sequential or RT-only approach).[54,55]
- Preoperative systemic therapy and postoperative RT is an option for patients with resectable N2 NSCLC (minimal N2 and treatable with lobectomy).[56,57]
- Preoperative concurrent chemotherapy/RT is an alternative option for patients with resectable N2 NSCLC and is recommended for resectable superior sulcus tumors.[58,59] 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.[60,61]
- The determination of resectability in trimodality therapy should be made prior to initiation of all treatment. Upfront multidisciplinary consultation is particularly important when considering surgical treatment of patients with stage III NSCLC.
- In patients with clinical stage I/II upstaged surgically to N2 with completely resected disease, two randomized studies did not show an overall survival benefit of PORT, although locoregional control was significantly improved.[62,63] 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.[64-67]
- 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.[61]

Conventionally Fractionated RT for Locally Advanced NSCLC

- IFI omitting ENI allows tumor dose escalation and is associated with a low risk of isolated nodal relapse, particularly in a patient staged with FDG-PET/CT.[68-72] Three randomized trials found improved survival for IFI versus ENI, possibly because it enabled dose escalation.[73-75] IFI is reasonable in order to optimize definitive dosing to the tumor and/or decrease normal tissue toxicity.[74,75]
- 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.[76] Dose escalation is associated with better survival in non-randomized comparisons in RT alone,[77] sequential chemotherapy/RT,[78] or concurrent chemotherapy/RT.[79] While optimal RT dose intensification remains a valid question, a high dose of 74 Gy is not currently recommended for routine use.[80-85]
  A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens,[86] and RTOG 1106 found that PET-based individualized accelerated RT dose intensification potentially improved local control but not overall survival.[87]

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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Conventionally Fractionated RT for Locally Advanced NSCLC (continued)

- **Dosing Regimens**
  - ▸ Doses of 45 to 54 Gy in 1.8 to 2 Gy fractions are standard preoperative doses.[88] Definitive RT doses delivered as preoperative chemotherapy/RT can safely be administered and achieve promising nodal clearance and survival rates,[89-92] 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.[93] 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.[94-96] 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.[97] 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 who have also received radical therapy to the intrathoracic disease.[98] 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.[99,100] In two randomized phase II trials, significantly improved progression-free survival and overall survival in one trial[101,102] were found for local consolidative therapy (RT or surgery) to oligometastatic lesions versus maintenance systemic therapy or observation for patients not progressing on systemic therapy.[101-103]
- In the setting of progression at a limited number of sites on a given line of systemic therapy (oligoprogression), local ablative therapy to the oligoprogressive sites may extend the duration of benefit of the current line of systemic therapy.
- When treating oligometastatic/oligoprogressive lesions, if SABR is not feasible, other dose-intensive accelerated/hypofractionated CRT regimens may be used.
- See the NCCN Guidelines for Central Nervous System Cancers regarding RT for brain metastases.
- A pooled analysis of two randomized trials indicated that adding radiotherapy to a certain immune checkpoint inhibitor (anti-PD-1) significantly increased responses and clinical outcomes in patients with metastatic NSCLC. [104] 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, performance status, and logistical considerations. Shorter courses of RT are preferred for patients with poor performance status and/or shorter life expectancy because they provide similar pain relief as longer courses, although there is a higher potential need for retreatment.[105-108] For palliation of thoracic symptoms, higher dose/longer-course thoracic RT (eg, ≥30 Gy in 10 fractions) is associated with modestly improved survival and symptoms, particularly in patients with good performance status.[109,110] 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 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. [111] 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.[112]

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PRINCIPLES OF RADIATION THERAPY

Table 1. Commonly Used Abbreviations in Radiation Therapy

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

*Refer to ICRU Report 83 for detailed definitions.

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PRINCIPLES OF RADIATION THERAPY

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

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25–34 Gy	1	Peripheral, small
45–60 Gy	3	Peripheral tumors
48–50 Gy	4	Central or peripheral tumors <4–5 cm
50–55 Gy	5	Central tumors
50–60 Gy	5	Peripheral tumors
60–70 Gy	8–10	Central tumors

Table 3. Maximum Dose Constraints for SABR*

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

*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).
^For central tumor location. NS = not specified.

Continued

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

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

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

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

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

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT with Concurrent Chemotherapy†,‡

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

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

†These constraints represent doses that generally should not be exceeded, based on a consensus survey of NCCN Member Institutions. Because the risk of toxicity increases progressively with dose to normal tissues, a key principle of radiation treatment planning is to keep normal tissue doses "as low as reasonably achievable" while adequately covering the target. The doses to any given 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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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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PRINCIPLES OF IMAGE-GUIDED THERMAL ABLATION THERAPY

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

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

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

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

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PERIOPERATIVE SYSTEMIC THERAPY

- Neoadjuvant Systemic Therapy in Patients Who Are Candidates for Immune Checkpoint Inhibitors, see below.
- **Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors**
- **Adjuvant Chemotherapy**
- **Systemic Therapy Following Previous Neoadjuvant or Adjuvant Systemic Therapy**

Neoadjuvant Systemic Therapy

- All patients should be evaluated for preoperative therapy, with strong consideration for nivolumab or pembrolizumab + chemotherapy for those patients with tumors ≥4 cm or node positive and no contraindications to immune checkpoint inhibitors.[a] 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,N2]). PD-L1 status can be incorporated with other clinical factors to determine patients who may benefit from induction chemotherapy and immunotherapy.
  Principles of Molecular and Biomarker Analysis (NSCL-H).
- Clinical trials for neoadjuvant nivolumab + chemotherapy excluded patients harboring *EGFR* mutations and *ALK* rearrangements. Thus, exclusion of these biomarkers, at a minimum, is recommended prior to consideration for neoadjuvant nivolumab + chemotherapy.
- After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction systemic therapy as an alternative.

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

- Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[1]
  ‣ 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 therapy every 3 weeks for 4 cycles and then continued as single-agent pembrolizumab as adjuvant treatment after surgery (category 1); **Systemic Therapy Following Previous Neoadjuvant or Adjuvant Systemic Therapy**[2]
  ‣ 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)

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[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* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

References

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PERIOPERATIVE SYSTEMIC 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[3]
Preferred (squamous)
• Cisplatin 75 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8, every 21 days for 4 cycles[4]
• Cisplatin 75 mg/m^2 day 1, docetaxel 75 mg/m^2 day 1 every 21 days for 4 cycles[5]
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[6]
• Cisplatin 100 mg/m^2 day 1, vinorelbine 30 mg/m^2 days 1, 8, 15, and 22, every 28 days for 4 cycles[7,8]
• 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[7]
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[9]
  ‣ Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m^2 days 1 and 8, every 21 days for 4 cycles[10] (squamous histology)
  ‣ Carboplatin AUC 5 day 1, pemetrexed 500 mg/m^2 day 1 every 21 days for 4 cycles[11] (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 Previous Neoadjuvant or Adjuvant Systemic Therapy

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PERIOPERATIVE SYSTEMIC THERAPY

Adjuvant Chemotherapy
- For stage IIA (T2b, N0) and negative margins, 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), stage IIIB (T3, N2) and negative margins (R0), adjuvant chemotherapy is recommended as a category 1.
- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages II–IIIA, IIIB [T3,N2]).
  Principles of Molecular and Biomarker Analysis (NSCL-H).

Preferred (nonsquamous)
- Cisplatin 75 mg/m^2 day 1, pemetrexed 500 mg/m^2 day 1 every 21 days for 4 cycles[3]

Preferred (squamous)
- Cisplatin 75 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8, every 21 days for 4 cycles[4]
- Cisplatin 75 mg/m^2 day 1, docetaxel 75 mg/m^2 day 1 every 21 days for 4 cycles[5]

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[6]
- Cisplatin 100 mg/m^2 day 1, vinorelbine 30 mg/m^2 days 1, 8, 15, and 22, every 28 days for 4 cycles[7,8]
- 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[7]

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[8]
  ‣ Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m^2 days 1 and 8, every 21 days for 4 cycles[10]
  ‣ Carboplatin AUC 5 day 1, pemetrexed 500 mg/m^2 day 1 every 21 days for 4 cycles[11] (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
Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors
Systemic Therapy Following Previous Neoadjuvant or Adjuvant Systemic Therapy

[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.

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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PERIOPERATIVE SYSTEMIC THERAPY

Systemic Therapy Following Previous Neoadjuvant or Adjuvant Systemic Therapy[c]
- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]).
  [Principles of Molecular and Biomarker Analysis (NSCL-H)](#).

- **Osimertinib 80 mg daily[12]**
  ‣ For patients with completely resected stage IB–IIIA or stage IIIB (T3, N2) NSCLC and positive for *EGFR* (exon 19 deletion, exon 21 L858R) mutations who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- **Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[13]**
  ‣ For patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA 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.[a]
- **Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks for up to 1 year**
  ‣ For patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC 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.[a,14] The benefit for patients with PD-L1 <1% is unclear.
  ‣ For patients with completely resected stage II–IIIA or stage IIIB (T3, N2) NSCLC who received previous neoadjuvant pembrolizumab + chemotherapy (category 1).[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* 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.

[References](#)

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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PERIOPERATIVE SYSTEMIC THERAPY – REFERENCES

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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]
• 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]
• Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[4,b,c,d,f]
• 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]
Preferred (squamous)
• Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[6,b,c,d,f]
• 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]

Consolidation Immunotherapy for Patients with Unresectable Stage II/III NSCLC, PS 0–1, and No Disease Progression After Definitive Concurrent Chemoradiation
Durvalumab 10 mg/kg IV every 2 weeks or 1500 mg every 4 weeks for up to 12 months (patients with a body weight of ≥30 kg)[7,8,g,h]
(category 1 for stage III; category 2A for stage II)

[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] If using durvalumab, additional chemotherapy after radiation is not recommended. If not using durvalumab, an additional 4 cycles of pemetrexed 500 mg/m² may be used.
[f] If using durvalumab, additional chemotherapy after radiation is not recommended. If not using durvalumab, an additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6 may be used.
[g] 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 immuno-oncology (IO) therapy.
[h] For patients who have received sequential chemoradiation, durvalumab can be considered as consolidation immunotherapy.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CONCURRENT CHEMORADIATION REGIMENS – REFERENCES

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NSCL-F
2 OF 2

CANCER SURVIVORSHIP CARE

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

Counseling Regarding Health Promotion and Wellness[1]
- Maintain a healthy weight
- Adopt a physically active lifestyle (regular physical activity: 30 minutes of moderate-intensity physical activity on most days of the week)
- Consume a healthy diet with emphasis on plant sources
- Limit consumption of alcohol if one consumes alcoholic beverages

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

Resources
- National Cancer Institute Facing Forward: Life After Cancer Treatment
https://www.cancer.gov/publications/patient-education/facing-forward

Cancer Screening Recommendations[2,3]
These recommendations are for 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

[1] 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.
[2] Memorial Sloan Kettering Cancer Center Screening Guidelines: https://www.mskcc.org/cancer-care/risk-assessment-screening/screening-guidelines.
[3] 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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NSCL-G

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 immunohistochemical analyses, which are distinct from immunohistochemical studies utilized to identify tumor type and lineage.
- Major elements of molecular testing that are critical for utilization and interpretation of molecular results include:
  ‣ Use of a laboratory that is properly accredited, with a minimum of 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 greater than 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.

Continued

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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.
  - ◊ Sanger sequencing requires the greatest degree of tumor enrichment. Unmodified Sanger sequencing is not appropriate for detection of mutations in tumor samples with less than 25% to 30% tumor after enrichment and is not appropriate for assays in which identification of subclonal events (eg, resistance mutations) is important. If Sanger sequencing is utilized, tumor enrichment methodologies are nearly always recommended.
  - ◊ Any method that interrogates sequences other than a subset of highly specific alterations (eg, NGS, Sanger) has the potential to identify variants of uncertain significance (VUS). Any variant classified as a VUS, even if in a gene in which other variants are clinically actionable, should not be considered as a basis for targeted therapy selection.
  - ◊ Other methodologies may be utilized, including multiplex approaches not listed above.
  - ◊ Fluorescence in situ hybridization (FISH) analysis is utilized for many assays examining copy number, amplification, and structural alterations such as gene rearrangements. 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 circulating tumor 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.

Continued

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Molecular Targets for Analysis**
  - ▸ **In general, the mutations/alterations described below are seen in a non-overlapping fashion, although between 1%–3% of NSCLC may harbor concurrent alterations.**
  - ▸ *EGFR* **(Epidermal Growth Factor Receptor) Gene Mutations: EGFR is a receptor tyrosine kinase normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies.**
    - ◊ **The most commonly described mutations in** *EGFR* **(exon 19 deletions, p.L858R point mutation in exon 21) are associated with responsiveness to oral EGFR tyrosine kinase inhibitor (TKI) therapy; most recent data indicate that tumors that do not harbor a sensitizing** *EGFR* **mutation should not be treated with EGFR TKI in any line of therapy.**
    - ◊ **Molecular testing for** *EGFR* **mutations should be performed when adjuvant TKI therapy is a consideration for NSCLC stage IB–IIIA and stage IIIB (T3, N2). 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 may under-detect** *EGFR*ex20 **insertion events; therefore, NGS-based strategies are preferred.**
    - ◊ **Some clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with the presence of an** *EGFR* **mutation; however, these features should not be utilized in selecting patients for testing.**
    - ◊ **Testing Methodologies: Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS are the most commonly deployed methodologies for examining** *EGFR* **mutation status.**

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Molecular Targets for Analysis (continued)**
  - ▸ *ALK* **(anaplastic lymphoma kinase) Gene Rearrangements:** ALK is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the ALK kinase domain.
    - ◊ The most common fusion partner seen with ALK is echinoderm microtubule-associated protein-like 4 (EML4), although a variety of other fusion partners have been identified.
    - ◊ The presence of an *ALK* rearrangement is associated with responsiveness to oral ALK TKIs.
    - ◊ Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of an *ALK* rearrangement; however, these features should not be utilized in selecting patients for testing.
    - ◊ Testing Methodologies: FISH break-apart probe methodology was the first methodology deployed widely. IHC can be deployed as an effective screening strategy. FDA-approved IHC can be utilized as a stand-alone test, not requiring confirmation by FISH. Numerous NGS methodologies can detect *ALK* fusions. Targeted real-time PCR assays are used in some settings, although it is unlikely to detect fusions with novel partners.
  - ▸ *ROS1* **(ROS proto-oncogene 1) Gene Rearrangements:** ROS1 is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the ROS1 kinase domain.
    - ◊ Numerous fusion partners are seen with *ROS1,* and common fusion partners include: *CD74, SLC34A2, CCDC6*, and GOPC (*FIG*).
    - ◊ The presence of a *ROS1* rearrangement is associated with responsiveness to oral ROS1 TKIs.
    - ◊ Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of a *ROS1* rearrangement; however, these features should not be utilized in selecting patients for testing.
    - ◊ Testing Methodologies: FISH break-apart probe methodology can be deployed; however, it may under-detect the FIG-ROS1 variant. IHC approaches can be deployed; however, IHC for *ROS1* fusions has low specificity, and follow-up confirmatory testing is a necessary component of utilizing ROS1 IHC as a screening modality. Numerous NGS methodologies can detect *ROS1* fusions, although DNA-based NGS may under-detect *ROS1* fusions. Targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners.
  - ▸ *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, Sanger sequencing (ideally paired with tumor enrichment), and NGS are the most commonly deployed methodologies for examining *BRAF* mutation status. While an anti-BRAF p.V600E-specific monoclonal antibody is commercially available, and some studies have examined utilizing this approach, it should only be deployed after extensive validation.

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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 an oral KRAS G12C inhibitor used for subsequent therapy, which was designed specifically for this mutation. Responsiveness to this class of inhibitor has not been prospectively evaluated with mutations other than *KRAS* p.G12C.
    ◊ Testing methodologies: NGS, real-time PCR, and Sanger sequencing (ideally paired with tumor enrichment) are the most commonly deployed methodologies for examining *KRAS* mutation status.
  ▸ *MET* (mesenchymal-epithelial transition) e*xon 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.
    ◊ Some clinicopathologic features, such as smoking status and histology, are associated with the presence of *ERBB2* activating mutations; however, these features should not be utilized in selecting patients for testing.
    ◊ Testing methodologies: While Sanger sequencing and 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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NSCL-H
5 OF 8

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Molecular Targets for Analysis (continued)**
  - ▸ *NTRK1/2/3* (neurotrophic tyrosine receptor kinase) gene fusions
    - ◊ The presence of *NTRK1/2/3* gene fusions is associated with responsiveness to oral TRK inhibitors.
    - ◊ *NTRK1/2/3* are tyrosine receptor kinases that are rarely rearranged in NSCLC as well as in other tumor types, resulting in dysregulation and inappropriate signaling.
    - ◊ Numerous fusion partners have been identified.
    - ◊ To date, no specific clinicopathologic features, other than absence of other driver alterations, have been identified in association with these fusions.
    - ◊ Point mutations in *NTRK1/2/3* are generally non-activating and have not been studied in association with targeted therapy.
    - ◊ Testing Methodologies: Various methodologies can be used to detect *NTRK1/2/3* gene fusions, including: FISH, IHC, PCR, and NGS; false negatives may occur. IHC methods are complicated by baseline expression in some tissues. FISH testing may require at least 3 probe sets for full analysis. NGS testing can detect a broad range of alterations. DNA-based NGS may under-detect *NTRK1* and *NTRK3* fusions.
- **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 the oncogenic driver 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.**

Continued

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**NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

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

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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]

[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 greater than 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.

[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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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]
- **Subsequent therapy**
  - Osimertinib[10]
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[11]

EGFR S768I, L861Q, and/or G719X
- **First-line therapy**
  - Afatinib[1,12]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,13]
- **Subsequent therapy**
  - Osimertinib[10]

EGFR Exon 20 Insertion Mutation
- **First-line therapy**
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[14]
- **Subsequent therapy**
  - Amivantamab-vmjw[15]

KRAS G12C Mutation[d]
- **Subsequent therapy**
  - Sotorasib[16]
  - Adagrasib[17]

ALK Rearrangement
- **First-line therapy**
  - Alectinib[18,19]
  - Brigatinib[20]
  - Ceritinib[21]
  - Crizotinib[18,22]
  - Lorlatinib[23]
- **Subsequent therapy**
  - Alectinib[24,25]
  - Brigatinib[26]
  - Ceritinib[27]
  - Lorlatinib[28]

ROS1 Rearrangement
- **First-line therapy**
  - Ceritinib[29]
  - Crizotinib[30]
  - Entrectinib[31]
  - Repotrectinib[32]
- **Subsequent therapy**
  - Lorlatinib[33]
  - Entrectinib[31]
  - Repotrectinib[32]

BRAF V600E Mutation
- **First-line therapy**
  - Dabrafenib/trametinib[34]
  - Encorafenib/binimetinib[35]
  - Dabrafenib[36]
  - Vemurafenib
- **Subsequent therapy**
  - Dabrafenib/trametinib[36,37]
  - Encorafenib/binimetinib[35]

NTRK1/2/3 Gene Fusion
- **First-line/Subsequent therapy**
  - Larotrectinib[38]
  - Entrectinib[39]

MET Exon 14 Skipping Mutation[d]
- **First-line therapy/Subsequent therapy**
  - Capmatinib[40]
  - Crizotinib[41]
  - Tepotinib[42]

RET Rearrangement[d]
- **First-line therapy/Subsequent therapy**
  - Selpercatinib[43]
  - Pralsetinib[44]
  - Cabozantinib[45,46]

ERBB2 (HER2) Mutation[d]
- **Subsequent therapy**
  - Fam-trastuzumab deruxtecan-nxki[47]
  - Ado-trastuzumab emtansine[48]

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 with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.

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

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

[d] For agents with a similar mechanism of action, it is not recommended to switch between these drugs at the time of progression.

References

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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**
<u>Preferred</u> • Pembrolizumab (category 1)[49,50] • (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[51,52] • Atezolizumab (category 1)[53] • Cemiplimab-rwlc (category 1)[54] • Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1)[55] <u>Other Recommended</u> • Carboplatin + paclitaxel + bevacizumab[c,e] + atezolizumab (category 1)[56] • Carboplatin + albumin-bound paclitaxel + atezolizumab[57] • Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[58] • Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55] • Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[59] • Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 2B)[59] <u>Useful in Certain Circumstances</u> • Nivolumab + ipilimumab (category 1)[60]	<u>Preferred</u> • Pembrolizumab (category 1)[49,50] • Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[61] • Atezolizumab (category 1)[53] • Cemiplimab-rwlc (category 1)[54] • Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55] <u>Other Recommended</u> • Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[58] • Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[59] • Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine (category 2B)[59] <u>Useful in Certain Circumstances</u> • Nivolumab + ipilimumab (category 1)[60]
PD-L1 ≥50% FIRST-LINE THERAPY (PS 3–4)[f]	
Best supportive care (NCCN Guidelines for Palliative Care)	

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 with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[b] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[e] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[f] Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status.

References

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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**
<u>Preferred</u> • (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[51,52] • Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1)[55] <u>Other Recommended</u> • Carboplatin + paclitaxel + bevacizumab[c,e] + atezolizumab (category 1)[56] • Carboplatin + albumin-bound paclitaxel + atezolizumab[57] • Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[58] • Nivolumab + ipilimumab (category 1)[60] • Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55] • Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 1)[59] • Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 1)[59] <u>Useful in Certain Circumstances</u> • Pembrolizumab (category 2B)[g,49,50]	<u>Preferred</u> • Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[61] • Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55] <u>Other Recommended</u> • Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[58] • Nivolumab + ipilimumab (category 1)[60] • Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel[59] • Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine[59] <u>Useful in Certain Circumstances</u> • Pembrolizumab (category 2B)[g,49,50]
PD-L1 ≥1%–49% FIRST-LINE THERAPY (PS 3–4)[f]	
Best supportive care (NCCN Guidelines for Palliative Care)	

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 with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[b] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[e] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[f] Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status.
[g] 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 (PS 0–2)	
Adenocarcinoma, Large Cell, NSCLC NOS	**Squamous Cell Carcinoma**
• Pembrolizumab (category 1)[g] • Pembrolizumab + pemetrexed (category 1)[h] • Atezolizumab and bevacizumab[c,e] (category 1)[i] • Atezolizumab[j] • Nivolumab + ipilimumab (category 1)[k] • Cemiplimab-rwlc (category 1)[l] • Cemiplimab-rwlc[m] ± pemetrexed[n] (category 1) • Durvalumab[o] ± pemetrexed[p]	• Pembrolizumab (category 1)[g,q] • Atezolizumab[j] • Nivolumab + ipilimumab (category 1)[k] • Cemiplimab-rwlc (category 1)[l,m] • Durvalumab[o]
PD-L1 ≥1%–49% CONTINUATION MAINTENANCE (PS 3–4)	
Adenocarcinoma, Large Cell, NSCLC NOS	**Squamous Cell Carcinoma**
• Pembrolizumab (category 2B)[g] • Pembrolizumab + pemetrexed (category 1)[h] • Atezolizumab and bevacizumab[c,e] (category 1)[i] • Atezolizumab[j] • Nivolumab + ipilimumab (category 1)[k] • Cemiplimab-rwlc[m] ± pemetrexed[n] (category 1) • Durvalumab[o] ± pemetrexed[p]	• Pembrolizumab[g,q] • Nivolumab + ipilimumab (category 1)[k] • Cemiplimab-rwlc (category 1)[m] • Durvalumab[o]

References

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

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

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

[g] If pembrolizumab monotherapy given.

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

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

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

[k] If nivolumab + ipilimumab ± chemotherapy given.

[l] If cemiplimab-rwlc monotherapy given.

[m] If cemiplimab-rwlc combination therapy given.

[n] If cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) given.

[o] If tremelimumab-actl combination therapy given. Refer to categories of evidence for first-line regimen.

[p] If tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed given. Refer to categories of evidence for first-line regimen.

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

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MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE – REFERENCES

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5 OF 6

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NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE – REFERENCES

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

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

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

<u>Preferred</u>
• Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
• Pembrolizumab/cisplatin/pemetrexed (category 1)[2,e]
• Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin) (category 1)[7,e]
<u>Other Recommended</u>
• Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,f,g,h,i]
• Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
• Nivolumab/ipilimumab[5,e]
• Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (category 1) [6,e]
• Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]
• Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e] (category 1)
• Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed[8,e] (category 1)
	<u>Useful in Certain Circumstances</u>
	• Bevacizumab[f]/carboplatin/paclitaxel (category 1)[9,g,h,i]
	• Bevacizumab[f]/carboplatin/pemetrexed[9,10,g,h,i]
	• Bevacizumab[f]/cisplatin/pemetrexed[11,g,h,i]
	• 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 (category 1)[22]
	• Gemcitabine/vinorelbine (category 1)[23]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 2)

<u>Preferred</u> • Carboplatin/pemetrexed[18] <u>Other Recommended</u> • Carboplatin/albumin-bound paclitaxel[25,26] • Carboplatin/docetaxel[13] • Carboplatin/etoposide[14,15] • Carboplatin/gemcitabine[16] • Carboplatin/paclitaxel[17]	<u>Useful in Certain Circumstances</u> • Albumin-bound paclitaxel[24] • Docetaxel[27,28] • Gemcitabine[29-31] • Gemcitabine/docetaxel[22] • Gemcitabine/vinorelbine[23] • Paclitaxel[32-34] • Pemetrexed[35]

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

Best supportive care (NCCN Guidelines for Palliative Care)

[a] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c] If first-line systemic therapy 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* 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] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[g] Bevacizumab should be given until progression.
[h] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[i] Criteria for treatment with bevacizumab: 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.
[j] Atezolizumab monotherapy is a treatment option for patients with PS 3, regardless of PD-L1 status.

References

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

SQUAMOUS CELL CARCINOMA (PS 0–1)	
No contraindications to PD-1 or PD-L1 inhibitors[d]	**Contraindications to PD-1 or PD-L1 inhibitors[d]**
<u>Preferred</u> • Pembrolizumab/carboplatin/paclitaxel (category 1)[36,e] • Pembrolizumab/carboplatin/albumin-bound paclitaxel (category 1)[36,e] • Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e] <u>Other Recommended</u> • Nivolumab/ipilimumab[5,e] • Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[6,e] • Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e] (category 1) • Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/gemcitabine[8,e] (category 1)	<u>Useful in Certain Circumstances</u> • Carboplatin/albumin-bound paclitaxel (category 1)[10] • Carboplatin/docetaxel (category 1)[13] • Carboplatin/gemcitabine (category 1)[16] • Carboplatin/paclitaxel (category 1)[17] • Cisplatin/docetaxel (category 1)[13] • Cisplatin/etoposide (category 1)[19] • Cisplatin/gemcitabine (category 1)[19,20] • Cisplatin/paclitaxel (category 1)[21] • Gemcitabine/docetaxel (category 1)[22] • Gemcitabine/vinorelbine (category 1)[23]
SQUAMOUS CELL CARCINOMA (PS 2)	
<u>Preferred</u> • Carboplatin/albumin-bound paclitaxel[25,26] • Carboplatin/gemcitabine[16] • Carboplatin/paclitaxel[17] <u>Other Recommended</u> • Carboplatin/docetaxel[13] • Carboplatin/etoposide[14,15]	<u>Useful in Certain Circumstances</u> • Albumin-bound paclitaxel[24] • Docetaxel[27,28] • Gemcitabine[29-31] • Gemcitabine/docetaxel[22] • Gemcitabine/vinorelbine[23] • Paclitaxel[32-34]
SQUAMOUS CELL CARCINOMA (PS 3–4[j])	
Best supportive care (NCCN Guidelines for Palliative Care)	

[a] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.

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

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

[d] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR* exon 19 deletion or L858R, *ALK* 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.

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

References

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

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

[k] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
[l] If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
[m] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[n] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.

[o] If nivolumab + ipilimumab ± chemotherapy given.
[p] If atezolizumab/carboplatin/albumin-bound paclitaxel given.
[q] If cemiplimab-rwlc combination therapy given.
[r] If cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) given.
[s] If tremelimumab-actl combination therapy given.
[t] If tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed given.
[u] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.

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References

NSCL-K
3 OF 5

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)	SQUAMOUS CELL CARCINOMA (PS 0–2)
<u>Preferred (no previous IO):</u> Systemic immune checkpoint inhibitors[e] • Nivolumab (category 1) • Pembrolizumab (category 1)[v] • Atezolizumab (category 1) <u>Other Recommended (no previous IO or previous IO):[w]</u> • Docetaxel • Pemetrexed • Gemcitabine • Ramucirumab/docetaxel • Albumin-bound paclitaxel	<u>Preferred (no previous IO):</u> Systemic immune checkpoint inhibitors[e] • Nivolumab (category 1) • Pembrolizumab (category 1)[v] • Atezolizumab (category 1) <u>Other Recommended (no previous IO or previous IO):[w]</u> • Docetaxel • Gemcitabine • Ramucirumab/docetaxel • Albumin-bound paclitaxel
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,k]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS[e,w]	SQUAMOUS CELL CARCINOMA[e,w]
• PS 0–2: nivolumab, pembrolizumab, or atezolizumab; docetaxel (category 2B); pemetrexed (category 2B); gemcitabine (category 2B); ramucirumab/docetaxel (category 2B); or albumin-bound paclitaxel (category 2B) • PS 3–4: Best supportive care • Options for further progression are best supportive care or clinical trial.	• PS 0–2: nivolumab, pembrolizumab, or atezolizumab; docetaxel (category 2B); gemcitabine (category 2B); ramucirumab/docetaxel (category 2B); or albumin-bound paclitaxel (category 2B) • PS 3–4: Best supportive care • Options for further progression are best supportive care or clinical trial.

[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* 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.
[k] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
[v] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.
[w] If not previously given.

References

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NSCL-K
4 OF 5

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**NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

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**NSCL-K
5 OF 5**

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**NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

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

[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.

ABBREVIATIONS

AIS	adenocarcinoma in situ	**GGO**	ground-glass opacity	**PCR**	polymerase chain reaction
AUC	area under the curve	**GTV**	gross tumor volume	**PD-1**	programmed cell death protein 1
				PD-L1	programmed death ligand 1
BAC	bronchioloalveolar carcinoma	**H&P**	history and physical	**PFT**	pulmonary function test
BED	biologically effective dose	**H1 blocker**	Histamine-1 blocker	**PORT**	postoperative radiotherapy
		H2 blocker	Histamine-2 blocker	**PS**	performance status
CBC	complete blood count			**PTV**	planning target volume
CBCT	cone-beam CT	**IFI**	involved field radiation		
CHIP	clonal hematopoiesis of indeterminate potential	**IGRT**	image-guided radiation therapy	**ROSE**	rapid on-site evaluation
		IGTA	image-guided thermal ablation		
CLIA	Clinical Laboratory Improvement Amendments	**IHC**	immunohistochemistry	**QUANTEC**	Quantitative Analysis of Normal Tissue Effects in the Clinic
		IMPT	intensity-modulated proton therapy		
CNS	central nervous system	**IMRT**	intensity-modulated radiation therapy	**SABR**	stereotactic ablative radiotherapy
COPD	chronic obstructive pulmonary disease			**SBRT**	stereotactic body radiation therapy
CPT	Current Procedural Terminology	**IO**	immuno-oncology	**SCLC**	small cell lung cancer
CRT	conformal radiation therapy	**IPF**	idiopathic pulmonary fibrosis	**SRS**	stereotactic radiosurgery
ctDNA	circulating tumor DNA	**ITV**	internal target volume	**SRT**	stereotactic radiation therapy
CTV	clinical target volume			**SUV**	standardized uptake value
		LDCT	low-dose computed tomography	**SVC**	superior vena cava
DLCO	diffusing capacity of the lung for carbon monoxide	**LVEF**	left ventricular ejection fraction		
				TBNA	transbronchial needle aspiration
EBUS	endobronchial ultrasound	**MIA**	minimally invasive adenocarcinoma	**TKI**	tyrosine kinase inhibitor
ENI	elective nodal irradiation	**MLD**	mean lung dose	**TNM**	tumor node metastasis
EUS	endoscopic ultrasound			**TTNA**	transthoracic needle aspiration
		NGS	next-generation sequencing		
FDG	fluorodeoxyglucose	**NOS**	not otherwise specified	**UIP**	usual interstitial pneumonia
FEV1	forced expiratory volume in the first second	**NSCC**	non-small cell carcinoma		
		NSCLC	non-small cell lung cancer	**VATS**	video-assisted thoracic surgery
FFPE	formalin-fixed paraffin-embedded	**NUT**	nuclear protein in testis	**VMAT**	volumetric modulated arc therapy
FISH	fluorescence in situ hybridization			**VUS**	variant of uncertain significance
FNA	fine-needle aspiration	**OAR**	organ(s) at risk		
				WBRT	whole brain radiation therapy

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Non-Small Cell Lung Cancer. Last updated: April 13, 2023.

Table of Contents

Overview

Lung cancer is the leading cause of cancer death in the United States.[1,2] In 2023, an estimated 238,340 new cases (117,550 in males and 120,790 in females) of lung and bronchial cancer will be diagnosed, and 127,070 deaths (67,160 in males and 59,910 in females) are estimated to occur because of the disease.[1] During the COVID pandemic, the diagnosis and treatment of lung cancer have been hampered; however, this has not been reflected in the 2023 estimates for incidence and mortality because of the typical delays in collecting and reporting the data.[1,3] Only 22.9% of all patients with lung cancer 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).[4] From 2012 to 2018, the overall 5-year relative survival rate for NSCLC with adenocarcinoma histology was 29.8% in the United States.[4,5] Since 2006 to 2007, the incidence of lung cancer decreased annually by 2.6% in men and 1.1% in women.[1] Common symptoms of lung cancer include cough, hemoptysis, dyspnea, weight loss, and chest pain; patients with symptoms are more likely to have chronic obstructive pulmonary disease (COPD).[6]

Much progress has been made recently for lung cancer, such as screening; minimally invasive techniques for diagnosis and treatment; advances in radiation therapy (RT), including stereotactic ablative radiotherapy (SABR); new targeted therapies; and new immunotherapies.[7-12] These new treatments are reflected in the 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.[13] From 1990 to 2020, the death rate from lung cancer dropped by 58% in men; from 2002 to 2020, the death rate dropped by 36% in women.[1] Patients with NSCLC who are eligible for targeted therapies or immunotherapies are now surviving longer; 5-year survival rates range from 15% to 50%, depending on the biomarker.[12,14-30] Thus, death rates for lung cancer have been declining, although there are still more deaths from lung cancer than from breast, prostate, colorectal, and brain cancers combined.[1]

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC were first published in 1996.[31] Subsequently, the NCCN Guidelines® have been updated at least once a year by the NCCN NSCLC Panel; there were 6 updates for the 2022 guidelines. The *Summary of the Guidelines Updates* describes the most recent revisions to the algorithms, which have been incorporated into this updated Discussion text (see the NCCN Guidelines for NSCLC and *Summary* in this Discussion). New references have been added, which support the new recommendations. For the 2023 update (Version 2), the NCCN NSCLC Panel added a recommendation for adjuvant pembrolizumab for eligible patients with completely resected early-stage NSCLC based on clinical trial data and FDA approval (see *Surgery Followed by Adjuvant Therapy: Trial Data and NCCN Recommendations* in this Discussion).[32]

All the systemic therapy regimens have been categorized by preference—based on the biomedical literature and experience of the panel members—using the following categories: 1) preferred interventions; 2) other recommended interventions; and 3) interventions that are useful in certain circumstances (see the NCCN Guidelines for NSCLC). These preference categories emphasize the preferred regimens in clinical practice and do not replace the NCCN Categories of Evidence and Consensus, such as category 1 or category 2A. The NCCN Categories of Preference and NCCN Categories of Evidence and Consensus are two separate systems.

The NCCN Guidelines provide specific category designations for all treatment interventions in the guidelines, which are based on evidence from the biomedical literature and consensus among the panel members. Category 1 recommendations indicate uniform NCCN consensus (at least 85% of the NCCN Member Institutions on the panel) that the intervention

is appropriate based on high-level evidence, such as randomized phase 3 trials. Category 2A recommendations indicate uniform NCCN consensus that the intervention is appropriate based on lower-level evidence, such as phase 2 trials. It is important to note that all recommendations are category 2A in the NCCN Guidelines unless otherwise indicated. Category 2B recommendations indicate NCCN consensus (50%–<85% of the NCCN Member Institutions on the panel) that the intervention is appropriate based on lower-level evidence. Category 3 recommendations indicate major NCCN disagreement (at least 50% of the NCCN Member Institutions) that the intervention is appropriate based on any level of evidence. For a category 3 recommendation to remain in the guideline, at least 25% of the NCCN Member Institutions on the panel must vote that the intervention is appropriate. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.

Risk Factors

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths.[2,33-37] Approximately 350 people die every day from lung cancer in the United States; most of these deaths (81%) are caused by cigarette smoking.[1] Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).[36,38] 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).[34,38-41]

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).[42,43] 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.[44-46] Asbestos is a known 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.[47] 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.[48] In women who received estrogen alone, the incidence or risk of death from lung cancer did not increase.[49]

Smoking Cessation

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.[35] Of patients aged 20 to 49 years who were recently diagnosed with lung cancer, 81% of men and 72% of the women had smoked.[3] 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.[35] Smoking harms nearly every organ in the body; individuals who smoke have increased mortality compared with those who do not smoke.[50] Those who do not smoke, but live with someone who smokes, have an increased risk for lung cancer due to secondhand smoke.[39] 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).[51-54] The 5 A's framework is a useful tool (that is, Ask, Advise, Assess, Assist, Arrange).[55] 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.[56] Some surgeons will not operate on individuals who currently smoke, because active smoking may increase postoperative pulmonary complications.[57] 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.[58] 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.[59,60] 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.[61] Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.[62-64] The effectiveness of varenicline for preventing relapse has not been clearly established.[65] 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.[66-69] Other side effects of varenicline include nausea, abnormal dreams, insomnia, and headache.[64,70,71] Bupropion may also be associated with similar serious neuropsychiatric symptoms. Nicotine replacement has fewer adverse effects than varenicline or bupropion.[72] In spite of the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.[72]

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.[2,73,74] 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.[75] The NLST showed that screening individuals with high-risk factors using low-dose CT decreased the mortality rate from lung cancer by 20%.[76] 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.[75,77] 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.[78] 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).[78-83] 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).[84-87] 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.[88] 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).[84-87,89] All NSCLC should be classified according to subtype using the WHO Guidelines.[84,85,87] 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.[90]

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.

Diagnostic Evaluation

Incidental Lung Nodules

Lung cancer screening is recommended for early diagnosis in asymptomatic patients at high risk for cancer.[75,78] 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.[91] 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.[92] 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.[93]

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).[94-98] 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.[95,96] 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.[96,99-101] 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.[89,96,99,100,102-104] 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.[102,105,106] 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).[92,95,96]

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.[76] 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.[107-109]

Larger Tumors

The NCCN Guidelines recommend that the diagnostic strategy should be individualized for each patient depending on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (eg, comorbidities), and local expertise. The diagnostic strategy needs to be decided in a multidisciplinary setting. Decisions 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).[110] 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.[111]

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.[112] 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).[113] 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 (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[10,114-123] 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.[124] 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).[125] 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.[111,126] Minimally invasive techniques can be used to obtain specimens in patients with advanced unresectable NSCLC;[127,128] however, diagnosis may be more difficult when using small biopsies and cytology.[103] 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.[129-133] 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.[134-136] 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.[85-87,137] The classification for lung adenocarcinoma was determined by an international panel and adopted by the WHO (see *Adenocarcinoma* in this Discussion).[85-87,89] The classification recommends IHC and molecular studies (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).[85,138] 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.[85,87] 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 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.[89] 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.[139,140] 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).[141]

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.[89] The categories of BAC or mixed subtype adenocarcinoma are no longer used to classify adenocarcinoma.[89] The classification for lung adenocarcinoma was developed by an international panel and adopted by WHO.[85-87,89] 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).[138]

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).[125,128,142] 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 cell carcinoma, metastatic malignancy, and primary pleural mesothelioma (particularly for pleural samplings).[125] IHC is useful for assessing poorly differentiated NSCLC in small biopsy and/or cytology specimens.[89,143]

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).[89] Napsin A positivity occurs in more than 80% of lung adenocarcinomas and may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.[144,145] 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.[89,143]

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.[143] However, TTF-1 is also positive in tumors such as thyroid cancer and rarely in a few other organ systems.[146] 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).[111,143,147] 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.[148,149] 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.[150] 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).[151-153] 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) (negative in adenocarcinoma).[151-154] 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.[155,156] The lung cancer staging system was revised by the International Association for the Study of Lung Cancer (IASLC)[157-159] and was adopted by the AJCC.[155,156,160,161] 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.[162] 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+);[163] 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).[164]

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%.[4] 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.[4] 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.[165] 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%.[166] 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.[21-28] 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*) 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.[167-172] 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).[173,174]

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.[175] 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).[176]

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).[177,178] 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.[179] 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 *Oral TKIs that Inhibit EGFR S768I, L861Q, and G719X 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 *Agents that Inhibit EGFR Exon 20 Insertion Mutations* in this Discussion).[180,181] 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 *Targeted Therapies* in this Discussion and the NCCN Guidelines for NSCLC).[175,182-185] 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.

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.[139,140,186,187] Molecular testing for actionable alterations can be considered in patients with metastatic squamous cell carcinoma based on the effectiveness of targeted therapies.[186,187] 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).[167-172] 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).[173] 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.[188] 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).[187,189-193] 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).[194]

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]).[195,196] 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.[197] In addition, CHIP can be identified following prior chemotherapy or radiotherapy, further confounding interpretation of variants such as in *TP53*.[198] Given the previous caveats, 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.[199]

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.[200,201] Data suggest that plasma ctDNA testing is a useful minimally invasive test that can be used to identify *ALK*, *BRAF*, *EGFR*, *HER*2, *MET* exon 14 skipping, *RET, ROS1*, and other oncogenic biomarkers that would not otherwise be identified in patients with metastatic NSCLC.[199,202-204] Molecular testing of plasma ctDNA should be done using clinically validated tests.[199]

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.[205] Testing for certain biomarkers is also recommended for eligible patients with resectable early-stage and locally advanced NSCLC (see *Surgery Followed by Adjuvant Therapy: Trial Data and NCCN Recommendations* 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).[175,206] 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.[207-215] 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).

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, *METex14* 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).[114] 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.[216,217] 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.[123] 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.[218] 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.[219-223] 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.[139,140] 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).[186]

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.[185,193,224-231] An IHC assay for *ALK* rearrangements has also been approved by the FDA. NGS can also be used to assess whether *ALK* rearrangements are present, if the platform has been appropriately designed and validated to detect *ALK* rearrangements.[232-234] If an actionable oncogenic genetic variant occurs in a patient, usually only one variant is present.[187,189-193,235,236] 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 *Oral TKIs that Inhibit 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).[186]

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.[237] Clinicians are using whole brain RT less often in patients with NSCLC and limited brain lesions.[238] 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).[239-242]

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.[190,243] 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.[244] Mutations in *BRAF* typically do not overlap with *EGFR* mutations, *MET*ex14 skipping mutation*s, RET* rearrangements, *ALK* rearrangements, or *ROS1* rearrangements.[190,191] 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.[139,140,190,191] 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 *Oral Agents that Inhibit BRAF Mutations* in this Discussion).[190] 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 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."[190,191,245] 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.[186]

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).[246] 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.[247] 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).[248,249] 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.[250] Patients with pure squamous cell carcinoma are less likely to have the common *EGFR* mutations; those with adenosquamous carcinoma may have mutations.[139,140,250] 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.[139,140,186,187]

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.[246] 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).[251-256] 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 is not statistically different for afatinib, erlotinib, or gefitinib.[251,252,257,258] 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).[259-264] Patients typically have disease progression after first-line EGFR TKI monotherapy; subsequent therapy recommendations are described in the algorithm [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion and the NCCN Guidelines for NSCLC]. 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.[252,258,265-267] *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.[212,267-273] Studies suggest T790M may rarely occur in patients who have not previously received afatinib, erlotinib, or gefitinib.[274] Germline T790M confers a high risk for lung cancer regardless of smoking status.[275-277] 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.[278-282] 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.[279] Acquired resistance can also be mediated by other molecular events, such as acquisition of *ALK* rearrangement, *MET* or *ERBB2* amplification, and other biomarkers.[283]

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 *Agents that Inhibit EGFR Mutations* in this Discussion).[21,251-256] 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.[284-287] 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).[185,284] 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.[247,286,288-290] Mutation screening assays using multiplex PCR can simultaneously detect more than 50 point mutations.[291] NGS is a preferred method for detecting *EGFR* variants, because targeted PCR approaches may miss some *EGFR* exon 20 insertion mutations.[214]

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 *Agents that Inhibit EGFR Mutations* 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.[266,292]

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).[248,249,257,293] 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 *Oral TKIs that Inhibit EGFR S768I, L861Q, and G719X Alterations* in this Discussion).[257,293] Other recommended TKI options in this setting include dacomitinib, erlotinib, or gefitinib.[294,295]

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.[181,261,296,297] Although there are many different *EGFR* exon 20 insertion mutations, three are more common (insASV, insSVD, and insNPH).[181] Most patients with *EGFR* exon 20 insertion mutations have low response rates (≤9%) to afatinib, erlotinib,

or gefitinib.[180,181] An exception is the p.A763_Y764insFQEA mutation; afatinib, erlotinib, or gefitinib are effective for patients with this *EGFR* exon 20 insertion.[259] 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.[298] First-line platinum-based chemotherapy (± immunotherapy) is a recommended option for patients with *EGFR* exon 20 mutations (eg, carboplatin plus paclitaxel).[299-301] 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).[180,302,303] The response rates (0%–25%) to immunotherapy regimens vary, depending on the specific *EGFR* exon 20 insertion mutation.[181,304,305]

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 *Agents that Inhibit EGFR Exon 20 Insertion Mutations* in this Discussion).[180,181] 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.[306] Patients tend to be women who have never smoked cigarettes; they have a higher incidence of brain metastases than those with other actionable mutations.[306,307] Although 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 *Agents that Inhibit 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.[308]

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.[121,177,213,309,310] *KRAS* mutation prevalence is associated with cigarette smoking, unlike many of the other actionable mutations (eg, *EGFR* mutations, *ALK* rearrangements).[311] Patients with *KRAS* mutations appear to have a shorter survival than patients with wild-type KRAS; therefore, *KRAS* mutations are prognostic biomarkers.[194,310,312] *KRAS* mutations do not generally overlap with *EGFR*, *ROS1*, *BRAF*, and *ALK* genetic variants.[187,190-193,313] Therefore, a tiered approach using *KRAS* testing may identify patients who may not benefit from further molecular biomarker testing.[175,206] *KRAS* mutations may infrequently overlap with *EGFR* mutations or *RET* rearrangements.[314,315] In patients with *KRAS* mutation-positive metastatic NSCLC, data suggest the response rate is about 26% for single-agent ICIs.[186,316] 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 *Oral Agents that Inhibit KRAS Mutations* in this Discussion).[317-319] 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.[189] *MET* genomic alterations do not typically overlap with

EGFR, *ROS1*, *BRAF*, and *ALK* genetic variants.[320] 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.[321,322] *MET*ex14 skipping mutations are more frequent in older women who have never smoked cigarettes.[323]

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 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.[186,324] Data suggest that patients with *MET* amplification respond to immunotherapy.[325]

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 *Oral TKIs that Inhibit METex14 Skipping Mutations* in this Discussion).[326,327] 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.[328-330] 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*.[329] 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.[331] In a clinical trial, *NTRK* gene fusions were detected with NGS (50 patients) and FISH (5 patients).[330] 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.[330,332]

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 *Oral TKIs that Inhibit NTRK1/2/3 Gene Fusions* in this Discussion).[330,333]

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.[334,335] *RET* rearrangements occur in about 1% to 2% of patients with NSCLC and are more frequent in patients with adenocarcinoma histology.[334-338] In European patients, *RET*

rearrangements occur in individuals who currently smoke cigarettes and those who have never nonsmoked.[336] *RET* rearrangements do not typically overlap with *EGFR*, *ROS1*, *BRAF*, *MET*ex14 skipping, and *ALK* genetic variants.[335] However, a few studies suggest that *RET* rearrangements may infrequently overlap with *EGFR* or *KRAS* mutations.[314,315] 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).[335] NGS has high specificity; however, RNA-based NGS is preferable to DNA-based NGS for fusion detection. In patients with *RET*-positive metastatic NSCLC, data suggest the response rate is about 6% to single-agent ICIs.[186]

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.[339-342] Previously, the panel deleted vandetanib for patients with *RET* rearrangements because there are better therapy options.[343,344] 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.[345,346] It is estimated that *ROS1* gene rearrangements occur in about 1% to 2% of patients with NSCLC.[346-349] 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.[192,346,350,351] *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.[139,140] 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).[224,346,348,351-355] False-negative results may occur with FISH, IHC, PCR and DNA-based NGS.[356] 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 *Oral TKIs that Inhibit 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.[332,350,351,357] 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 *Oral TKIs that Inhibit ROS1 Rearrangements* in this Discussion).[358]

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.[359] 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.[186] Local therapy may be considered for limited progression.

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.[360-362] Cemiplimab-rwlc, nivolumab, and pembrolizumab inhibit PD-1 receptors.[141,363,364] Atezolizumab and durvalumab inhibit PD-L1.[365,366] 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).[141,367]

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).[368,369] 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.[368] Unique anti-PD-L1 IHC assays have been developed for each one of the different ICIs.[368,370-372] 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.[372] 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.[186,373-376]

TMB
TMB is an approximate measure of the total number of somatic mutations.[377] Theoretically, high TMB levels will correlate with high neoantigen levels that will activate an antitumor immune response.[378] 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.[331,379] 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.[380] However, updated data from CHECKMATE 227 showed that overall survival was improved with nivolumab plus ipilimumab regardless of TMB or PD-L1 expression levels.[381] 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.[380-383] 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 NSCLC.[384] TMB does not identify patients who will respond to chemotherapy; therefore, TMB has limited value for assessing combination immunotherapy plus chemotherapy regimens.[378] 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.[378]

In addition to the lack of clinical data to support use of TMB as an immune biomarker, there are technical problems with measuring TMB.[377] 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.[377] 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.[173,377,381] 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.[173]

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.[385]

Surgery

In general, surgery provides the best chance for cure in patients with stage I or II disease.[386] 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.[386-392] Although frailty is an increasingly recognized predictor of surgical and other treatment morbidity, a preferred frailty assessment system has not been established.[393-395]

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).[396] 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 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.[386,397,398] 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).[387,399-404] 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.[386,398] Wide wedge resection may improve outcomes.[405]

Patients with medically inoperable early-stage NSCLC may be candidates for definitive RT, preferably SABR, also known as stereotactic body RT (SBRT).[406,407] If SABR is considered for patients at high risk for surgical morbidity, a multidisciplinary evaluation is recommended (see *Stereotactic Ablative Radiotherapy* in this Discussion).[406,408-410]

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.[411,412] 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.[411] 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.[155] The lymph node map from the IASLC may be useful.[413] 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).[414,415] Published studies suggest that thoracoscopic lobectomy has several advantages over lobectomy by thoracotomy.[416-420] Acute and chronic pain associated with thoracoscopic lobectomy is minimal; thus, this procedure requires a shorter length of hospitalization.[421,422] Thoracoscopic lobectomy is also associated with low postoperative morbidity and mortality, minimal

risk of intraoperative bleeding, or minimal locoregional recurrence.[423-427] Thoracoscopic lobectomy is associated with less morbidity, fewer complications, and more rapid return to function than lobectomy by thoracotomy.[428-431]

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.[432-436] Thoracoscopic lobectomy has also been shown to improve discharge independence in older populations and patients at high risk.[437,438] Data show that thoracoscopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.[439,440] 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).[441-444] Robotic VATS seems to be more expensive with longer operating times than conventional VATS.[445,446]

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.[447,448] Randomized controlled trials suggest that surgery does not increase survival in these patients.[449,450] However, one of these trials (EORTC) only enrolled patients with unresectable disease.[450] 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.[451] 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.[452-454] 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).[454] 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.[452,455] Postoperative RT may be considered for select patients with negative margins and high-risk N2 disease (see *Chemoradiation: Trial Data and NCCN Recommendations* in this Discussion and *Principles of Radiation Therapy* in the algorithm). It is controversial whether pneumonectomy after preoperative chemoradiotherapy is appropriate.[449,456-462] 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.[457,463]

The NCCN NSCLC Panel believes that surgery may be appropriate for select patients with N2 disease.[447,457,464] 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.[465,466] 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.

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.[467-477] 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.[452,455,473-477]

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.[410,452,455,478-485] 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.[474,486-492] 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).[493] 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.[494,495] 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.[496,497] 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).[491,498-501] 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.[502]

Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints
Commonly used prescription RT (or SABR) doses and normal tissue dose constraints are summarized in the *Principles of Radiation Therapy* in the NSCLC algorithm (see Tables 2–5 in the NCCN Guidelines for NSCLC).[468,470,482,503-508] 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;[509,510] the ACR Practice Parameters and Technical Standards are also a helpful reference.[488,511,512] 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*).[513] 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.[514-518]

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).[475,519-524] These constraints are mainly empirical and have not, for the most part, been validated rigorously.[503,523,525-530] 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).[531,532] 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.[520,533-537] 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.[537-543] 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.[534,536,537,539-547]

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).[406,407,410,485,548,549] 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.[408,550-552] 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).[386,553-559] Resection is recommended for patients with early-stage NSCLC who are medically fit (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).[560] 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.[561] 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.[562] 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).[563-570]

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).[447,449,454,461,571] Before surgical resection of stage IIIA NSCLC, induction systemic therapy or induction chemoradiotherapy is recommended to potentially shrink the tumor(s).[454,465] 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.[453,466] Preoperative concurrent chemoradiation is recommended for resectable superior sulcus tumors and is an option for other resectable stage IIA to IIIA NSCLC.[505] 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.[465,466] The NCCN NSCLC Panel recommends a preoperative RT dose of 45 to 54 Gy in 1.8 to 2 Gy fractions over 5 weeks.[453,572] Definitive RT doses delivered as preoperative chemo/RT can safely be administered and achieve promising nodal clearance and survival rates;[506-508,573] 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.[506-508] 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.[574] 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.[469,575,576] 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 postoperative RT technique.[452,455,577] 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).[485,578-580] 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).[581-584] 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.[578,585] 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.[586] Definitive RT to oligometastases, particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.[587,588] 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.[589,590] 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).[591] 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).[592] 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.[589-591]

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.[406,593-596] SABR has achieved good primary tumor control rates and overall survival that is higher than conventionally fractionated RT.[406] 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.[410,597-601] 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%.[407] 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.[386,407,501,559,560,600,602-607] 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.[548] 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.

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.[473,597,599,608] 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.[608] 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.[473] 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.[594,601,609-615]

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).[386,601,603,608,616] If possible, biopsy should confirm NSCLC before use of SABR.[406,617,618] 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.[619,620] 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).[408,550-552]

Locoregional recurrences can occur after SABR.[560,599,621-626] Late recurrences have been reported more than 5 years after SABR, highlighting the need for careful surveillance.[627,628] 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.[629,630] This careful follow-up is particularly relevant, because selected patients with recurrences after SABR may benefit from surgery or re-treatment with SABR.[627,631-635]

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).[406,598,600,607,636-646] 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.[646,647] Prescription doses do not completely describe the actual delivered doses.[648,649] 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).[408,639,650-652] The RTOG 0813 trial evaluated 5-fraction regimens and found no high-grade toxicities at 50 Gy in 5 fractions.[653,654]

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).[396,587,588,601,655-658] 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.[655,656] 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.[659-662] Hypofractionated or dose-intensified conventional 3D-CRT is a less preferred option if an established SABR program is not available.[663-665] 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.[386,410,559]

Whole Brain RT and Stereotactic Radiosurgery

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.[6,666] Control of brain metastases

preserves neurocognitive function.[667,668] 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.[669-671] 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.[668,672] Thus, SRS alone is recommended for patients with limited brain metastases.[239] 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.[238] 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.[673,674] A randomized trial demonstrated that using IMRT to avoid the hippocampus decreases memory impairment after whole brain RT.[675] 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.[676] 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.[677,678]

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.[238,612,666,679-685] 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.[679,686-688] Treatment should be individualized for patients with recurrent or progressive brain lesions.[689] 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).[239-242]

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.[690-693] 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).[447,694-700] A randomized trial found no difference in survival with preoperative versus postoperative chemotherapy.[701] 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.[386,702] Concurrent chemoradiation is more efficacious than sequential chemoradiation for patients with unresectable stage III disease.[703-706] 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.[707-711]

For patients with stage IV disease who have a good PS, platinum-based chemotherapy with or without immunotherapy is beneficial.[712-719] 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.[720,721] Patients should receive treatment for debilitating symptoms.[6,722,723] A study also suggests that social support, such as being married, is as effective as systemic therapy.[724] Data suggest that systematic symptom monitoring during outpatient chemotherapy treatment increases overall survival when compared with usual care.[725-727] 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).[728] 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).[396,586,589,591,601,655,656] The trials supporting the recommendations for combined modality therapy are discussed in the following sections.

Surgery Followed by Adjuvant Therapy: Trial Data and NCCN Recommendations

Chemotherapy

The International Adjuvant Lung Cancer Trial (IALT) assessed cisplatin-based postoperative therapy in patients with completely resected stage I, II, or III NSCLC.[691] 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.[729] Data show that postoperative chemotherapy prevents recurrences.

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.[692] 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.[730] 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.[693] 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.[693] 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;[731] however, most clinicians in the United States prefer to use regimens with less toxicity.[732,733]

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).[734] A subgroup analysis found that cisplatin plus vinorelbine also increased survival.[731] 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.[391,735]

The CALGB 9633 trial assessed paclitaxel plus carboplatin in patients with stage IB (T2a,N0,M0) lung cancer.[736-738] 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%, $P=.02$).[737,738] 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).[739] It is important to note that the CALGB trial was underpowered for patients with stage 1B disease.[740]

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.[732] 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.[732] Overall survival at 3 years was similar between the arms (75% vs. 77%; P = .858).[741]

The NCCN NSCLC Panel does not recommend postoperative chemotherapy for resected stage IA disease based on the trials described in the previous paragraphs.[742] 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).[690,742]

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).[732,741] Cisplatin plus gemcitabine or cisplatin plus docetaxel are the preferred perioperative chemotherapy options for patients with squamous cell NSCLC.[743,744] Other recommended options include cisplatin plus vinorelbine or cisplatin plus etoposide.[691-693] 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).[745-748] 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.[749] 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.[750] 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.[749] 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 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).[162] 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.[751] 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).[32] 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.[751] 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.[32] 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.[186] 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 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.[699] 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.[701]

Several trials suggest that preoperative therapy is beneficial in patients with N2 disease.[447,454,698] Other trials suggest that preoperative therapy is beneficial in patients with earlier stage disease.[695,696,700] 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.[700]

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).[695] 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).[694] These results are similar to those reported in another meta-analysis (HR, 0.89; 95% CI, 0.81–0.98; P = .02).[695] The benefit from preoperative chemotherapy is similar to that attained with postoperative chemotherapy.[695,699,701,734]

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).[110] 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% 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.[695,699,701,734] 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.[110,760] 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.[186] 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).[110]

Chemoradiation: Trial Data and NCCN Recommendations
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.[452,455] 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%).[452] 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 (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.[455] 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.[452,455] 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.[452,455,761,767] To minimize

potential lung and heart toxicities, highly conformal RT techniques such as IMRT or proton therapy are preferred.[468,532,768,769]

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.[703-706,771] 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.[389,774]

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.[468,470,471,768]

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).[534,703,705,777-782] 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.[534] The different 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).[360-362,365] 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.[365,786] 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).[19,786] After 5 years, 42.9% of patients who received durvalumab were alive versus 33.4% of those who received placebo.[16] 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.[365,786] 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 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).[505,534,778,783] 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.

Chemotherapy: Trial Data and NCCN Recommendations

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.[716-718] 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.[739,744,788-790] However, survival rates are higher for patients with stage IV NSCLC who are eligible for either the newer targeted therapy or immunotherapy regimens.[12,17-30] 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.[744,793-799] 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 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.[744] 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 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 to cisplatin plus gemcitabine adds value and is cost-effective, the NCCN NSCLC Panel does not agree.[826]

Targeted Therapies

Specific targeted therapies are available for the treatment of eligible patients with metastatic NSCLC.[184,827,828] Afatinib, adagrasib, alectinib, brigatinib, cabozantinib, capmatinib, ceritinib, crizotinib, dabrafenib, dacomitinib, entrectinib, erlotinib, gefitinib, larotrectinib, lorlatinib, osimertinib, pralsetinib, selpercatinib, sotorasib, tepotinib, and trametinib are oral TKIs. Alectinib inhibits *ALK* and *RET* rearrangements.[829] Brigatinib inhibits various *ALK* rearrangements and other targets.[830] Ceritinib inhibits *ALK* and *ROS1* rearrangements. Crizotinib inhibits *ALK* rearrangements, *ROS1* rearrangements, and *MET* tyrosine kinases (ie, high-level *MET* amplification, *MET*ex14 skipping mutation). Erlotinib, gefitinib, afatinib, and dacomitinib inhibit *EGFR* mutations (eg, exon 19 deletions, exon 21 L858R, exon 18 G719X, exon 21 L861Q, exon 20 S768I); osimertinib inhibits these *EGFR* mutations and T790M.[252] Lorlatinib inhibits *ALK* and *ROS1* rearrangements.[357,358,831-833] Dabrafenib inhibits *BRAF* p.V600E mutations; trametinib inhibits MEK; both agents inhibit different kinases in the RAS/RAF/MEK/ERK pathway.[190,191] Entrectinib and larotrectinib inhibit *TRK* fusion proteins.[330,333,834] Capmatinib and tepotinib inhibit several MET tyrosine kinases including *MET*ex14 skipping mutations and high-level *MET* amplification.[169,172,326,835] Selpercatinib, pralsetinib, and cabozantinib inhibit *RET* rearrangements.[339-342] Adagrasib and sotorasib inhibit *KRAS* G12C mutations.[317,319] Bevacizumab and ramucirumab are recombinant monoclonal antibodies that target the vascular endothelial growth factor (VEGF) or VEGF receptor, respectively. Cetuximab is a monoclonal antibody that targets EGFR. Other targeted therapies are being developed (see *Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC* in the NCCN Guidelines for NSCLC). Flare phenomenon may occur in some patients who discontinue targeted therapies for driver mutations such as *ALK*, *EGFR*, *MET*ex14 skipping, *RET*, or *ROS1*. If disease flare occurs, then the targeted therapies should be restarted.[836-839]

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 (ie, *EGFR* exon 19 deletions, *EGFR* exon 21 L858R mutations, *ALK* rearrangements)—should receive first-line targeted therapy for that oncogene and not first-line ICIs, because targeted therapies yield higher response rates (eg, osimertinib, 80%) than ICIs (poor response rates) in the first-line setting, targeted therapy is better tolerated, and these patients are unlikely to respond to ICIs.[186,374,840] Molecular testing results for the actionable oncogenic mutations should be known before starting systemic therapy with ICI regimens in eligible patients with advanced NSCLC, if clinically feasible. If it is not feasible to do molecular testing, then patients are treated as though they do not have driver oncogenes.[186,373-375,840] If molecular testing results are pending and patients require an urgent start to therapy, clinicians should consider holding immunotherapy for one cycle (ie, just use platinum-based chemotherapy regimens). 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. Likewise, monitoring is also recommended during maintenance or subsequent therapy with CT, with or without contrast, every 6 to 12 weeks.

Oral TKIs that Inhibit ALK Rearrangements

About 5% of patients with NSCLC have *ALK* gene rearrangements. The NCCN NSCLC Panel recommends *ALK* rearrangement testing (category 1) in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of several agents for patients with *ALK* rearrangements (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC). *ALK* testing can be considered in patients with metastatic squamous cell carcinoma. The NCCN NSCLC Panel recommends five agents for patients with *ALK*-positive metastatic NSCLC—alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib—based on clinical trial data and FDA approvals, which are described in the following sections.

Alectinib

Alectinib is a second-generation oral TKI that inhibits *ALK* rearrangements.[829]

First-Line Therapy

ALEX, a phase 3 randomized trial, assessed first-line therapy with alectinib versus crizotinib in 303 patients with *ALK*-positive advanced NSCLC including those with asymptomatic CNS disease.[220] Disease progression or death occurred in fewer patients receiving alectinib (41% [62/152]; median follow-up of 18.6 months) when compared with crizotinib (68% [102/151]; median follow-up of 17.6 months). The HR was 0.47 (95% CI, 0.34–0.65; *P* < .001) for disease progression or death. PFS was significantly increased with alectinib (68.4%; 95% CI, 61.0%–75.9%) versus crizotinib (48.7%; 95% CI, 40.4%–56.9%). The median PFS was not reached for alectinib (95% CI, 17.7–not reached) when compared with crizotinib at 11.1 months (95% CI, 9.1–13.1). Fewer patients receiving alectinib had CNS progression (12% [18/152]) versus crizotinib (45% [68/151]). Response rates were 83% (126/152) in the alectinib group versus 75% (114/151) in the crizotinib group (*P* = .09). Patients receiving

alectinib had fewer grade 3 to 5 adverse events when compared with crizotinib (41% [63/152] vs. 50% [75/151], respectively) even though patients received alectinib for a longer duration than crizotinib (median, 17.9 vs. 10.7 months). Fewer deaths were reported with alectinib (3.3% [5/152]) versus crizotinib (4.6% [7/151]); two treatment-related deaths were reported in the crizotinib arm and none in the alectinib arm.

J-ALEX, a phase 3 randomized trial, assessed first-line therapy with alectinib versus crizotinib in 207 Japanese patients with *ALK*-positive advanced NSCLC.[841] Median PFS was not reached with alectinib (95% CI, 20.3 months–not reached) versus 10.2 months (95% CI, 8.2–12.0) with crizotinib (HR, 0.34; 99.7% CI, 0.17–0.71; stratified log-rank *P* < .0001). Grade 3 or 4 adverse events were less frequent with alectinib (26% [27/103]) when compared with crizotinib (52% [54/104]); adverse events did not lead to death in either group. Fewer patients stopped taking alectinib (9%) because of an adverse event when compared with crizotinib (20%).

The NCCN NSCLC Panel recommends alectinib as a first-line therapy option for patients with *ALK*-positive metastatic NSCLC based on clinical trial data and FDA approval.[220,841,842] Panel members voted that alectinib is a preferred first-line therapy option for patients with *ALK*-positive metastatic NSCLC based on these trials. Alectinib is a category 1 (preferred) option if an *ALK* rearrangement is discovered before giving first-line systemic therapy; alectinib is a preferred monotherapy option if an *ALK* rearrangement is discovered during first-line systemic therapy (eg, carboplatin plus paclitaxel). Brigatinib, ceritinib, crizotinib, and lorlatinib are also recommended as first-line therapy options in patients with *ALK*-positive NSCLC. The NCCN NSCLC Panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred first-line therapy options for patients with

ALK-positive metastatic NSCLC. Ceritinib is an "other recommended" option, whereas crizotinib is useful in certain circumstances.

Subsequent Therapy

Phase 2 trials assessed alectinib in patients with ALK-positive metastatic NSCLC and disease progression on crizotinib; overall response rates were 48% to 50%.[182,843] In the larger trial (138 patients), patients on alectinib had a response rate of 50% (95% CI, 41%–59%), and median duration of response of 11.2 months (95% CI, 9.6–not reached).[182] For CNS disease, the control rate was 83% (95% CI, 74%–91%) and the median duration of response was 10.3 months (95% CI, 7.6–11.2). Of 84 patients with baseline CNS metastases, 23 (27%) had a complete CNS response to alectinib. Of 23 patients with baseline CNS metastases and no previous brain RT, 10 (43%) had a complete CNS response to alectinib. Most adverse events were only grade 1 to 2 (constipation, fatigue, and peripheral edema); 4 patients (3%) had grade 3 dyspnea. One death due to intestinal perforation may have been related to alectinib. The NCCN NSCLC Panel recommends alectinib as a subsequent therapy option for patients with ALK-positive metastatic NSCLC and disease progression after crizotinib based on these trials and FDA approval.[182,842,843] Brigatinib, ceritinib, and lorlatinib are also recommended as subsequent therapy options in patients with ALK-positive NSCLC and disease progression after crizotinib. Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib unless an adverse side effect requiring discontinuation has occurred (eg, pneumonitis).

Brigatinib

Brigatinib is a second-generation oral TKI that inhibits ALK rearrangements.

First-Line Therapy

ALTA-1L, a phase 3 randomized trial, assessed brigatinib versus crizotinib as first-line therapy for patients with ALK-positive metastatic NSCLC.[223] At the first interim analysis, PFS was increased in patients receiving brigatinib (67%; 95% CI, 56%–75%) versus those receiving crizotinib (43%; 95% CI, 32%–53%) (HR for disease progression or death, 0.49; 95% CI, 0.33–0.74; P < .001). Intracranial response was also increased with brigatinib (78%; 95% CI, 52%–94%) versus crizotinib (29%; 95% CI, 11%–52%). At the second interim analysis (24.9 months of follow-up), brigatinib continued to show improved PFS when compared with crizotinib (HR 0.43; 95% CI, 0.31–0.61; median, 29.4 vs. 9.2 months).[844] After 3 years, the PFS was 43% for brigatinib versus 19% for crizotinib (HR, 0.48; 95% CI, 0.35–0.66). The median overall survival was not reached in either arm.[845]

The NCCN NSCLC Panel recommends brigatinib as a first-line therapy option for patients with ALK-positive NSCLC based on clinical trial data and FDA approval.[223] Brigatinib is a category 1 (preferred) option if an ALK rearrangement is discovered before giving first-line systemic therapy. Brigatinib is a preferred option if an ALK rearrangement is discovered during first-line systemic therapy (eg, carboplatin plus paclitaxel). Other first-line therapy options include alectinib, ceritinib, crizotinib, and lorlatinib for patients with ALK-positive NSCLC. The NCCN NSCLC Panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred options for patients with ALK-positive metastatic NSCLC; ceritinib is an "other recommended" option and crizotinib is useful in certain circumstances.[844]

Subsequent Therapy

ALTA, a phase 2 study, assessed two different doses of brigatinib—90 mg (arm A) or 180 mg (arm B) every day—in patients with ALK-positive metastatic NSCLC and disease progression on, or who were intolerant to, crizotinib.[846,847] The overall response rates were 45% (97% CI, 34%–56%)

and 54% (97% CI, 43%–65%) in arms A and B, respectively. Many patients had brain metastases (71% and 67%, respectively). The intracranial overall response rates were 42% (11/26) and 67% (12/18), respectively, in patients with measurable brain metastases. The median PFS was 9.2 months (95% CI, 7.4–15.6) and 12.9 months (95% CI, 11.1–not reached), respectively. Grade 3 or higher adverse events included hypertension (6% and 6%, respectively) and pneumonia (3% and 5%, respectively).

The NCCN NSCLC Panel recommends brigatinib as a subsequent therapy option for patients with *ALK*-positive NSCLC and disease progression after crizotinib based on clinical trial data and FDA approval.[846,847] Patients receiving brigatinib should be carefully monitored for respiratory symptoms, especially during the first week of treatment. Alectinib, ceritinib, and lorlatinib are also recommended as subsequent therapy options in patients with *ALK*-positive NSCLC and disease progression after crizotinib. Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib unless an adverse side effect requiring discontinuation has occurred (eg, pneumonitis).

Ceritinib
Ceritinib is a second-generation oral TKI that inhibits *ALK* and *ROS1* rearrangements.[848]

First-Line Therapy
ASCEND-4, a phase 3 randomized trial, assessed ceritinib versus platinum-based chemotherapy as first-line therapy for patients with *ALK*-positive metastatic NSCLC.[222] The median PFS was 16.6 months (95% CI, 12.6–27.2) for ceritinib and 8.1 months (95% CI, 5.8–11.1) for chemotherapy (HR, 0.55; 95% CI, 0.42–0.73; *P* < .00001). For ceritinib, common adverse events included diarrhea (85% [160/189] of patients), nausea (69% [130/189]), vomiting (66% [125/189]), and an increase in

ALT (60% [114/189]). For chemotherapy, common adverse events included nausea (55% [97/175 patients]), vomiting (36% [63/175]), and anemia (35% [62/175]).

The NCCN NSCLC Panel recommends ceritinib as a first-line therapy option for patients with *ALK*-positive metastatic NSCLC based on clinical trial data and FDA approval. Ceritinib is a category 1 (other recommended) option if an *ALK* rearrangement is discovered before giving first-line systemic therapy; ceritinib is a treatment if an *ALK* rearrangement is discovered during first-line systemic therapy (eg, carboplatin plus paclitaxel). Alectinib, brigatinib, crizotinib, and lorlatinib are also recommended as first-line therapy options in patients with *ALK*-positive NSCLC. The NCCN NSCLC Panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred options for patients with *ALK*-positive metastatic NSCLC; ceritinib is an "other recommended" option and crizotinib is useful in certain circumstances.

Subsequent Therapy
ASCEND-5, a phase 3 randomized trial, assessed subsequent therapy with ceritinib versus chemotherapy (with pemetrexed or docetaxel) in patients with advanced *ALK*-positive NSCLC who had previously received at least two or more treatments (including chemotherapy and crizotinib) and had disease progression.[849] The median PFS for ceritinib was 5.4 months (95% CI, 4.1–6.9) versus a median PFS of 1.6 months for chemotherapy (95% CI, 1.4–2.8; HR, 0.49; 95% CI, 0.36–0.67; *P* < .0001). Serious adverse events were reported in 43% (49/115) of patients receiving ceritinib versus 32% (36/113) of those receiving chemotherapy. ASCEND-2, a phase 2 study, assessed ceritinib in patients who had previously received at least two or more treatments, with disease progression on crizotinib, and with brain metastases.[850] The overall response rate was 38%; the duration of response was 9.7 months (95%

CI, 7.1–11.1).[850] The intracranial overall response rate was 45.0% (95% CI, 23.1%–68.5%).

The NCCN NSCLC Panel recommends ceritinib as a subsequent therapy option for patients with *ALK*-positive metastatic NSCLC and disease progression after crizotinib based on clinical trial data and FDA approval.[849] Alectinib, brigatinib, and lorlatinib are also recommended as subsequent therapy options in patients with *ALK*-positive NSCLC and disease progression after crizotinib. Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib unless an adverse side effect requiring discontinuation has occurred (eg, pneumonitis).

Crizotinib

Crizotinib is a first-generation oral TKI that inhibits *ALK* rearrangements, *ROS1* rearrangements, and some *MET* tyrosine kinases (high-level *MET* amplification or *MET*ex14 skipping mutation).[192,221,320,851-855]

First-Line Therapy

Randomized phase 3 trials have compared crizotinib with first-line chemotherapy (PROFILE 1014) and with subsequent chemotherapy (PROFILE 1007) for patients with *ALK*-positive metastatic NSCLC.[10,221,856] First-line therapy with crizotinib improved PFS, response rate (74% vs. 45%; *P* < .001), lung cancer symptoms, and quality of life when compared with chemotherapy (pemetrexed with either cisplatin or carboplatin).[221] Crizotinib yields high response rates (>60%) when used in patients with advanced NSCLC who have *ALK* rearrangements, including those with brain metastases.[123,221,857-859] Patients whose disease responds to crizotinib may have rapid improvement in symptoms; median time to progression on crizotinib is about 7 months to 1 year.[860,861] Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in

renal function).[858,862,863] However, some patients have had pneumonitis; crizotinib should be discontinued in these patients.[853] Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib unless an adverse side effect requiring discontinuation has occurred (eg, pneumonitis).

The NCCN NSCLC Panel recommends crizotinib as a first-line treatment option for patients with *ALK* rearrangement-positive metastatic NSCLC based on clinical trial data and FDA approval.[221] Crizotinib is a category 1 (useful in certain circumstances) option if an *ALK* rearrangement is discovered before giving first-line systemic therapy; crizotinib is a treatment option if an *ALK* rearrangement is discovered during first-line systemic therapy (eg, carboplatin plus paclitaxel). Alectinib, brigatinib, ceritinib, and lorlatinib are also recommended as first-line therapy options in patients with *ALK*-positive NSCLC. The NCCN NSCLC Panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred options for patients with *ALK*-positive metastatic NSCLC, whereas ceritinib is an "other recommended" option and crizotinib is useful in certain circumstances. Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib unless an adverse side effect requiring discontinuation has occurred (eg, pneumonitis).

Subsequent Therapy

Subsequent therapy with crizotinib improved PFS (7.7 vs. 3.0 months; *P*<.001) and response rate (65% vs. 20%; *P*<.001) when compared with either docetaxel or pemetrexed in patients with *ALK*-positive NSCLC and disease progression after first-line chemotherapy who had not previously received ALK inhibitors.[852] Therefore, crizotinib may also be continued for patients with *ALK* rearrangements and disease progression on crizotinib, depending on the type of progression.[852] The NCCN NSCLC Panel does not recommend continuing crizotinib for patients with brain metastases

and disease progression after first-line therapy with crizotinib; the other ALK inhibitors are recommended options in this setting because they have better CNS response rates (ie, alectinib, brigatinib, ceritinib, lorlatinib).[849,850,864,865]

Lorlatinib

Lorlatinib is an oral third-generation TKI that targets ALK and ROS1 tyrosine kinases and has good CNS penetration; it inhibits a broad range of *ALK* resistance mutations that develop after treatment with first- and second-generation ALK inhibitors.[358,831-833]

First-Line Therapy

CROWN, a phase 3 randomized trial, assessed lorlatinib versus crizotinib as first-line therapy for patients with *ALK*-positive metastatic NSCLC.[219] At 12 months, 78% (95% CI, 70%–84%) of patients were alive without disease progression in the lorlatinib group versus 39% (95% CI, 30%–48%) in the crizotinib group (HR for disease progression or death, 0.28; 95% CI, 0.19–0.41; *P* < .001). The objective response rate was 76% (95% CI, 68%–83%) for patients receiving lorlatinib and 58% (95% CI, 49%–66%) for those receiving crizotinib. For patients with measurable brain metastases, 82% (95% CI, 57%–96%) of those receiving lorlatinib had an intracranial response and 23% (95% CI, 5%–54%) of those receiving crizotinib responded. Of patients who received lorlatinib, 71% had a complete intracranial response. Hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects were the most common adverse events seen with lorlatinib. More grade 3 or 4 adverse events (mainly altered lipid levels) occurred with lorlatinib than with crizotinib (72% vs. 56%, respectively). Discontinuation of treatment because of adverse events was similar in both groups (7% for lorlatinib and 9% for crizotinib). Updated data from the CROWN study show 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.[866] 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.[866]

The NCCN NSCLC Panel recommends lorlatinib as a first-line therapy option for patients with *ALK*-positive metastatic NSCLC based on clinical trial data and FDA approval.[219,866] Panel members voted that lorlatinib is a preferred first-line therapy option for patients with *ALK*-positive metastatic NSCLC based on trial data.[219] Lorlatinib is a category 1 (preferred) option if an *ALK* rearrangement is discovered before giving first-line systemic therapy; lorlatinib is a preferred option if an *ALK* rearrangement is discovered during first-line systemic therapy (eg, carboplatin plus paclitaxel). Alectinib, brigatinib, ceritinib, and crizotinib are also recommended as first-line therapy options in patients with *ALK*-positive metastatic NSCLC. The NCCN NSCLC Panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred options for patients with *ALK*-positive metastatic NSCLC; ceritinib is an "other recommended" option and crizotinib is useful in certain circumstances.

Subsequent Therapy

Data show that lorlatinib is effective in select patients with disease progression after treatment with ALK inhibitors, including those with CNS metastases.[831,832] A phase 2 trial assessed lorlatinib in patients with *ALK*-positive or *ROS1*-positive metastatic NSCLC and disease progression after ALK inhibitor therapy; many patients had asymptomatic CNS metastases.[831] In patients who had received at least one previous ALK inhibitor, objective responses were achieved in 47% of patients (93/198; 95% CI, 39.9%–54.2%); there were 4 complete responses and 89 partial responses. In those with measurable baseline CNS lesions, an

objective intracranial response was observed in 63% of patients (51/81; 95% CI, 51.5%–73.4%). Lorlatinib was effective in patients who had received up to three previous ALK inhibitors. Grade 3 to 4 adverse events included hypercholesterolemia and hypertriglyceridemia (43/275 [16%] for both). Serious treatment-related adverse events occurred in 7% of patients (19/275) including cognitive effects in 1% (2/275); the cognitive effects resulted in permanent discontinuation of lorlatinib. No treatment-related deaths were reported. Data from this phase 2 trial also show 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.[833] The objective response rate with lorlatinib was 62% when using plasma ctDNA (and 69% when using 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.

The NCCN NSCLC Panel recommends lorlatinib as a subsequent therapy option for select patients with *ALK*-positive metastatic NSCLC and disease progression after treatment with ALK inhibitors based on clinical trial data and FDA approval.[832,833] Lorlatinib is recommended as a subsequent therapy option for select patients with *ALK* G1202R-positive metastatic NSCLC after progression on alectinib, brigatinib, or ceritinib (depending on the type of progression) based on clinical trial data.[833] At progression, the panel recommends considering plasma and/or tissue-based testing using broad molecular profiling for genomic resistance mechanisms.[833] Lorlatinib is recommended as a subsequent therapy option for select patients with *ALK*-positive metastatic NSCLC after progression on crizotinib. If not previously given, lorlatinib is also recommended as a subsequent therapy option for *ALK*-positive metastatic NSCLC after progression on crizotinib followed by progression on either alectinib, brigatinib, or ceritinib.

Oral Agents that Inhibit BRAF Mutations
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. Rare *BRAF* mutations include p.V600K and p.V600D. The NCCN NSCLC Panel recommends *BRAF* mutation testing in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of several agents for patients with *BRAF* mutations (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[867-870] *BRAF* mutation testing can be considered in patients with metastatic squamous cell carcinoma.

Dabrafenib and Trametinib
Dabrafenib and trametinib inhibit kinases in the RAS/RAF/MEK/ERK pathway.[190,191] Dabrafenib inhibits *BRAF* p.V600E mutations; trametinib inhibits MEK 1/2, which is downstream of *BRAF* signaling.

First-Line Therapy
A phase 2 trial assessed first-line combination therapy with dabrafenib plus trametinib for 36 patients with metastatic NSCLC and *BRAF* p.V600E mutations.[18,867] The overall response rate was 64% (23/36; 95% CI, 46%–79%); there were 2 complete responses. The median PFS was 10.9 months (95% CI, 7.0–16.6). Many patients (69% [25/36]) had one or more grade 3 or 4 adverse events. Serious adverse events included increased alanine aminotransferase (ALT) (14% [5/36]), increased aspartate transaminase (AST) (8% [3/36]), pyrexia (11% [4/36]), and decreased ejection fraction (8% [3/36]). An updated analysis reported that patients receiving dabrafenib plus trametinib had a median overall survival of 17.3 months (95% CI, 12.3–40.2).[18] After 5 years, the overall survival rate was 22%.

The NCCN NSCLC Panel recommends combination therapy with dabrafenib plus trametinib as a preferred first-line therapy option for patients with metastatic NSCLC and *BRAF* p.V600E mutations based on these trials and FDA approval.[867,868,870] Single-agent therapy with dabrafenib or vemurafenib is also an option for patients with *BRAF* p.V600E mutations who do not tolerate combination therapy with dabrafenib plus trametinib.[191,868,871] Other systemic therapy regimens are also recommended options for patients with *BRAF* p.V600E mutations; the same initial systemic regimens used for patients with metastatic NSCLC may be used (eg, carboplatin plus paclitaxel). The NCCN NSCLC Panel has preference stratified the first-line therapy options for patients with

BRAF p.V600E mutation-positive metastatic NSCLC and decided that: 1) dabrafenib plus trametinib is the preferred option; 2) other systemic therapy regimens (eg, carboplatin plus paclitaxel) are other recommended options; and 3) single-agent dabrafenib or vemurafenib are useful in certain circumstances. For the 2023 update (Version 1), the NCCN Panel revised the preference stratification for the other systemic therapy options to "other recommended options" from "useful in certain circumstances."

Subsequent Therapy
A phase 2 study assessed the dabrafenib plus trametinib regimen as subsequent therapy in 57 patients with advanced NSCLC and *BRAF* p.V600E mutations and disease progression on chemotherapy.[18,190,869] The overall response rate was 68% (23/36; 95% CI, 55%–80%); PFS was 9.7 months (6.9–19.6). Serious adverse events occurred in 56% (32/57) of patients, including pyrexia, anemia, confused state, hemoptysis, hypercalcemia, and cutaneous squamous cell carcinoma. Grade 3 to 4 adverse events included neutropenia in 9% of patients (5/57), hyponatremia in 7% (4/57), and anemia in 5% (3/57). Four patients died during the study, but these deaths were not felt to be related to treatment (deaths were due to retroperitoneal hemorrhage, subarachnoid

hemorrhage, respiratory distress, or severe disease progression). An updated analysis reported that the median overall survival was 18.2 months (95% CI, 14.3–28.6).[18] After 5 years, the overall survival rate was 19%.

The NCCN NSCLC Panel recommends dabrafenib plus trametinib as a subsequent therapy option if patients with *BRAF* p.V600E mutations have disease progression after first-line systemic therapy regimens (eg, carboplatin plus paclitaxel) and have not received *BRAF* p.V600E inhibitors as first-line therapy.[190,869] Single-agent therapy with dabrafenib or vemurafenib is also an option for patients with *BRAF* p.V600E mutations who do not tolerate combination therapy with dabrafenib plus trametinib.[191,868,871] Clinicians should be aware of common adverse events that may occur with dabrafenib plus trametinib including pyrexia, vomiting, and nausea along with less frequent and unique adverse events, such as cutaneous, ocular, and hemorrhagic events.[872]

Agents that Inhibit EGFR Mutations

Oral TKIs that Inhibit EGFR Exon 19 Deletions and Exon 21 L858R Mutations
The NCCN NSCLC Panel recommends *EGFR* mutation testing (category 1) in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of several agents for patients with *EGFR* mutations.[252,258] *EGFR* mutation testing can be considered in patients with metastatic squamous cell carcinoma. The NCCN NSCLC Panel recommends afatinib, dacomitinib, erlotinib (± bevacizumab or ramucirumab), gefitinib, and osimertinib for patients with metastatic NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations based on clinical trial data and FDA approvals, which are described in the following sections.

Afatinib

Afatinib is a second-generation oral TKI that irreversibly inhibits the ErbB/HER family of receptors including EGFR and ERBB2.[873,874] LUX-Lung 3, a phase 3 randomized trial, reported that first-line therapy with afatinib improved PFS when compared with cisplatin plus pemetrexed in patients with metastatic adenocarcinoma who had *EGFR* mutations (11.1 vs. 6.9 months, *P* = .001).[251] The NCCN NSCLC Panel recommends afatinib as a first-line therapy option in patients with metastatic NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations based on the clinical trial and FDA approval.[251,873,875-877] Afatinib is a category 1 (other recommended) option if an *EGFR* exon 19 deletion or *EGFR* exon 21 L858R mutation is discovered before giving first-line systemic therapy. Afatinib is an option if an *EGFR* exon 19 deletion or *EGFR* exon 21 L858R mutation is discovered during first-line systemic therapy (eg, carboplatin plus paclitaxel).

The NCCN NSCLC Panel has preference stratified the systemic therapy regimens for patients with metastatic NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations and decided that afatinib is an "other recommended" option; osimertinib is the preferred option in this setting. Afatinib may also be continued in patients with disease progression if they do not have multiple systemic symptomatic lesions (see *Continuation of Targeted Therapy After Progression on Initial Therapy* in this Discussion).[246] However, afatinib is not recommended as subsequent therapy in patients with metastatic squamous cell NSCLC but without *EGFR* mutations based on a phase 3 randomized trial showing low response rates (11%); it is less efficacious and safe compared to other available options [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion].[878] Afatinib is also recommended for eligible patients with metastatic NSCLC and less common *EGFR* mutations including *EGFR* S768I, L861Q, and/or G719X mutations (see *Oral TKIs that Inhibit EGFR S768I, L861Q, and G719X Alterations* in this Discussion).[879]

A phase 2B trial assessed afatinib compared with gefitinib for first-line therapy in patients with metastatic adenocarcinoma and common *EGFR* mutations.[880] The median PFS was 11.0 months (95% CI, 10.6–12.9) with afatinib versus 10.9 months (95% CI, 9.1–11.5) with gefitinib (HR, 0.73; 95% CI, 0.57–0.95; *P* = .017). These slight PFS differences are not clinically relevant. Updated results indicate that overall survival was not significantly different between afatinib and gefitinib (27.9 vs. 24.5 months; HR, 0.86; 95% CI, 0.66–1.12; *P* = .2580).[881] Patients receiving afatinib had more serious treatment-related side effects when compared with those receiving gefitinib (11% [17/160] for afatinib vs. 4% [7/159] for gefitinib). One patient receiving gefitinib died from treatment-related hepatic and renal failure; other deaths were not considered to be related to treatment (9% vs. 6% [15/160 vs. 10/159]). More patients receiving afatinib had diarrhea (13% vs. 1%), whereas more patients receiving gefitinib had elevations in liver enzyme levels (0% vs. 9%). The NCCN Guidelines do not state that afatinib is more efficacious than gefitinib (see the NCCN Guidelines with Evidence Blocks™ for NSCLC, available at www.NCCN.org).[882] Afatinib is rated as slightly less safe than erlotinib or gefitinib (ie, a rating of 3 for afatinib vs. 4 for erlotinib and gefitinib).

Erlotinib and Gefitinib

Erlotinib and gefitinib are first-generation oral TKIs that inhibit *EGFR* exon 19 deletions and *EGFR* exon 21 L858R mutations (both are common mutations) as well as *EGFR* G719X, L861Q, and/or S768I (less common mutations) (see *Oral TKIs that Inhibit EGFR G719X, L861Q, and S768I Alterations* in this Discussion).

Clinical Trial Data

IPASS, a phase 3 randomized trial, assessed first-line therapy with gefitinib alone versus carboplatin plus paclitaxel in Asian patients with *EGFR*-positive metastatic NSCLC.[258] Patients with *EGFR* mutations who received gefitinib had longer PFS (24.9% vs. 6.7%), increased response

rate (71.2% vs. 47.3%), and improved quality of life with fewer side effects (eg, neutropenia) compared with carboplatin plus paclitaxel.[258] Updated results from the IPASS trial showed that overall survival was similar in patients receiving gefitinib or chemotherapy regardless of *EGFR* mutation status.[883] These results probably occurred because patients who had been assigned to first-line chemotherapy were able to receive TKIs as subsequent therapy if they were found to have *EGFR* mutations.

EURTAC, a phase 3 randomized trial, assessed first-line therapy with erlotinib versus chemotherapy in European patients with metastatic NSCLC and *EGFR* mutations.[252] For erlotinib, the median PFS was 9.7 months (95% CI, 8.4–12.3) compared with 5.2 months (95% CI, 4.5–5.8) for chemotherapy (HR, 0.37; 95% CI, 0.25–0.54; *P* < .0001). Fewer patients receiving erlotinib had severe adverse events or died when compared with those receiving chemotherapy. Previously, erlotinib was often used in the United States in patients with common *EGFR* mutations because of restrictions on the use of gefitinib. However, gefitinib was re-approved by the FDA based on a phase 4 study and is available in the United States.[183,884]

CALGB 30406, a phase 3 randomized trial, compared first-line erlotinib monotherapy versus erlotinib plus carboplatin plus paclitaxel in patients (mainly Caucasian) with advanced NSCLC and *EGFR* mutations.[885] Erlotinib monotherapy was associated with fewer side effects in patients with *EGFR* mutations compared with erlotinib plus chemotherapy. Thus, it is appropriate to interrupt or complete planned chemotherapy and switch to EGFR TKI therapy in patients found to have *EGFR* mutations during first-line chemotherapy.[886] The NCCN Guidelines do not recommend adding EGFR TKIs to current chemotherapy based on this CALGB study.[885] EGFR TKIs may be continued in patients with disease progression if they do not have multiple systemic symptomatic lesions

(see *Continuation of Targeted Therapy After Progression on Initial Therapy* in this Discussion).

WJOG 5108L, a phase 3 randomized trial, assessed gefitinib versus erlotinib for patients with advanced lung cancer who had been previously treated with chemotherapy; most patients (72%) were positive for *EGFR* mutations.[882] The median PFS was 8.3 months for gefitinib versus 10.0 months for erlotinib in patients positive for *EGFR* mutations (HR, 1.093; 95% CI, 0.879–1.358; *P* = .424). The main grade 3 or 4 toxicities included rash (gefitinib: 2.2% vs. erlotinib: 18.1%) and increases in ALT/AST levels (gefitinib: 6.1%/13.0% vs. erlotinib: 2.2%/3.3%).

An analysis of 5 clinical trials in patients (n = 223) with NSCLC (stage IIIB or IV), mainly from the Western hemisphere, found that those with *EGFR* mutations who received TKIs had a 67% response rate and an overall survival of about 24 months.[887] The TORCH trial suggested that *EGFR* mutation testing should be done in patients with advanced nonsquamous NSCLC.[888] Survival was longer in patients with wild-type EGFR who received first-line chemotherapy compared with those who received erlotinib first followed by subsequent chemotherapy (11.6 vs. 8.7 months). The OPTIMAL trial reported that PFS was increased in patients with *EGFR* mutations who received erlotinib.[255,256] EGFR TKIs are recommended in patients with metastatic NSCLC and *EGFR* mutations, because quality of life is improved when compared with chemotherapy. Erlotinib and gefitinib are orally active TKIs that are very well tolerated by most patients.[889,890]

RELAY, a phase 3 randomized trial, compared first-line therapy with erlotinib plus ramucirumab versus erlotinib alone in patients with advanced NSCLC and *EGFR* mutations.[891] PFS was 19.4 months (95% CI, 15.4–21.6) with erlotinib plus ramucirumab versus 12.4 months (95% CI, 11.0–13.5) with erlotinib alone (HR, 0.59; 95% CI, 0.46–0.76; *P* < .0001). The overall response rate was similar (erlotinib plus ramucirumab: 76% vs.

erlotinib alone: 75%). Serious adverse events (grade 3–4) occurred in 72% (159/221) of patients receiving erlotinib plus ramucirumab (including hypertension) versus 54% (121/225) in those receiving erlotinib alone (including increased ALT). One treatment-related death occurred in a patient receiving erlotinib plus ramucirumab.

NEJ026, a phase 3 randomized trial, compared first-line erlotinib plus bevacizumab versus erlotinib alone in 228 patients with *EGFR*-positive advanced nonsquamous NSCLC.[892,893] At interim analysis, PFS was 16.9 months (95% CI, 14.2–21.0) for erlotinib plus bevacizumab versus 13.3 months (95% CI, 11.1–15.3) for erlotinib alone (HR, 0.605; 95% CI, 0.417–0.877; *P* = .016).[893] Grade 3 or worse events occurred in 88% (98/112) of patients receiving erlotinib plus bevacizumab versus 46% (53/114) of those receiving erlotinib alone. Grade 4 adverse events occurred in 8% (9/112) of patients receiving erlotinib plus bevacizumab (including neutropenia, hepatic dysfunction) versus 4% (5/114) of patients receiving erlotinib alone (hepatic dysfunction); no treatment-related deaths were reported.[893] Updated data showed that median overall survival was 50.7 months (95% CI, 37.3–not estimable) in those receiving erlotinib plus bevacizumab versus 46.2 months (38.2–not estimable) in those receiving erlotinib alone (HR, 1.007; 95% CI, 0.681–1.490; *P* = .97).[892]

NCCN Recommendations
The NCCN NSCLC Panel recommends erlotinib and gefitinib as first-line therapy options in patients with metastatic nonsquamous NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations (regardless of their PS) based on these trials and FDA approvals.[121,258,894,895] Erlotinib and gefitinib are category 1 (other recommended) options if an *EGFR* exon 19 deletion or *EGFR* exon 21 L858R mutation is discovered before giving first-line systemic therapy; erlotinib and gefitinib are also treatment options if an *EGFR* exon 19 deletion or *EGFR* exon 21 L858R mutation is discovered during first-line systemic therapy (eg, carboplatin plus paclitaxel).

The NCCN NSCLC Panel recommends erlotinib plus ramucirumab as a first-line therapy option for patients with metastatic NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations (other recommended intervention) based on clinical data.[891] The panel also recommends erlotinib plus bevacizumab as a first-line therapy option for eligible patients with metastatic nonsquamous NSCLC who have common *EGFR* mutations and no contraindications to bevacizumab (other recommended) based on clinical data.[892,893] The NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the regimens containing bevacizumab used for eligible patients with metastatic NSCLC.[896-900] Erlotinib (± bevacizumab or ramucirumab) or gefitinib may also be continued in patients with disease progression if they do not have multiple systemic symptomatic lesions [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion].[246] However, erlotinib is not recommended as subsequent therapy in patients with metastatic squamous cell NSCLC but without *EGFR* mutations based on a phase 3 randomized trial showing low response rates (3%); it is less efficacious and safe compared to other available options.[878]

The NCCN NSCLC Panel has preference stratified the systemic therapy regimens and decided that erlotinib (± bevacizumab or ramucirumab) and gefitinib are "other recommended" first-line options for patients with metastatic NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations; osimertinib is the preferred option in this setting. Erlotinib and gefitinib are also recommended for eligible patients with metastatic NSCLC and less common *EGFR* mutations, such as *EGFR* S768I, L861Q, and/or G719X mutations (see *Oral TKIs that Inhibit EGFR S768I, L861Q, and G719X Alterations* in this Discussion). Flare phenomenon may occur in some patients who discontinue EGFR TKIs. If disease flare occurs, then the EGFR TKIs should be restarted.

Dacomitinib

Dacomitinib is a second-generation oral TKI that irreversibly inhibits ErbB/HER receptors including EGFR, HER1, HER2, and HER4.

Clinical Trial Data

ARCHER 1050, a phase 3 randomized trial, compared dacomitinib versus gefitinib as first-line therapy for patients with *EGFR*-positive metastatic NSCLC.[901,902] Patients with brain metastases were not eligible for enrollment. PFS was increased in patients receiving dacomitinib (14.7 months; 95% CI, 11.1–16.6) compared with those receiving gefitinib (9.2 months; 95% CI, 9.1–11.0). Serious adverse events related to treatment were reported in 21 (9%) patients given dacomitinib and in 10 (4%) patients given gefitinib. Treatment-related deaths included two patients in the dacomitinib group (one related to untreated diarrhea and one to untreated cholelithiasis/liver disease) and one patient in the gefitinib group (related to sigmoid colon diverticulitis/rupture complicated by pneumonia). An updated analysis reported that the median overall survival was 34.1 months (95% CI, 29.5–39.8) in patients receiving dacomitinib compared with 27.0 months (95% CI, 24.4–31.6) in those receiving gefitinib (HR, 0.748; 95% CI, 0.591–0.947; two-sided *P* = .0155).[901,903]

NCCN Recommendations

The NCCN NSCLC Panel recommends dacomitinib as a first-line treatment option for patients with metastatic NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations based on clinical trial data and FDA approval.[901,904] Dacomitinib is a category 1 (other recommended) option if an *EGFR* exon 19 deletion or *EGFR* exon 21 L858R mutation is discovered before giving first-line systemic therapy; dacomitinib is an option if an *EGFR* exon 19 deletion or *EGFR* exon 21 L858R mutation is discovered during first-line systemic therapy (eg, carboplatin plus paclitaxel). The NCCN NSCLC Panel has preference stratified the systemic therapy regimens and decided that dacomitinib is an "other recommended" option; osimertinib is the preferred option in this setting. Dacomitinib is also recommended for eligible patients with metastatic NSCLC and less common *EGFR* mutations, such as *EGFR* S768I, L861Q, and/or G719X mutations (see *Oral TKIs that Inhibit EGFR S768I, L861Q, and G719X Alterations* in this Discussion).

Osimertinib

Osimertinib is a third-generation oral TKI that inhibits the common and uncommon *EGFR* mutations and T790M. Common *EGFR* mutations include exon 19 deletion and exon 21 L858R; less common *EGFR* mutations include S768I, L861Q, and/or G719X (see *EGFR Mutations* in this Discussion). Patients with these mutations are sensitive to small-molecule oral EGFR TKIs, such as afatinib, dacomitinib, erlotinib, gefitinib, and osimertinib.[246] *EGFR* T790M is a mutation associated with acquired resistance to first-line therapy with EGFR TKIs and has been reported in about 60% of patients with disease progression after initial response to first-line EGFR TKIs, such as erlotinib or gefitinib.[212,267-273] Most patients with *EGFR* mutations and metastatic NSCLC typically have disease progression after about 9.7 to 13 months of therapy with erlotinib, gefitinib, or afatinib.[252,258,266,267] Data show that patients receiving osimertinib as first-line therapy have PFS of about 19 months.[373,905]

First-Line Therapy

Clinical Trial Data

FLAURA, a phase 3 randomized trial, assessed first-line therapy with osimertinib compared with either erlotinib or gefitinib in patients with metastatic NSCLC and *EGFR* mutations regardless of T790M status.[21,373,905,906] PFS was longer with osimertinib (18.9 months; 95% CI, 15.2–21.4) compared with either erlotinib or gefitinib (10.2 months; 95% CI, 9.6–11.1; HR, 0.46; 95% CI, 0.37–0.57; *P* < .001]). The median duration of response was longer with osimertinib compared with erlotinib or gefitinib (median response, 17.2 vs. 8.5 months). Only 6% (17/279) of patients receiving osimertinib had CNS progression events when compared with 15% (42/277) of those receiving erlotinib or gefitinib. Grade

3 or higher adverse events were reported in 34% (94/279) of patients receiving osimertinib and 45% (124/277) of patients receiving erlotinib or gefitinib. An updated analysis showed that median overall survival was 38.6 months with osimertinib (95% CI, 34.5–41.8) compared with 31.8 months (95% CI, 26.6–36.0) for either erlotinib or gefitinib (HR, 0.8; 95% CI, 0.64–1.0; *P* = .046).[21]

NCCN Recommendations

The NCCN NSCLC Panel recommends osimertinib as a preferred first-line therapy option for patients with metastatic NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations based on clinical data and FDA approval.[21,373] Osimertinib is a category 1 (preferred) recommended option if an *EGFR* exon 19 deletion or *EGFR* exon 21 L858R mutation is discovered before giving first-line systemic therapy, and osimertinib is a preferred option if an *EGFR* mutation is discovered during first-line systemic therapy (eg, carboplatin plus paclitaxel).[21] 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.[907,908] If patients require an urgent start to first-line therapy, but molecular testing results are pending, then clinicians should consider holding immunotherapy regimens and only using chemotherapy regimens for the first cycle. Flare phenomenon may occur in some patients who discontinue EGFR TKIs. If disease flare occurs, then the EGFR TKIs should be restarted.[836-839]

Osimertinib is also recommended as an adjuvant therapy option for eligible patients with completely resected stage IB to IIIA or stage IIIB (only T3,N2) NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations who have previously received adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy (see *Surgery Followed by Adjuvant Therapy: Trial Data and NCCN Recommendations* in this Discussion).[749] In addition, osimertinib is recommended for eligible

patients with metastatic NSCLC and less common *EGFR* mutations, such as *EGFR* S768I, L861Q, and/or G719X mutations (see *Oral TKIs that Inhibit EGFR S768I, L861Q, and G719X Alterations* in this Discussion).[293]

Subsequent Therapy

Clinical Trial Data

AURA3, a phase 3 randomized trial, assessed osimertinib versus platinum-pemetrexed chemotherapy in patients with *EGFR* T790M-positive metastatic NSCLC and disease progression on first-line erlotinib, gefitinib, or afatinib. PFS was longer with osimertinib compared with chemotherapy (10.1 vs. 4.4 months; HR, 0.30; 95% CI, 0.23–0.41; *P* < .001).[266] PFS was also longer in patients with CNS metastases who received osimertinib versus chemotherapy (8.5 vs. 4.2 months; HR, 0.32; 95% CI, 0.21–0.49). In addition, the objective response rate was increased with osimertinib (71%; 95% CI, 65%–76%) compared with chemotherapy (31%; 95% CI, 24%–40%) (odds ratio for objective response, 5.39; 95% CI, 3.47–8.48; *P* < .001). The disease control rate was about 93% with osimertinib (95% CI, 90%–96%) and about 74% with chemotherapy (95% CI, 66%–81%). Patients receiving osimertinib had fewer grade 3 or higher adverse events compared with those receiving chemotherapy (23% vs. 47% [63/279 vs. 64/136]). There were four fatal events with osimertinib (respiratory failure [2 patients], pneumonitis, and ischemic stroke) and one with chemotherapy (hypovolemic shock).

The BLOOM study (n = 41) assessed osimertinib (160 mg once daily) in patients with *EGFR* mutations (regardless of T790M status) who had progressive leptomeningeal disease.[909,910] Most patients were women (71%) and all were Asian. Most patients had previously received gefitinib (76%). The median overall survival was 11 months (95% CI, 8.0–18).[909] The overall response rate was 41% (95% CI, 26%–58%). TC clearance in the cerebrospinal fluid was confirmed in 28% of patients (11/40; 95% CI, 15%–44%). Neurologic function improved in 57% (12/21) of patients with

abnormal baseline assessments. Grade 3 or higher adverse events were reported in 66% (27/41) of patients. There were seven deaths due to adverse events, but they were not considered to be related to osimertinib.

NCCN Recommendations
The NCCN NSCLC Panel recommends broad molecular profiling for T790M (category 1) and other genomic resistance mutations for eligible patients with *EGFR* mutation-positive NSCLC and disease progression on certain EGFR TKIs based on the efficacy of osimertinib. The NCCN NSCLC Panel recommends osimertinib (category 1) as a subsequent therapy option for patients with metastatic *EGFR* T790M–positive NSCLC and disease progression on certain EGFR TKIs (including erlotinib [± ramucirumab or bevacizumab]) based on clinical trial data and FDA approval [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion].[266]

For patients with *EGFR* mutations who have disease progression during or after first-line therapy with osimertinib, recommended subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes: 1) considering local therapy (eg, SABR or surgery); 2) continuing osimertinib; or 3) a first-line systemic therapy regimen for metastatic NSCLC (such as carboplatin plus paclitaxel). There are no data to support using erlotinib (with or without ramucirumab or bevacizumab), gefitinib, afatinib, or dacomitinib after progression on first-line therapy with osimertinib. T790M can be assessed using an FDA-approved test or another validated laboratory test done in a CLIA-approved laboratory. Data suggest that plasma genotyping (also known as plasma ctDNA testing or liquid biopsy) may be considered at progression instead of tissue biopsy to detect whether patients have T790M; however, if plasma ctDNA testing is negative, then tissue biopsy is recommended.[911-913]

The NCCN NSCLC Panel also recommends osimertinib (category 1) for patients with T790M who have symptomatic brain metastases after

progression on erlotinib (with or without ramucirumab or bevacizumab), gefitinib, afatinib, or dacomitinib based on data showing an improvement.[266,904,914-916] The NCCN Panel recommends that osimertinib (regardless of T790M status) can be considered for patients with *EGFR* mutations who have progressive CNS disease or leptomeningeal disease based on clinical trial data.[909,910]

Oral TKIs that Inhibit EGFR S768I, L861Q, and G719X Alterations
EGFR exon 18 G719X, exon 21 L861Q, and exon 20 S768I are less common *EGFR* mutations (10%) that are also sensitive to first-, second-, and third-generation EGFR TKIs, such as afatinib, dacomitinib, erlotinib, gefitinib, and osimertinib.[248,249,293-295,879] *EGFR* exon 18 G719X mutations occur more frequently than exon 21 L861Q; exon 20 S768I mutations are the least frequent. The NCCN NSCLC Panel recommends testing for *EGFR* S768I, L861Q, and G719X mutations in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of EGFR TKIs as first-line therapy options for patients with these mutations.[293,295,879] *EGFR* S768I, L861Q, and G719X mutation testing can be considered in patients with metastatic squamous cell carcinoma.

Clinical Trial Data
KCSG-LU15-09, a phase 2 trial, assessed first-line therapy with osimertinib in 37 patients with metastatic NSCLC and less common *EGFR* mutations, including S768I, L861Q, and G719X.[293] The median PFS was 8.2 months (95% CI, 5.9–10.5 months). The objective response rate was 50% (18/36; 95% CI, 33%–67%). Manageable adverse events included rash, pruritis, decreased appetite, diarrhea, and dyspnea.[293]

A post-hoc analysis of several LUX-Lung trials (LUX-Lung 2, 3, and 6) assessed afatinib in a few patients with *EGFR* L861Q, G719X, and S768I mutation-positive metastatic NSCLC.[879] Median overall survival was 19.4 months (95% CI, 16.4–26.9). Of those with *EGFR* S768I mutations,

100% (95% CI, 63.1%–100%) responded to afatinib. Of patients with *EGFR* G719X mutations, 77.8% (95% CI, 52.4%–93.6%) had an objective response to afatinib. Of those with *EGFR L861Q*, 56% (95% CI, 29.9%–80.2%) responded to afatinib.

NCCN Recommendations

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 EGFR TKIs as first-line therapy options for patients with these mutations.[293,295,879] The panel recommends afatinib or osimertinib as first-line therapy options (preferred) for patients with metastatic NSCLC who have these less common *EGFR* mutations based on clinical trial data.[293,879] The NCCN NSCLC Panel has preference stratified the systemic therapy regimens and decided that afatinib or osimertinib are preferred options for patients with metastatic NSCLC and *EGFR* L861Q, G719X, and S768I mutations; other recommended options include erlotinib, gefitinib, or dacomitinib.

Agents that Inhibit EGFR Exon 20 Insertion Mutations

EGFR exon 20 mutations are a heterogenous group; most variants do not respond to first-, second- or third-generation EGFR TKIs. However, some *EGFR* exon 20 alterations, such as p.A763_Y764insFQEA, are sensitive to EGFR TKIs; p.A763_Y764insLQEA may be sensitive to first and third-generation EGFR TKIs. First-line platinum-based chemotherapy is typically recommended for most patients with *EGFR* exon 20 insertion-positive metastatic NSCLC (eg, carboplatin plus paclitaxel).[299,301] The response rates (0%–25%) to immunotherapy regimens vary, depending on the specific *EGFR* exon 20 insertion mutation.[181,304] Response rates to classic subsequent therapy regimens, such as docetaxel, are low (14%) in patients with metastatic NSCLC and disease progression after first-line therapy.

The NCCN NSCLC Panel recommends testing for *EGFR* exon 20 insertion mutations in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of several agents as subsequent therapy options for patients with *EGFR* exon 20 insertion-positive metastatic NSCLC.[180,181] *EGFR* exon 20 insertion mutation testing can be considered in patients with metastatic squamous cell carcinoma.

Amivantamab

Amivantamab-vmjw is a bispecific human antibody to EGFR and MET receptors that bypasses resistance to EGFR TKIs and has immune-cell directing activity.[180]

Subsequent Therapy

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.[180] The reported overall response rate was 40% (95% CI, 29%–51%) with 3 complete responses. The median PFS was 8.3 months (95% CI, 6.5–10.9). Common treatment-related adverse events included cutaneous reactions, infusion-related reactions, and paronychia. The most common grade 3 to 4 adverse events included hypokalemia (5% [6/114]) as well as pulmonary embolism, neutropenia, diarrhea, and rash (4% for each [4/114]). Eight deaths were reported in the safety assessment (7% [8/114]).

The NCCN NSCLC Panel recommends amivantamab as a subsequent therapy option for patients with *EGFR* exon 20 insertion mutation-positive metastatic NSCLC and disease progression on or after systemic therapy options based on clinical trial data and FDA approval.[180] If patients have disease progression on amivantamab, then the panel recommends either mobocertinib or subsequent systemic therapy options (eg, albumin-bound paclitaxel). If the patient has previously received amivantamab, then they

can receive mobocertinib as third-line or beyond therapy and vice versa because these agents have different mechanisms of action. For the 2023 update (Version 1), the NCCN Panel added a caveat that amivantamab or mobocertinib can be used as third-line or beyond therapy if the patient has previously received only one, or none, of these agents.

Mobocertinib

Mobocertinib is an oral TKI that selectively inhibits diverse *EGFR* and *ERBB2 (HER2)* exon 20 insertion mutations.[181,297]

Subsequent Therapy

Phase 1/2 trials (n =114) assessed subsequent therapy with mobocertinib for patients with *EGFR* exon 20 insertion mutation-positive metastatic NSCLC who had received first-line platinum-based chemotherapy.[181,297] The objective response rate was 28% (95% CI, 20%–37%). Median overall survival was 24 months (95% CI, 14.6–28.8). Patients with brain metastases had a lower overall response rate (18%; 95% CI, 7%–33%) to mobocertinib compared to those without brain metastases (34%; 95% CI, 23%–46%). Diarrhea and rash were the most common treatment-related adverse events. Grade 3 or 4 treatment-related adverse events were reported in 47% of patients (54/114); diarrhea was the most common grade 3 or 4 adverse event (21% [24/114]).[297] One death (cardiac failure) was reported to be related to treatment with mobocertinib.

The NCCN NSCLC Panel recommends mobocertinib as a subsequent therapy option for patients with *EGFR* exon 20 insertion-positive metastatic NSCLC and disease progression on or after initial systemic therapy options based on clinical trial data and FDA approval.[181] If patients have disease progression on mobocertinib, then the panel recommends either amivantamab or subsequent systemic therapy options (eg, albumin-bound paclitaxel). If the patient has previously received mobocertinib, then they can receive amivantamab as third-line or beyond therapy and vice versa because these agents have different mechanisms

of action. For the 2023 update (Version 1), the NCCN Panel added a caveat that mobocertinib or amivantamab can be used as third-line or beyond therapy if the patient has previously received only one, or none, of these agents.

Monoclonal Antibody that Inhibits EGFR

Cetuximab

Cetuximab is a monoclonal antibody that targets EGFR. Data suggest that an afatinib plus cetuximab regimen may be useful for patients who have progressed after receiving erlotinib, afatinib, or gefitinib and after chemotherapy.[917] Patients with T790M-positive and T790M-negative tumors had a similar response rate to an afatinib plus cetuximab regimen (32% vs. 25%; *P* = .341). The NCCN NSCLC Panel recommends considering afatinib plus cetuximab as an option for patients with disease progression after receiving afatinib, dacomitinib, erlotinib (± bevacizumab or ramucirumab), or gefitinib and after chemotherapy based on these data.

FLEX, a large phase 3 randomized trial, assessed cisplatin plus vinorelbine with (or without) cetuximab for patients with advanced NSCLC; most patients had stage IV disease.[918] Adding cetuximab slightly increased overall survival (11.3 vs. 10.1 months; HR for death, 0.87; 95% CI, 0.762–0.996; *P* = .044). Patients receiving cetuximab had increased grade 4 events versus control (62% vs. 52%, *P* < .01); cetuximab was also associated with grade 2 acne-like rash.

The NCCN NSCLC Panel does not recommend the cetuximab plus cisplatin plus vinorelbine regimen based on the clinical data.[918] The benefits of this cetuximab-based regimen are very slight, it is a difficult regimen to administer, and patients have poorer tolerance for this regimen when compared with other regimens; for example, almost 40% of patients

have grade 4 neutropenia.[714] Patients may also have comorbid conditions that prevent them from receiving cisplatin such as poor kidney function. Cisplatin plus vinorelbine with (or without) cetuximab is generally not used in the United States because of concerns about toxicity.[714,732,918] Although the FLEX trial results were reported to be statistically significant, panel members feel they were not clinically significant.[714] The NCCN NSCLC Panel does not recommend the cisplatin plus vinorelbine or the carboplatin plus vinorelbine regimens for patients with metastatic NSCLC.

Monoclonal Antibody-Drug Conjugates that Inhibit ERBB2 (HER2) Mutations

Ado-Trastuzumab Emtansine

Ado-trastuzumab emtansine (also known as T-DM1) is a humanized antibody-drug conjugate consisting of trastuzumab, which is an antibody (immunoglobulin G1) targeting HER2, and emtansine, which is a microtubule inhibitor.[170] A phase 2 basket trial assessed ado-trastuzumab emtansine in patients with metastatic NSCLC and *ERBB2* (*HER2*) mutations.[170,919] The partial response rate was 44% (95% CI, 22%–69%). The median PFS was 5 months (95% CI, 3–9). Minor toxicities (grade 1–2) included infusion reactions, thrombocytopenia, and transaminitis; no treatment-related deaths were reported. Patients (n = 18) were mostly women (72%), did not smoke cigarettes, and all had adenocarcinoma histology. Another study assessed ado-trastuzumab emtansine in 22 patients with metastatic NSCLC and *ERBB2* (*HER2*) exon 20 mutations.[920] The overall response rate with ado-trastuzumab emtansine was 38% (95% CI, 23%–56%). The median overall survival was 8.1 months.

Fam-Trastuzumab Deruxtecan-nxki

Fam-trastuzumab deruxtecan-nxki is a humanized monoclonal antibody-drug conjugate consisting of trastuzumab linked to deruxtecan, which is a topoisomerase I inhibitor; the agent remains stable until it is cleaved by peptides in cancer cells.[171] DESTINY-Lung01, a phase 2

study, assessed fam-trastuzumab deruxtecan-nxki in 91 patients with metastatic nonsquamous NSCLC and *ERBB2* mutations.[171,921,922] Most patients had *ERBB2* (*HER2*) exon 20 insertion mutations (86%); 66% were women, 57% had never smoked cigarettes, 36% had CNS metastases at baseline, and all had nonsquamous NSCLC. Updated results show that the overall response rate with fam-trastuzumab deruxtecan-nxki was 55% (95% CI, 44%–65%); most patients had received prior treatment.[171] However, responses were also noted in patients who did not have *ERBB2* (*HER2*) mutations. Median overall survival was 17.8 months (95% CI, 13.8–22.1).[171] Grade 3 or higher adverse events occurred in 46% of patients including neutropenia (19%). Two patients died from drug-related interstitial lung disease.

NCCN Recommendations

The NCCN NSCLC Panel recommends fam-trastuzumab deruxtecan-nxki as a subsequent therapy option for patients with metastatic NSCLC and *ERBB2* (*HER2*) mutations based on clinical trial data and FDA approval.[171,921,922] The NCCN NSCLC Panel also recommends ado-trastuzumab emtansine as a subsequent therapy option for patients with *ERBB2* (*HER2*) mutation–positive metastatic NSCLC.[170] The panel preference stratified the recommended regimens for patients with *ERBB2* (*HER2*) mutation–positive metastatic NSCLC and voted that fam-trastuzumab deruxtecan-nxki is a preferred subsequent therapy option; ado-trastuzumab emtansine is an other recommended subsequent therapy option. The NCCN NSCLC Panel does not recommend single-agent therapy with trastuzumab or afatinib for patients with *ERBB2* (*HER2*) mutations, because response rates are lower and treatment is less effective with these agents.[923,924]

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. Testing for these biomarkers can be considered in patients with metastatic squamous cell carcinoma. Previously, *ERBB2 (HER2)* mutations were listed as emerging biomarkers, but they are now included in the standard list because of the FDA approval. Resources are available to assess whether the *ERBB2* (*HER2*) mutations are oncogenic or likely to be oncogenic (see oncoKB.org). The panel recommends first-line therapy with platinum-based chemotherapy with or without immunotherapy for patients with metastatic NSCLC and *ERBB2 (HER2)* mutations. Data suggest that patients with *ERBB2* mutations respond to first-line immunotherapy regimens.[308] The response to immunotherapy ranges from 7% to 27% in patients with *ERBB2* (*HER2*) exon 20 insertion mutations.[186,925]

Oral Agents that Inhibit KRAS Mutations
KRAS is a G-protein with GTPase activity that is part of the MAP/ERK pathway; point mutations in KRAS most commonly occur at codon 12. Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have *KRAS* mutations; *KRAS* is the most common mutation in this population.[121,177,213,309,310] *KRAS* mutation prevalence is associated with cigarette smoking, unlike many of the other actionable mutations (eg, *EGFR* mutations, *ALK* rearrangements).[311] The NCCN NSCLC Panel recommends testing for *KRAS* mutations in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of adagrasib and sotorasib as subsequent therapy options for patients with *KRAS* p.G12C mutation-positive metastatic NSCLC.[317-319] *KRAS* mutation testing can be considered in patients with metastatic squamous cell carcinoma.

Adagrasib
Adagrasib is an oral RAS GTPase family inhibitor that inhibits *KRAS* p.G12C mutations in patients with metastatic NSCLC who have been previously treated with combination chemotherapy regimens (±

immunotherapy). Adagrasib has a long half-life of 23 hours. A phase 2 study assessed adagrasib as subsequent therapy in 116 patients with *KRAS* p.G12C mutation-positive advanced NSCLC who had previously received platinum-based chemotherapy (± immunotherapy).[317] Most patients had metastatic NSCLC (89%); a few had locally advanced NSCLC (11%). Adenocarcinoma was the most common histology (97%). Most patients had previously smoked (86%), although a few currently smoked (9.5%). The median overall survival was 12.6 months (95% CI, 9.2–19.2). The objective response rate was 42.9% (95% CI, 33.5%–52.6%). The intracranial response rate was 33.3% (95% CI, 18.0%–51.8%). Grade 3 or higher adverse events occurred in 44.8% of patients (52/116), including anemia, pneumonia, dyspnea, acute kidney injury, hyponatremia, fatigue, nausea, and increased ALT and AST levels. There were two deaths (one from cardiac failure, one from pulmonary hemorrhage).

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.[317] However, responsiveness to adagrasib has not been assessed for mutations other than *KRAS* G12C. The NCCN Panel clarified that adagrasib may be used as third-line or beyond therapy if the patient has not previously received KRAS p.G12C targeted therapy. Because adagrasib and sotorasib have similar mechanisms of action, switching to sotorasib is not recommended after progression on adagrasib.

Sotorasib
Sotorasib is an oral RAS GTPase family inhibitor that inhibits *KRAS* p.G12C mutations in patients with metastatic NSCLC who have been previously treated with combination chemotherapy regimens (±

immunotherapy). Sotorasib has a half-life of 5 hours. CodeBreaK 200, a randomized phase 3 trial, assessed subsequent therapy with sotorasib versus docetaxel in 345 patients with *KRAS* p.G12C mutation-positive advanced NSCLC who had previously received platinum-based chemotherapy plus immunotherapy.[318] Median PFS was 5.6 months (95% CI, 4.3–7.8) in patients receiving sotorasib compared with 4.5 months (95% CI, 3.0–5.7) in those receiving docetaxel (HR, 0.66; 95% CI, 0.51–0.86; *P* = .0017). A phase 2 study assessed sotorasib as subsequent therapy in 126 patients with *KRAS* p.G12C mutation-positive advanced NSCLC who had previously received platinum-based chemotherapy (± immunotherapy).[319] Adenocarcinoma was the most common histology (95%). Most patients had previously smoked (81%), although a few currently smoked (12%). The median overall survival was 12.5 months (95% CI, 10.0–could not be evaluated). The response rate was 37.1% (95% CI, 28.6%–46.2%). Treatment-related grade 3 adverse events occurred in 19.8% of patients (25/126), including diarrhea, and increased ALT and AST levels; one grade 4 event occurred (dyspnea and pneumonitis).

The NCCN NSCLC Panel recommends sotorasib 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.[319] However, responsiveness to sotorasib has not been assessed for mutations other than *KRAS* G12C. For the 2023 update (Version 1), the NCCN Panel clarified that sotorasib is recommended as third-line or beyond therapy if the patient has not previously received targeted therapy for KRAS p.G12C mutations. Because sotorasib and adagrasib have similar mechanisms of action, switching to adagrasib is not recommended after progression on sotorasib.

Oral TKIs that Inhibit METex14 Skipping Mutations

Oncogenic driver genomic alterations in MET include *MET*ex14 skipping mutations, *MET* GCN gain or amplification, and MET protein overexpression (see *MET Genomic Alterations* in this Discussion). The NCCN Panel recommends testing for *MET*ex14 skipping mutations in eligible patients with metastatic NSCLC based on clinical trial data and FDA approvals for several agents.[172,327,835] Although high-level *MET* amplification is an emerging biomarker in the NCCN Guidelines, the panel feels that optimal biomarker testing will include this biomarker based on clinical trial data.[167-169,172] Note that the definition of high-level *MET* amplification is evolving and may differ depending on which assay is used. When using NGS, a copy number greater than 10 is consistent with high-level *MET* amplification.

Capmatinib

Capmatinib is an oral TKI that selectively inhibits *MET* genomic alterations. Capmatinib has been assessed in phase 1 and 2 studies of patients with advanced NSCLC.[172,326,926,927] 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.[172,326] Updated results from GEOMETRY show that first-line therapy with capmatinib yielded an overall response rate of 68% (95% CI, 48%–84%) in 28 patients with *MET*ex14 skipping mutations; the median PFS was 9.13 months (5.52–13.9 months) for first-line therapy.[172] Subsequent therapy with capmatinib yielded an overall response rate of 41% (95% CI, 29%–53%) in 69 patients with *MET*ex14 skipping mutations; the median PFS was 5.42 months (95% CI, 4.17–6.97 months) for subsequent therapy.[172] Updated results from GEOMETRY suggest that capmatinib is effective for patients with brain metastases.[172,926] Of patients with brain metastases, 54% (7/13) responded to capmatinib; 4 patients had a complete response in the brain. However, 43% (3/7) of patients

whose disease responded had previously received RT.[172] Common adverse events for patients with *MET*ex14 skipping mutations across all cohorts included peripheral edema (65%), nausea (46%), and vomiting (26%), but most of these events were grades 1 to 2.[172] Grade 3 to 4 adverse events occurred in 75% of patients. One treatment-related death occurred. There were fewer adverse gastrointestinal events when capmatinib was administered without fasting.

The NCCN NSCLC Panel recommends capmatinib as either a first-line therapy or subsequent therapy option (preferred) for patients with metastatic NSCLC and *MET*ex14 skipping mutations based on clinical trial data and FDA approval.[172,326,926] Capmatinib may be used as a subsequent therapy option if it, tepotinib, or crizotinib were not previously given as first-line therapy. The panel preference stratified the recommended regimens for patients with *MET*ex14 skipping mutation–positive metastatic NSCLC and decided that capmatinib and tepotinib are preferred first-line therapy or subsequent therapy options. The panel preference stratified crizotinib as useful in certain circumstances for either a first-line therapy or subsequent therapy option.[327] Systemic therapy regimens were preference stratified as useful in certain circumstances as first-line therapy options (eg, carboplatin plus paclitaxel). These platinum doublets may be used as subsequent therapy for patients with disease progression on capmatinib, tepotinib, or crizotinib.

GEOMETRY also assessed capmatinib in patients with metastatic NSCLC and high-level *MET* amplification.[172] For first-line capmatinib, response rates were 40% (95% CI, 16%–68%); for second-line capmatinib, response rates were 29% (95% CI, 19%–41%). Adverse events for patients with high-level *MET* amplification across all cohorts included peripheral edema (49%), vomiting (30%), and nausea (48%); most of these events were grade 1 or 2. Grade 3 to 4 adverse events occurred in 68% of patients. The NCCN Panel recommends capmatinib, crizotinib,

and tepotinib for patients with metastatic NSCLC and high-level *MET* amplification (GCN of ≥10) based on clinical trial data.[167-169,172] As previously mentioned, high-level *MET* amplification is an emerging biomarker in the NCCN Guidelines.

Crizotinib

Crizotinib is an oral TKI that inhibits some MET tyrosine kinases (high-level *MET* amplification or *MET*ex14 skipping mutation), *ALK* rearrangements, and *ROS1* rearrangements; it is approved by the FDA for patients with metastatic NSCLC who have *ALK* or *ROS1* rearrangements. A phase 2 study assessed crizotinib in 69 patients with advanced NSCLC who were positive for *MET*ex14 skipping mutations.[327] The objective response rate was 32% (95% CI, 21%–45%). Median PFS was 7.3 months (95% CI, 5.4–9.1 months).

The NCCN NSCLC Panel recommends crizotinib as a first-line therapy or subsequent therapy option (useful in certain circumstances) for patients with metastatic NSCLC and *MET*ex14 skipping mutations based on these data.[327] Crizotinib may be used as a subsequent therapy option if it, tepotinib, or capmatinib were not previously given as first-line therapy for *MET*ex14 skipping mutation–positive metastatic NSCLC. The panel preference stratified the recommended regimens for patients with *MET*ex14 skipping mutation–positive metastatic NSCLC and decided that capmatinib and tepotinib are preferred first-line therapy or subsequent therapy options based on clinical trial data.[326] The panel decided that crizotinib is useful in certain circumstances as either a first-line therapy or subsequent therapy option.[327] Systemic therapy regimens are also recommended as useful in certain circumstances for first-line therapy (eg, carboplatin plus paclitaxel). These platinum doublets may be used as subsequent therapy options for patients with disease progression on capmatinib, tepotinib, or crizotinib. The NCCN Panel also recommends capmatinib, crizotinib, and tepotinib for patients with metastatic NSCLC

who are positive for high-level *MET* amplification (GCN of ≥10) based on clinical trial data.[167-169,172]

Tepotinib

Tepotinib is an oral TKI that selectively inhibits *MET*ex14 skipping mutations and high-level *MET* amplification (see *MET Genomic Alterations* in this Discussion). 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.[169,835,928] The response rate to tepotinib was 46% (95% CI, 36%–57%); PFS was 8.5 months (95% CI, 6.7–11) in the combined biopsy group (tissue biopsy plus plasma ctDNA). Grade 3 or higher adverse events occurred in 28% of patients receiving tepotinib, such as peripheral edema (7%); 11% of patients had to permanently discontinue tepotinib because of peripheral edema, pleural effusion, or dyspnea. One treatment-related death occurred. Another cohort of the VISION trial assessed tepotinib in 24 patients with advanced NSCLC and *MET* amplification but without *MET*ex14 skipping mutations.[169] Preliminary data suggest the overall response rate is about 42% (10/24).

The NCCN NSCLC Panel recommends tepotinib as either a first-line or subsequent therapy option (preferred) for eligible patients with metastatic NSCLC who are positive for *MET*ex14 skipping mutations based on clinical trial data and FDA approval.[835] Tepotinib may be used as a subsequent therapy option for *MET*ex14 skipping mutation–positive metastatic NSCLC if tepotinib, capmatinib, or crizotinib were not previously given as first-line therapy. The NCCN NSCLC Panel preference stratified the recommended regimens for patients with *MET*ex14 skipping mutation–positive metastatic NSCLC and decided that tepotinib and capmatinib are preferred first-line therapy or subsequent therapy options based on clinical trial data.[172,835] The NCCN NSCLC Panel recommends tepotinib for patients with advanced NSCLC and high-level *MET* amplification based on

preliminary data; capmatinib and crizotinib are also recommended options in this setting.[167-169,172] As previously mentioned, high-level *MET* amplification is an emerging biomarker in the NCCN Guidelines.

Oral TKIs that Inhibit NTRK1/2/3 Gene Fusions

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 (see *NTRK1/2/3 Gene Fusions* in this Discussion).[330] The NCCN Panel recommends testing for *NTRK1/2/3* gene fusions in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on clinical trial data. *NTRK1/2/3* gene fusion testing can be considered in patients with metastatic squamous cell carcinoma.

Entrectinib

Entrectinib is an oral TKI that inhibits *TRK* fusion proteins across a range of solid tumors in younger and older patients with unresectable or metastatic disease; thus, entrectinib is an age- and tumor-agnostic therapy. Entrectinib has been assessed in several phase 1 and 2 trials in patients with *NTRK* gene fusion–positive metastatic NSCLC (phase 2 STARTRK-2 trial, phase 1 STARTRK-1 trial, and phase 1 ALKA-372-001 trial).[333,350,929] Pooled data from these 3 trials in 10 patients with *NTRK* gene fusion–positive NSCLC showed that entrectinib yielded an overall response rate of 70% (95% CI, 35%–93%; 7/10: 7/7 adenocarcinoma NSCLC, 0/3 squamous cell carcinoma, unclassified, or undifferentiated NSCLC); there was one complete response.[333] Most patients (70%) with *NTRK* gene fusion–positive NSCLC had received one or more lines of previous therapy. In 6 patients with CNS disease, entrectinib yielded an intracranial response rate of 67% (4/6; 2 complete responses and 2 partial responses). Grade 3 adverse events with entrectinib across a range of solid tumors included anemia and increased weight. Grade 4 adverse events occurred in 3 patients (ie, increased AST, increased ALT, blood uric acid, hyperuricemia). Nervous system disorders were the most

common serious treatment-related adverse event (4% [3/68] and 3% [10/355]). No treatment-related deaths were reported.

The NCCN NSCLC Panel recommends entrectinib as either a first-line or subsequent therapy option for *NTRK1/2/3* gene fusion–positive metastatic NSCLC based on these data.[333] Entrectinib may be used as a subsequent therapy option if larotrectinib or entrectinib were not previously given as first-line therapy. The NCCN NSCLC Panel has preference stratified the recommended regimens for patients with *NTRK1/2/3* gene fusion–positive metastatic NSCLC and decided that entrectinib and larotrectinib are preferred first-line therapy options. Systemic therapy regimens are also recommended (useful in certain circumstances) for patients with *NTRK1/2/3* gene fusions; the same initial systemic regimens used for patients with metastatic NSCLC may be used (eg, carboplatin plus paclitaxel).

Larotrectinib

Larotrectinib is an oral TKI that inhibits *TRK* fusion proteins across a diverse range of solid tumors in younger and older patients with unresectable or metastatic disease; thus, larotrectinib is an age- and tumor-agnostic therapy.[330] A study in 55 patients with *NTRK* gene fusion–positive disease across a range of solid tumors showed that larotrectinib yielded an overall response rate of 75% (95% CI, 61%–85%).[330] An updated analysis showed that 90% of patients were still alive after 1 year, 18% of patients had a complete response, 69% of patients were still responding, and 58% of patients did not have disease progression.[834] An additional 35 patients with *NTRK* gene fusion–positive disease had an overall response rate of 74%.[834] Fewer than 3% of patients had adverse events of grade 3 to 4. A combined analysis of pediatric and adult patients reported an overall response rate of 79% (95% CI, 72%–85%).

The NCCN NSCLC Panel recommends larotrectinib as either a first-line or subsequent therapy option for patients with *NTRK1/2/3* gene fusion–

positive metastatic NSCLC based on these data.[330,834] Larotrectinib may be used as a subsequent therapy option for patients with *NTRK1/2/3* gene fusion–positive metastatic NSCLC if larotrectinib or entrectinib were not previously given as first-line therapy. The panel has preference stratified the systemic therapy options for patients with *NTRK1/2/3* gene fusion–positive metastatic NSCLC and decided that larotrectinib and entrectinib are preferred first-line therapy options. Other systemic therapy regimens (eg, carboplatin plus paclitaxel) are also recommended as either first-line or subsequent therapy options and categorized as useful in certain circumstances.

Oral TKIs that Inhibit RET *Rearrangements*

Previously, the panel deleted vandetanib as an option for *RET* rearrangement–positive metastatic NSCLC because there are better therapy options.[343,344]

Cabozantinib

Cabozantinib is an oral TKI that inhibits *RET* rearrangements but also inhibits other kinases. A phase 2 study assessed cabozantinib in 26 patients.[341,342,930] The overall response rate was 28% (95% CI, 12%–49%). Many patients (19 [73%]) needed dose reductions because of adverse events. The most common grade 3 adverse events included lipase elevation (4 patients [15%]), increased ALT (2 [8%]), decreased platelet count (2 [8%]), and hypophosphatemia (2 [8%]). The NCCN NSCLC Panel recommends cabozantinib as a first-line or subsequent therapy option (useful in certain circumstances) for *RET* rearrangement–positive metastatic NSCLC based on these data.[341,342] Cabozantinib may be used as a subsequent therapy option if pralsetinib, selpercatinib, or cabozantinib were not previously given as first-line therapy for *RET* rearrangement–positive metastatic NSCLC.

Pralsetinib

Pralsetinib is an oral TKI that selectively inhibits *RET* rearrangements. ARROW, a phase 1/2 study, assessed pralsetinib in patients with metastatic NSCLC and *RET* rearrangements.[339] First-line therapy with pralsetinib yielded an overall response rate of 70% (19/27; 95% CI, 50%–86%); 3 patients (11%) had a complete response. Second-line therapy with pralsetinib yielded an overall response rate of 61% (53/87; 95% CI, 50%–71%); 5 patients (6%) had a complete response. Nine patients had measurable brain metastases, and 56% of them responded to pralsetinib; 3 patients had an intracranial complete response. Grade 3 or more adverse events with pralsetinib include anemia (10%), neutropenia (18%), and hypertension (11%). Common adverse events with pralsetinib included increased AST levels (31%), increased ALT levels (21%), anemia (22%), hypertension (20%), constipation (21%), and neutropenia (19%). Only 4% of patients (5/132) had to stop taking pralsetinib because of side effects. No treatment-related deaths were reported. The NCCN NSCLC Panel recommends pralsetinib as a first-line or subsequent therapy option (preferred) for patients with metastatic NSCLC who are positive for *RET* rearrangements based on clinical trial data and FDA approval.[339] Pralsetinib may be used as a subsequent therapy option for patients with *RET* rearrangement–positive metastatic NSCLC if pralsetinib, selpercatinib, or cabozantinib were not previously given as first-line therapy.

Selpercatinib
Selpercatinib is an oral TKI that selectively inhibits *RET* rearrangements. Libretto-001, a phase 1/2 study, assessed selpercatinib in patients with NSCLC and *RET* rearrangements.[340,931] Updated results from Libretto-001 show that first-line therapy with selpercatinib yielded an overall response rate of 85% (33/39; 95% CI, 70%–94%).[340] Second-line therapy with selpercatinib yielded an overall response rate of 64% (67/105; 95% CI, 54%–73%); the median PFS was 18.4 months (95% CI, 16.4–24.8). Of patients with brain metastases, 91% (10/11) responded to selpercatinib.

Common grade 3 or more adverse events with selpercatinib included hypertension (14%), increased liver enzyme levels (12%), hyponatremia (6%), and lymphopenia (6%). Only 2% of patients (12/531) had to stop taking selpercatinib because of side effects.

The NCCN NSCLC Panel recommends selpercatinib as a first-line or subsequent therapy option (preferred) for patients with metastatic NSCLC who are positive for *RET* rearrangements based on clinical trial data and FDA approval.[926,931] Selpercatinib may be used as a subsequent therapy option for patients with for *RET* rearrangement–positive metastatic NSCLC if selpercatinib, pralsetinib, or cabozantinib were not previously given as first-line therapy.

Preference Stratification
The NCCN NSCLC Panel preference stratified the recommended regimens for *RET* rearrangement–positive metastatic NSCLC and decided that selpercatinib and pralsetinib are preferred first-line or subsequent therapy options based on clinical trial data.[339,340] The panel decided that cabozantinib is useful in certain circumstances.[341,342,930] Selpercatinib, pralsetinib, or cabozantinib may be used as subsequent therapy options if they were not previously given as first-line therapy for *RET* rearrangement–positive metastatic NSCLC. Systemic therapy regimens (other recommended regimens) are also recommended as first-line therapy options for patients with metastatic NSCLC who are positive for *RET* rearrangements; these systemic regimens include platinum doublets (eg, carboplatin plus paclitaxel). These platinum doublets may be used as subsequent therapy options for patients with disease progression on pralsetinib, selpercatinib, or cabozantinib.

Oral TKIs that Inhibit ROS1 Rearrangements
Although ROS1 is a distinct receptor tyrosine kinase, it is very similar to ALK and members of the insulin receptor family.[345,346] It is estimated that

ROS1 gene rearrangements occur in about 1% to 2% of patients with NSCLC.[346-349] The NCCN Panel recommends testing for *ROS1* rearrangements in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on clinical trial data and FDA approvals of several agents.[330,332,350,357,834,929] *ROS1* rearrangement testing can be considered in patients with metastatic squamous cell carcinoma. The panel recommends four agents for patients with *ROS1*-positive metastatic NSCLC—ceritinib, crizotinib, entrectinib, and lorlatinib—based on clinical trial data and FDA approvals, which are described in the following sections.

Ceritinib

Ceritinib is a second-generation oral TKI that inhibits *ALK* and *ROS1* rearrangements.[848] A phase 2 trial assessed ceritinib as first-line therapy in patients (n = 28 evaluable) with NSCLC and *ROS1* rearrangements.[848] One complete response and 19 partial responses (overall response rate, 62% [95% CI, 45%–77%]) were reported in patients receiving ceritinib. PFS was 19.3 months (95% CI, 1–37) for crizotinib-naïve patients and 9.3 months (95% CI, 0–22) for all patients. The median overall survival was 24 months (95% CI, 5–43).

The NCCN NSCLC Panel recommends ceritinib as a first-line therapy option for patients with *ROS1*-positive metastatic NSCLC based on clinical trial data.[848] Ceritinib is an option if a *ROS1* rearrangement is discovered before giving, or during, first-line systemic therapy (eg, carboplatin plus paclitaxel). The NCCN NSCLC Panel has preference stratified the first-line therapy options for patients with *ROS1*-positive metastatic NSCLC. The panel decided 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. Ceritinib is an "other recommended" option for patients with *ROS1*-positive metastatic NSCLC. Lorlatinib is

recommended as a subsequent therapy option in certain patients with *ROS1*-positive metastatic NSCLC whose disease becomes resistant to ceritinib, crizotinib, or entrectinib.[358] However, entrectinib is recommended as a subsequent therapy option for patients with CNS progression after crizotinib or ceritinib.

Crizotinib

Crizotinib is a first-generation oral TKI that inhibits *ALK* rearrangements, *ROS1* rearrangements, and some *MET* tyrosine kinases (high-level *MET* amplification or *MET*ex14 skipping mutation).[192,221,320,851-855] Crizotinib is very effective for patients with *ROS1* rearrangements with response rates of about 70% to 80% including complete responses.[192,346,351,932,933] A phase 2 trial assessed crizotinib in 127 East Asian patients with *ROS1*-positive advanced NSCLC who had received 3 or fewer lines of therapy. The overall response rate was 72% (95% CI, 63%–79%) with 17 complete responses; the median duration of response was 19.7 months (95% CI, 14.1–not reached). The median PFS was 15.9 months (95% CI, 12.9–24.0).[933]

PROFILE 1001, a phase 2 study, assessed crizotinib in 50 patients with advanced NSCLC and *ROS1* rearrangements.[346] Crizotinib yielded an objective response rate of 72% (95% CI, 58%–84%); there were 3 complete responses and 33 partial responses.[346] The median duration of response was 17.6 months (95% CI, 14.5–not reached), and the median PFS was 19.2 months (95% CI, 14.4–not reached). Updated results from PROFILE 1001 reported an overall response rate of 72% (95% CI, 58%–83%) with crizotinib including 6 confirmed complete responses in 53 patients with *ROS1*-positive advanced NSCLC.[25] The median overall survival was 51.4 months (95% CI, 29.3–not reached). No grade 4 or higher treatment-related adverse events were reported.

The EUCROSS study reported that crizotinib yielded an overall response rate of 70% (21/30; 95% CI, 51%–85%) in 30 patients with *ROS1*-positive advanced NSCLC.[932] Adverse events related to treatment occurred in 97% (33/34) of patients. A retrospective European study in patients (n = 30 evaluable) with stage IV NSCLC and *ROS1* rearrangements also assessed crizotinib.[192] There were 5 complete responses (overall response rate, 80%; disease control rate, 86.7%). The median PFS was 9.1 months. Many patients (n = 26) received pemetrexed (either alone or in combination with platinum and either before or after crizotinib) and had a response rate of 57.7% and a median PFS of 7.2 months.

The NCCN NSCLC Panel recommends *ROS1* testing in certain patients with metastatic NSCLC based on data showing the efficacy of several agents for patients with *ROS1* rearrangements and on FDA approvals (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC).[192,346,351] The panel recommends crizotinib as a first-line treatment option for patients with *ROS1*-positive metastatic NSCLC based on clinical trial data and FDA approval.[25,346,932,933] Crizotinib is a preferred option if a *ROS1* rearrangement is discovered before giving, or during, first-line systemic therapy (eg, carboplatin plus paclitaxel). The NCCN NSCLC Panel decided that crizotinib and entrectinib are preferred agents for first-line therapy in patients with *ROS1*-positive metastatic NSCLC, compared with ceritinib, because they are better tolerated, have been assessed in more patients, and are approved by the FDA. Lorlatinib is recommended as a subsequent therapy option in patients with *ROS1*-positive metastatic NSCLC whose disease becomes resistant to crizotinib, ceritinib, or entrectinib.[358] However, entrectinib is recommended as a subsequent therapy option for patients with CNS progression after crizotinib or ceritinib.[359]

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Entrectinib

Entrectinib is an oral TKI that inhibits several tyrosine kinases including *ROS1* and *TRK* (see *ROS1 Rearrangements* and *NTRK1/2/3 Gene Rearrangements* in this Discussion).[332,934] 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).[350,929] Pooled data from these 3 trials in 53 patients with *ROS1*-positive metastatic NSCLC receiving first-line entrectinib showed an overall response rate of 77% (41/53; 95% CI, 64%–88%; 3 complete responses).[350,359] The intracranial overall response rate was 55% (95% CI, 32%–77%; 4 complete responses, 7 partial responses).[350,929] In the larger *ROS1* population (n = 134), grade 3 to 4 adverse events were seen in 34% of patients. Fifteen patients had serious adverse events such

as nervous system disorders (4 patients [3%]) and cardiac disorders (3 patients [2%]). No treatment-related deaths were reported. Although entrectinib has better CNS penetration than crizotinib, it is more toxic.[359]

The NCCN NSCLC Panel recommends entrectinib as a first-line therapy option (preferred) for patients with *ROS1*-positive metastatic NSCLC based on these data and FDA approval.[332,350,357,929] Entrectinib is recommended as a subsequent therapy option for patients with *ROS1*-positive metastatic NSCLC and disease progression with brain metastases on crizotinib or ceritinib.[359] Subsequent therapy with lorlatinib is also recommended for select patients with *ROS1*-positive metastatic NSCLC and disease progression after treatment with crizotinib, ceritinib, or entrectinib. The panel has preference stratified the recommended regimens for patients with *ROS1*-positive metastatic NSCLC and decided that entrectinib and crizotinib are preferred first-line therapy options; ceritinib is stratified as an "other recommended" option.

Lorlatinib

Lorlatinib is an oral third-generation TKI that targets *ALK* and *ROS1* tyrosine kinases and has good CNS penetration; it inhibits a broad range of *ALK* resistance mutations that develop after treatment with first- and second-generation ALK inhibitors.[358,831-833] A phase 1 to 2 trial assessed lorlatinib in patients with *ROS1*-positive metastatic NSCLC.[358] Many patients (58% [40/69]) had previously received crizotinib; some patients were TKI naïve (30% [21/69]). Objective responses were achieved in 35% (14/40) of patients who had previously received crizotinib and 62% (13/21) of TKI-naïve patients. An intracranial response was observed in 50% (12/24) of patients who had previously received crizotinib and 64% (7/11) of TKI-naïve patients. Serious treatment-related adverse events occurred in 7% (5/69) of patients; no treatment-related deaths were reported.

The NCCN NSCLC Panel recommends lorlatinib as a subsequent therapy option for select patients with *ROS1*-positive metastatic NSCLC and

disease progression after treatment with ceritinib, crizotinib, or entrectinib, depending on the type of progression.[358] However, entrectinib is recommended as a subsequent therapy option for patients with CNS progression after crizotinib or ceritinib. For the 2023 update (Version 1), the NCCN Panel now recommends lorlatinib as a subsequent therapy option, if not previously given, for patients with *ROS1*-positive metastatic NSCLC and symptomatic brain metastases.[935,936]

Agents that Inhibit VEGF or VEGF Receptors

Bevacizumab
Bevacizumab is a recombinant monoclonal antibody that targets VEGF. ECOG 4599, a phase 3 randomized trial, assessed bevacizumab added to paclitaxel plus carboplatin versus chemotherapy alone in patients with recurrent or advanced nonsquamous NSCLC (stage IIIB–IV).[806] In the bevacizumab plus chemotherapy group, median survival was 12.3 months versus 10.3 months with chemotherapy alone (HR for death, 0.79; P=.003). Clinically significant bleeding occurred more often with bevacizumab plus chemotherapy versus chemotherapy alone (4.4% vs. 0.7%, respectively; $P < .001$). Fifteen treatment-related deaths were reported with bevacizumab plus chemotherapy.

Bevacizumab may be added to the following regimens: carboplatin plus paclitaxel (category 1), carboplatin plus pemetrexed, or cisplatin plus pemetrexed. The NCCN NSCLC Panel has preference stratified the systemic therapy regimens and decided that these specific bevacizumab plus chemotherapy options are "useful in certain circumstances" for eligible patients with metastatic NSCLC.[806,937] These bevacizumab plus chemotherapy regimens are first-line therapy options for patients with PS 0 to 1, nonsquamous NSCLC or NSCLC NOS, negative test results for actionable driver mutations, PD-L1 expression less than 1%, and/or contraindications to PD-1 or PD-L1 inhibitors. Bevacizumab plus chemotherapy regimens 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. Bevacizumab in combination with a PD-L1 inhibitor plus chemotherapy (eg, ABCP) is a first-line therapy option (category 1, other recommended) regardless of PD-L1 expression for patients with PS 0 to 1, nonsquamous NSCLC or NSCLC NOS, negative test results for actionable driver mutations, and no contraindications to PD-1 or PD-L1 inhibitors or bevacizumab (see *Immune Checkpoint Inhibitors* in this Discussion). 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.

To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: nonsquamous NSCLC and no recent history of hemoptysis. Any regimen with a high risk for thrombocytopenia—and, therefore, possible bleeding—should be used with caution when combined with bevacizumab. Bevacizumab is not recommended for patients with squamous cell NSCLC. The NCCN NSCLC Panel recommends that bevacizumab biosimilars may be used in any of the recommended regimens containing bevacizumab that are used for eligible patients with metastatic NSCLC.[896-900]

NEJ026, a phase 3 randomized trial, compared first-line bevacizumab plus erlotinib versus erlotinib alone in 228 patients with *EGFR*-positive advanced nonsquamous NSCLC.[892,893] At interim analysis, PFS was 16.9 months (95% CI, 14.2–21.0) for erlotinib plus bevacizumab versus 13.3 months (95% CI, 11.1–15.3) for erlotinib alone (HR, 0.605; 95% CI, 0.417–

0.877; *P* = .016).[893] Grade 3 or worse events occurred in 88% (98/112) of patients receiving erlotinib/bevacizumab versus 46% (53/114) of those receiving erlotinib alone. Grade 4 adverse events occurred in 8% (9/112) of patients receiving erlotinib plus bevacizumab (including neutropenia, hepatic dysfunction) versus 4% (5/114) of patients receiving erlotinib alone (hepatic dysfunction). No treatment-related deaths were reported.[892,893] Updated data show that median overall survival was 50.7 months (95% CI, 37.3–not estimable) in those receiving erlotinib plus bevacizumab versus 46.2 months (95% CI, 38.2–not estimable) in those receiving erlotinib alone (HR, 1.007; 95% CI, 0.681–1.490; *P* = .97).[892] The NCCN NSCLC Panel recommends erlotinib plus bevacizumab as a first-line therapy option for eligible patients with metastatic nonsquamous NSCLC, *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations, and no contraindications to bevacizumab (other recommended) based on clinical trial data.[892,893] The panel recommends osimertinib as a preferred first-line therapy option for patients with *EGFR* positive metastatic NSCLC.

Ramucirumab
Ramucirumab is a recombinant monoclonal antibody that targets VEGF receptors.

First-Line Therapy
RELAY, a phase 3 randomized trial, compared first-line therapy with ramucirumab plus erlotinib versus erlotinib alone in patients with advanced NSCLC and the common *EGFR* mutations.[891] PFS was 19.4 months (95% CI, 15.4–21.6) with ramucirumab plus erlotinib versus 12.4 months (95% CI, 11.0–13.5) with erlotinib alone (HR, 0.59; 95% CI, 0.46–0.76; *P*<.0001). Serious adverse events (grade 3–4) occurred in 72% (159/221) of patients receiving erlotinib plus ramucirumab (including hypertension) versus 54% (121/225) in those receiving erlotinib alone (including increased ALT). One treatment-related death (hemothorax) occurred in a patient receiving erlotinib plus ramucirumab The NCCN NSCLC Panel

recommends erlotinib plus ramucirumab as a first-line therapy option for patients with metastatic NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations (other recommended intervention) based on clinical trial data.[891] The panel recommends osimertinib as a preferred first-line therapy option for patients with *EGFR*-positive metastatic NSCLC.

Subsequent Therapy
REVEL, a phase 3 randomized trial, assessed ramucirumab plus docetaxel versus docetaxel alone in patients with metastatic NSCLC and disease progression.[938] The median overall survival was 10.5 months for ramucirumab plus docetaxel versus 9.1 months for docetaxel alone (HR, 0.86; 95% CI, 0.75–0.98; *P* < .023). More than 70% of patients had grade 3 or higher adverse events in both groups (79% for ramucirumab plus docetaxel vs. 71% for docetaxel alone). Adverse events of special concern with ramucirumab plus docetaxel therapy include risk for severe hemorrhage, grade 3 to 4 gastrointestinal bleeding, gastrointestinal perforation or fistula, impaired wound healing, and poorly controlled hypertension. There were 16 deaths from grade 3 or worse pulmonary hemorrhage and other adverse events in the REVEL trial: there were 8 deaths in the ramucirumab plus docetaxel arm and 8 deaths in the docetaxel alone arm. The NCCN NSCLC Panel recommends ramucirumab plus docetaxel as a subsequent therapy option for patients with metastatic NSCLC, regardless of histology, based on clinical data and FDA approval.[938,939]

Agents that Inhibit High-Level MET Amplifications
High-level *MET* amplifications are designated as emerging biomarkers in the NCCN Guidelines because there is less evidence for using targeted agents for these biomarkers. In addition, the recommended agents have not been FDA approved for these mutations in patients with NSCLC, although they are approved for other cancers. The panel decided that

optimal biomarker testing should include testing for high-level *MET* amplifications in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on clinical trial data.[167-169,172,940,941] Testing for high-level *MET* amplifications can be considered in patients with squamous cell carcinoma. The definition of high-level *MET* amplification is evolving and may differ depending on which assay is used. When using NGS, a copy number greater than 10 is consistent with high-level *MET* amplification.[172]

Capmatinib

Capmatinib is an oral TKI that selectively inhibits *MET* genomic alterations. GEOMETRY assessed capmatinib in patients with metastatic NSCLC and high-level *MET* amplification.[172] For first-line capmatinib, response rates were 40% (95% CI, 16%–68%); for second-line capmatinib, response rates were 29% (95% CI, 19%–41%). Adverse events for patients with high-level *MET* amplification across all cohorts included peripheral edema (49%), vomiting (30%), and nausea (48%); most of these events were grade 1 or 2. Grade 3 to 4 adverse events occurred in 68% of patients. Another trial assessed capmatinib in patients with *MET* alterations. The median overall survival was 21.5 months (95% CI, 20.8–not applicable) for 10 patients with high-level *MET* amplification who received capmatinib.[940]

The NCCN NSCLC Panel recommends capmatinib for patients with advanced NSCLC and high-level *MET* amplification based on clinical trial data; tepotinib and crizotinib are also recommended options in this setting.[167-169,172,941]

Crizotinib

Crizotinib is an oral TKI that inhibits some MET tyrosine kinases (high-level *MET* amplification or *MET*ex14 skipping mutation), *ALK* rearrangements, and *ROS1* rearrangements. A subgroup analysis of

PROFILE 1001 assessed crizotinib in patients with advanced NSCLC and different levels of *MET* amplification; 40% (6/15) of patients responded to crizotinib if they had *MET* amplification with a GCN of 6 or more by NGS.[941] Two of these patients whose disease responded had concurrent *MET*ex14 skipping mutations. The overall response rate to crizotinib was 29% in patients with a GCN of 10 or more. Patients who had concurrent *KRAS, BRAF*, or *EGFR* mutations did not respond to crizotinib. Most patients had adenocarcinoma and had received at least one line of therapy. The median overall survival was 11.4 months (95% CI, 7.2–19.3) in the group with higher *MET* amplification. There was one treatment-related death.

A patient with stage IV moderately differentiated adenocarcinoma had a partial response on first-line therapy with carboplatin plus gemcitabine plus bevacizumab; she received maintenance therapy with bevacizumab.[167] Her tumor was found to have high-level *MET* amplification (MET/CEPT ratio >5.0) and was negative for *ALK* rearrangements. The patient had a rapid and durable response to single-agent therapy with crizotinib (54.8% reduction in aggregate tumor measurement). She had mild, grade 1 side effects including asymptomatic sinus bradycardia and transient visual disturbances.

The NCCN NSCLC Panel recommends crizotinib for patients with advanced NSCLC and high-level *MET* amplification based on clinical trial data; tepotinib and capmatinib are also recommended options in this setting.[167-169,172,941]

Tepotinib

Tepotinib is an oral TKI that selectively inhibits *MET*ex14 skipping mutations and high-level *MET* amplification; it is approved by the FDA for patients with metastatic NSCLC who have *MET*ex14 skipping mutations. Another cohort of the VISION trial assessed tepotinib in 24 patients with advanced NSCLC and *MET* amplification but without *MET*ex14 skipping

mutations.[169] Preliminary data suggest the overall response rate is about 42% (10/24). The NCCN NSCLC Panel recommends tepotinib for patients with advanced NSCLC and high-level *MET* amplification based on preliminary data; capmatinib and crizotinib are also recommended options in this setting.[167-169,172]

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.[360-362] Cemiplimab-rwlc, nivolumab, and pembrolizumab inhibit PD-1 receptors;[363,364,141] atezolizumab and durvalumab inhibit PD-L1.[365,366] 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).[186] 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.[367] 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.[186,373-375,840] 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.[907,908] A few case reports suggest that patients treated with ICIs who have acquired resistance may have transformation to SCLC.[942]

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).[173,377,381] 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.[173]

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.[943] ICIs may also be used in other settings; clinical trial data and appropriate use are described in greater detail elsewhere. For example, 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).[32,751] 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: Trial Data and NCCN Recommendations* in this Discussion).[365]

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.[944]

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.[897] 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.[360,364,840,945,946] 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%.[374] Patients with *ALK*-positive NSCLC and very high PD-L1 expression levels do not respond to pembrolizumab.[186,840] In the trials assessing the efficacy of first-line therapy with pembrolizumab with (or without) chemotherapy, most of the patients were wild type for *EGFR* or *ALK* variants. Maintenance immunotherapy is recommended, if tolerated, until progression for all the subsequent therapy regimens.

ICIs are associated with unique immune-mediated adverse events, such as endocrine disorders, that are not seen with traditional cytotoxic chemotherapy; therefore, health care providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage the adverse events, and educate their patients about possible side effects (see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).[947,948] 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.[949-951]

Atezolizumab

Atezolizumab is a humanized monoclonal immunoglobulin G1 antibody that inhibits PD-L1, which improves antitumor immune response.[366] Immune-mediated adverse events may occur with ICIs, including atezolizumab.[945,952] 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: Trial Data and NCCN Recommendations in this Discussion).[751]

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.[953,954] 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.[953,955] Data suggest that different methods of testing for PD-L1 levels are not equivalent.[370,371] 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 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).[953,955] 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.[953,954] 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.[141,363,944,953]

IMpower150, a phase 3 randomized trial, compared first-line therapy with the ABCP regimen versus bevacizumab plus chemotherapy for patients with metastatic nonsquamous NSCLC.[952] 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).[956] 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.[952] 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, METex14 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 ABCP, that are used for eligible patients with metastatic NSCLC based on clinical data and FDA approvals.[896-900]

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.[957] 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.[957] 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.[945,958] 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.[945,958] 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.[366,945,958] 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.[363] Immune-mediated adverse events may occur with ICIs, including cemiplimab-rwlc.[363] For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered 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.[363] 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.[363] 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.[141,363,944,953]

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.[959] 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.

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.[959] 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.[959]

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.[360,364,141] PD-1 receptors are expressed on activated cytotoxic T cells.[360-362] 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.[960] Immune-mediated adverse events may occur with ICIs, including nivolumab or nivolumab plus ipilimumab.[381] 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.[381]

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).[380] 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.[380] However, updated data from CHECKMATE 227 showed that overall survival was improved with nivolumab plus ipilimumab regardless of TMB or PD-L1 expression levels.[381]

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 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; $P = .007$).[381] 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).[961] 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.[380,381,383] 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).[173] 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.[173]

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.[962] 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).[963] In patients receiving nivolumab plus ipilimumab plus 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.[962,964] 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.[360] 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).[360] 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 squamous cell and disease progression on or after first-line chemotherapy.[364] 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).[364] 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.[965] 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.[20]

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.[360,364,965,966] Testing for PD-L1 is not required for prescribing nivolumab but may provide useful information.[372] 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.[360,364,946,967] 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.[362,968-974] 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.[364,141] 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.[368,369] 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.[368] Unique anti-PD-L1 IHC assays have been developed for each one of the different ICIs currently available.[368,372] The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.[372]

Immune-mediated adverse events may occur with ICIs, including pembrolizumab.[968,970,975] For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered based on the severity of the reaction (see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at www.NCCN.org). Pembrolizumab should also be discontinued for patients with severe or life-threatening pneumonitis 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: Trial Data and NCCN Recommendations* in this Discussion).[32]

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.[12,15,141] 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%).[141] 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).[15] 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%).[12] 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.[944] 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%.[22] 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%.[22]

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).[367] 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 approval.[141,944,976] 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.[141,363,944,953] 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.[944,976] 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.[712] 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.[977] 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

MS-85

clinical trial data and FDA approval.[712,713] 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 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).[978] 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).[979]

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.[978,980] 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.[946] 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; 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.[14]

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.[946,981,982] 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.[983] 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.[983] 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.[984] 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, lymphocytopenia, increased lipase levels, hyponatremia, and thrombocytopenia.[984] 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.[985]

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.[984] 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.[984]

Maintenance Therapy

Maintenance therapy refers to therapy given for patients with advanced NSCLC after 4 to 6 cycles of first-line therapy.[986] 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).[987] 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. 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).[988] Updated results from PARAMOUNT reported that continuation maintenance therapy with pemetrexed also improves overall survival (13.9 vs. 11.0 months).[989] 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.[988-990]

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.[991,992] 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).[991]

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.[991,992] 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.[806,990,993] 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.[896-900] 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).[743,994] 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.[995] The data showed a slight difference in PFS but no difference in overall survival (13 vs. 11 months, respectively; P = .195). The NCCN NSCLC Panel recommends gemcitabine (category 2B) as continuation maintenance therapy regardless of histology in patients with metastatic NSCLC, negative test results for 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.[810,996] 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.[997,998] 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.[998,999]

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.[1000] 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.[743,1001] 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.[1002] Previously, the panel deleted the recommendation for switch maintenance therapy with docetaxel for patients with squamous cell NSCLC because there are better options.[1002,1003]

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).[94-98] 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.[52,1004-1006] 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.[112,1007-1009] 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.[112] 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.[1010] 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.[1011] This strategy resulted in a 16% incidence of positive N2 nodes discovered only at the time of thoracotomy.

For identifying N2 disease, chest CT scans had sensitivity and specificity rates of 69% and 71%, respectively. Using 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.[1012] 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.[1007] 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.[1013] Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported.[1014] 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.[1015] 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%.[1016] Kernstine et al compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.[1017] 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.[1018,1019] When patients with early-stage disease are accurately staged using FDG PET/CT, inappropriate surgery is avoided.[1020]

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.[112,1021,1022] However, FDG PET/CT is even more sensitive and is recommended by the panel.[1020,1023,1024] 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.[112,1025] 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.[1026-1029] 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.[1030] In patients with positive nodes on CT or PET, EBUS-TNBA can be used to clarify the results.[1031,1032] In patients with negative findings on EBUS-TNBA, conventional mediastinoscopy can be done to confirm the results.[1027,1032-1034] 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.[1035] 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).[386,407,410,485,549,1036] 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).[386,553-559] 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 options are organized according to the location of the tumor, such as the superior sulcus, chest wall, proximal airway, or mediastinum.[396] 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.[396,505,507,1037-1039] The overall 5-year survival rate is approximately 40%.[505] 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).[781,1040]

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: Trial Data and NCCN Recommendations* in this Discussion and the NCCN Guidelines for NSCLC).[19,365,786] 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).[19,449,703,786] Additional chemotherapy (ie, consolidation chemotherapy) is an option if patients will not be receiving durvalumab.[534,778] 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.[484,704] Recommended therapy for 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).[1041] 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%.[1042] 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.[1043]

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.[1044,1045] 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.[89,396,1046,1047] 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).[1048,1049] Although criteria have been established for diagnosing multiple lung cancers, no definitive method has been established before treatment.[1049-1052] 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.[1052] Data suggest that

NGS testing may help determine whether separate lung nodules are clonally related.[1053-1055]

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.[1046,1056-1058] 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).[1045,1046] VATS or SABR are reasonable options depending on the number and distribution of the tumors requiring local treatment.[1059] Multiple lung nodules (eg, solid, subsolid nodules) may also be detected on CT scans; some of these nodules can be followed with imaging, whereas others need to be biopsied or excised (see *Incidental Lung Nodules* in this Discussion and the NCCN Guidelines for Lung Cancer Screening, available at www.NCCN.org).[1060]

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).[1061,1062] 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).[449,703,781,786,1063-1065]

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: Trial Data and NCCN Recommendations* in this Discussion and the NCCN Guidelines for NSCLC).[19,365,786] 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.[534,778] 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).[449,703,781,786,1063-1066] 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.[19,365,786] Consolidation chemotherapy is an option for eligible patients.[534,778] However, consolidation chemotherapy is not recommended if patients will be receiving durvalumab.

Limited Metastatic Disease

In general, systemic therapy is recommended for patients with metastatic disease (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).[886] 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).[161] 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.[1067] 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.[1068,1069]

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.[586,1070] 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).[1071,1072]

Neoadjuvant or Adjuvant Therapy

Chemotherapy, Chemoradiation, Immunotherapy, and Targeted Therapy

On the basis of clinical studies,[691-693] 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 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).[739,744,790] 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.[739,1073] These neoadjuvant or adjuvant regimens may also be used for sequential chemoradiation.[745-748]

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.[698,1074-1076] 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.[1075,1076] 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.[1077-1079]

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).[738,1080] 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).[469,738]

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).[751] 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.[32] 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.[749] 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) 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.[734,1081] 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.[734]

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).[452] 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 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.[1082] 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.[452,455] Postoperative RT may be considered for select

patients with negative margins and high-risk N2 disease (see *Chemoradiation: Trial Data and NCCN Recommendations 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.[469,576,1081,1083,1084]

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.[783,1085,1086] Other preferred concurrent chemoradiation regimens include 1) paclitaxel plus carboplatin; and 2) cisplatin plus etoposide;, these regimens may be used regardless of histology.[534,780] 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.[452,455,767] 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.[470,471,703,704,781,784,785]

Surveillance

Because recurrence is common after treatment for NSCLC, surveillance is recommended in the NCCN Guidelines for eligible patients with no 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.[1087-1092] 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.[76] 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).[76] 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).[1090,1091,1093-1096] 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.[1087] 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.[1097] 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.[1098]

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).[6] An SVC stent may be used with either concurrent chemoradiation or RT to treat SVC obstruction. For patients with endobronchial obstruction, relieving airway obstruction may increase survival, especially in patients who are severely compromised, and may improve their quality of life.[1099] 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).[482,581,1100] 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).[609,610,613,656,1101-1104] 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.[479,633-635,1105-1108]

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).[1109] The FDA has approved the use of zoledronic acid and denosumab in patients with bone metastases from solid tumors.[1110,1111] 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.[184,1109,1112-1115]

For patients with recurrent and metastatic disease, the NCCN Guidelines recommend that histologic subtype should be determined before therapy so that the best treatment can be selected (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).[790] Biomarker testing for somatic, disease-associated variants/mutations (ie, oncogenic driver events) is recommended before starting therapy, if feasible, in eligible patients with metastatic NSCLC, because targeted therapy has been shown to decrease tumor burden, decrease symptoms, and dramatically improve the quality of life for patients with specific variants. If molecular testing results are pending and patients require an urgent start to therapy, clinicians can consider holding immunotherapy for one cycle (ie, just use platinum-based chemotherapy regimens). In the NCCN Guidelines, many targeted agents are recommended for first-line therapy in patients with specific actionable mutations such as afatinib, alectinib, brigatinib, capmatinib, ceritinib, crizotinib, dacomitinib (± trametinib), entrectinib, erlotinib, gefitinib, lorlatinib, osimertinib, pralsetinib, selpercatinib, and tepotinib (see *Molecular and Biomarker-Driven Therapy for Advanced or Metastatic Disease* in the algorithm).[886] The number of available targeted agents is increasing. For example, newer agents are now recommended as second-line and beyond (subsequent) therapy options—such as adagrasib, amivantamab, fam-trastuzumab deruxtecan-nxki, mobocertinib, and sotorasib—in patients with specific actionable driver mutations.

Additional targeted therapies for patients with other somatic genomic alterations are also recommended, although there is less evidence for these agents and they have not been FDA approved for lung cancer (see

Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC in the NCCN Guidelines for NSCLC). The following targeted agents are recommended as monotherapy options for patients with metastatic NSCLC and emerging genetic variants: capmatinib, crizotinib, or tepotinib for high-level *MET* amplification; (see *Agents that Inhibit High-Level MET Amplifications* in this Discussion).[169-172,921,922] Certain targeted therapies—such as alectinib, brigatinib, ceritinib, lorlatinib, and osimertinib—are recommended as subsequent therapies (if not previously given) for patients with the indicated somatic genomic alterations whose disease becomes resistant to first-line targeted therapies; other targeted therapies are being investigated for resistance.

Biomarker testing for actionable oncogenic driver mutations is recommended in the NCCN Guidelines based on the improved outcomes associated with use of targeted therapy in eligible patients with metastatic NSCLC (see *Principles of Molecular and Biomarker Analysis* in the NCCN Guidelines for NSCLC and *Predictive and Prognostic Biomarkers* in this Discussion). It is important to note that 1) several different tests may be used to identify the same biomarker, including FDA-approved biomarker tests and validated laboratory tests done in CLIA-approved laboratories; and 2) biomarker testing is rapidly changing and improving. *EGFR* mutation testing (category 1) is recommended in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or NSCLC NOS, because EGFR TKIs are recommended for patients with certain *EGFR* mutations.[121,246,254,258,1116] Testing for *ALK* rearrangements (category 1) is also recommended in patients with nonsquamous NSCLC, because ALK inhibitors are effective for patients with metastatic NSCLC who are positive for *ALK* rearrangements.[185,1117] The NCCN NSCLC Panel also recommends testing for other biomarkers such as *BRAF, ERBB2 (HER2), KRAS, METex14, NTRK1/2/3, RET, ROS1* rearrangements (see *Predictive and Prognostic Biomarkers* in this Discussion). The NCCN NSCLC Panel also recommends upfront PD-L1 expression testing

(category 1) before first-line therapy in patients with metastatic NSCLC to assess whether patients are candidates for ICIs. In 2020, the NCCN Panel deleted TMB as an emerging immune biomarker for patients with metastatic NSCLC based on clinical trial data and other issues (see *TMB* in this Discussion).

Molecular testing is recommended in all patients with metastatic nonsquamous NSCLC and NSCLC NOS. Compared with patients with nonsquamous NSCLC, those with squamous cell carcinoma have fewer actionable mutations (eg, *ALK* rearrangements, the common *EGFR* mutations) when considered as individual mutations. However, the cumulative incidence of targetable molecular alterations in squamous cell carcinoma across all alterations ranges from 2% to 10%; therefore, molecular testing can be considered in these patients, particularly if a diagnosis is based on a small sampling.[139,140,186,187] 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 never smoking status and mixed histology. Treatment recommendations and eligibility criteria for patients with nonsquamous NSCLC, NSCLC NOS, and squamous cell carcinoma are described in the NCCN Guidelines. These recommendations are briefly summarized in the following paragraphs. Data supporting the combination platinum-based chemotherapy options are described in the following sections (see *Trial Data* in this Discussion).

Single-agent targeted therapy is recommended for patients with actionable driver mutations [ie, *ALK* rearrangements, *EGFR* activating mutations, *ERBB2 (HER2)* mutations, *KRAS* p.G12C mutations, *MET*ex14 skipping, *NTRK1/2/3* fusions, *RET* rearrangements, *ROS1* rearrangements], or those with emerging driver mutations (see *Molecular and Biomarker-Driven Therapy for Advanced or Metastatic Disease* and *Emerging Biomarkers to Identify Novel Therapies for Patients with*

Metastatic NSCLC in the NCCN Guidelines for NSCLC). Chemotherapy plus immunotherapy regimens are recommended for patients without targetable somatic genomic alterations (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). Chemotherapy plus immunotherapy regimens—such as pembrolizumab plus carboplatin (or cisplatin) plus pemetrexed—are recommended for patients with metastatic nonsquamous NSCLC and negative test results for actionable driver mutations (also known as wild-type), regardless of PD-L1 expression (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC, the NCCN Drugs & Biologics Compendium [NCCN Compendium®] for NSCLC, and the NCCN Guidelines with Evidence Blocks™ for NSCLC).[790] These immunotherapy plus 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.

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).[886,1118] 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%.[1119] 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.[1120] 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).[1121] Systemic therapy for older patients with advanced NSCLC needs to be carefully selected to avoid adverse reactions.[1122] 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.

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).[739,744,788-790,797,798,818] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.[1123] 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.[800-803,1124]

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.[806,1125] 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).[1119] AVAiL, a phase 3 randomized trial, compared cisplatin plus gemcitabine with (or without) bevacizumab; survival was not increased with the addition of bevacizumab.[1126,1127] 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.[896-900]

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* ≤ .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.[1128]

Number of Cycles of First-Line Systemic Therapy

Data from the PARAMOUNT trial suggest that 4 cycles of platinum-based therapy is not optimal;[988] 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; however, patients have more adverse events.[1129] 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.[807,990]

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.[265,1130-1132] Patients with responsive or stable disease can continue to receive a total of 4 to 6 cycles of systemic therapy.[715,807,1133] 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.[998] 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.[1000] 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.[1000]

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 or erlotinib after initial cytotoxic therapy with cisplatin plus gemcitabine in patients with advanced NSCLC.[743,994] 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).[743,994] A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression in patients with advanced NSCLC.[1002] Many patients in the delayed chemotherapy arm did not receive docetaxel.[1003]

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).[743,806,812,918,988,992,994] Switch maintenance therapy with pemetrexed is a recommended option for patients with nonsquamous NSCLC.[743,994,997,998] The benefits of continuation maintenance therapy with gemcitabine were very slight; therefore, the recommendation is only category 2B.[743] 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.[1003]

Continuation of Targeted Therapy After Progression on Initial Therapy

Patients may continue to derive benefit from EGFR TKIs, ALK inhibitors, or ROS1 inhibitors after disease progression on first-line targeted therapy; discontinuation of these TKIs leads to more rapid progression of disease (symptoms, tumor size, FDG avidity on PET scan) that is termed the *flare phenomenon*.[836-839] This strategy mirrors the experience in other oncogene-addicted cancers.[837] Afatinib, dacomitinib, erlotinib, gefitinib, or osimertinib may be continued after development of acquired resistance in patients with lung adenocarcinoma and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations; local therapy should be considered (eg, SRS to brain metastases or spine, SABR for limited thoracic or other metastatic disease).[661,1071,1072,1134,1135]

Accumulating data suggest how cancers become resistant to EGFR inhibitors.[1136,1137] The most common known mechanism is the acquisition of T790M (which is a secondary mutation in *EGFR*), which renders the kinase resistant to afatinib, dacomitinib, erlotinib, or gefitinib.[1138,1139]

Therefore, if patients are T790M positive, osimertinib is recommended (category 1) and afatinib, dacomitinib, erlotinib, or gefitinib are discontinued. Amplification of the *MET* oncogene is another validated resistance mechanism in patients who become resistant to osimertinib.[1136,1140,1141] Furthermore, data show that when cancers start to progress, which were once sensitive to EGFR inhibitors, discontinuation of the EGFR TKI can lead to a much more accelerated progression of the cancer.[836,838] Thus, continuing EGFR TKIs is beneficial in many patients even after their cancers develop resistance to EGFR TKIs.[1135]

The NCCN NSCLC Panel recommends continuing erlotinib (± bevacizumab or ramucirumab), afatinib, dacomitinib, gefitinib, or osimertinib and considering local therapy in patients with asymptomatic progression; however, treatment varies for patients with symptomatic progression (see the NCCN Guidelines for NSCLC).[1134,1142-1145] Osimertinib is recommended (category 1) for patients with symptomatic brain metastases, T790M positive, and disease progression on erlotinib, gefitinib, dacomitinib, or afatinib.[266] Erlotinib (± bevacizumab or ramucirumab), gefitinib, dacomitinib, or afatinib can be continued for these patients with symptomatic brain metastases who are negative for T790M; additional therapy may be added or substituted (eg, local therapy, systemic therapy). First-line systemic therapy options are recommended for patients with multiple symptomatic lesions who are negative for T790M. Osimertinib is recommended (category 1) as subsequent therapy for patients positive for T790M and disease progression on erlotinib, gefitinib, dacomitinib, or afatinib. After progression on osimertinib, patients with *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations may continue to derive benefit from osimertinib; other options are also recommended [see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion]. After progression on alectinib, brigatinib, crizotinib, or ceritinib, patients with *ALK* rearrangements may continue to derive benefit from these agents; other options are also recommended.

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).[1146-1155] 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.[265,1130,1132,1156-1158] 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.

Response rates to single-agent ICIs vary among patients with different actionable mutations.[186] Data suggest that patients with *EGFR* mutations or *ALK* rearrangements have a low response rate to single-agent ICIs when compared with patients without these mutations (response rate, 3.6% vs. 23%, respectively).[186,840,1159] Therefore, subsequent therapy with atezolizumab, nivolumab, or pembrolizumab is less effective in patients with *EGFR* mutations or *ALK* rearrangements. Patients with *ALK*-positive NSCLC and very high PD-L1 expression do not respond to pembrolizumab.[840] In patients with *MET*ex14 mutation-positive metastatic NSCLC, the response rate is about 16% for single-agent ICIs, even those with high PD-L1 expression.[186,324] Data in the second-line setting suggest

that PD-1/PD-L1 inhibitor monotherapy is less effective in patients with metastatic NSCLC who have *EGFR* exon 19 deletions, *EGFR* exon 21 L858R mutations, or *ALK* rearrangements, regardless of PD-L1 expression.[186,360,945,946,965]

Among patients with *EFGR* exon 19 deletions or *EGFR* exon 21 L858R mutations, no improvement in overall survival has been noted in the phase 3 trials assessing subsequent therapy with atezolizumab, nivolumab, or pembrolizumab compared to docetaxel, but there were not enough patients with these mutations to determine whether there were statistically significant differences.[360,840,946,958] The PD-1 or PD-L1 inhibitors were not worse than chemotherapy and were better tolerated. In the phase 3 trials for atezolizumab, nivolumab, or pembrolizumab versus docetaxel as subsequent therapy for patients with metastatic NSCLC, subset analyses were done in patients with *EGFR* mutations to determine the best subsequent therapy.[360,946,958] The HRs for overall survival do not favor docetaxel over atezolizumab (HR, 1.24; CI, 0.7–2.2), nivolumab (HR, 1.18; CI, 0.69–2.0), or pembrolizumab (HR, 0.88; CI, 0.45–1.7); the CIs for the HRs are wide probably because there were so few patients with *EGFR* mutations. The HRs for PFS do favor docetaxel for patients with *EGFR* mutations when compared with either nivolumab (HR, 1.46; CI, 0.90–2.37) or pembrolizumab (HR, 1.79; CI, 0.94–3.42). But again, the CIs are wide. The evidence is weak for recommending docetaxel, atezolizumab, nivolumab, or pembrolizumab as subsequent therapy options for patients with *EGFR* mutations. A meta-analysis suggests that docetaxel improves overall survival when compared with atezolizumab, nivolumab, or pembrolizumab.[1159]

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).[360,364,945,946,958,965] 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.[360-362]

For patients with *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations and disease progression during or after first-line EGFR TKIs (ie, erlotinib [± bevacizumab or ramucirumab], afatinib, gefitinib, dacomitinib, or osimertinib therapy), recommended subsequent therapy options depend on whether the progression is asymptomatic or symptomatic and include: 1) considering local therapy; 2) continuing erlotinib (± bevacizumab or ramucirumab), afatinib, gefitinib, dacomitinib, or osimertinib; 3) switching to osimertinib if not previously given and T790M positive; or 4) taking a first-line systemic therapy regimen for metastatic NSCLC, such as carboplatin plus paclitaxel.[246,1143-1145] The NCCN NSCLC Panel recommends osimertinib (category 1) as a subsequent therapy option for patients with T790M-positive metastatic NSCLC, brain metastases, and disease progression on afatinib, dacomitinib, erlotinib (± bevacizumab or ramucirumab), or gefitinib.[266,904,914,915] Data suggest that an afatinib plus cetuximab regimen may be useful for patients who have progressed after receiving erlotinib, afatinib, or gefitinib and after chemotherapy.[917] Patients with T790M-positive and T790M-negative tumors had a similar response rate to an afatinib plus cetuximab regimen (32% vs. 25%; *P* = .341). The NCCN NSCLC Panel recommends considering afatinib plus cetuximab as an option for patients with *EGFR* mutations and disease progression after receiving EGFR TKIs—afatinib, dacomitinib, erlotinib (± bevacizumab or ramucirumab), gefitinib, or osimertinib—and after chemotherapy based on these data.

Subsequent therapy is recommended for patients with advanced NSCLC and *EGFR* exon 19 deletions or *EGFR* exon 21 L858R mutations and disease progression during or after first-line therapy with osimertinib.

Recommended subsequent therapy options depend on whether the progression is asymptomatic or symptomatic and include: 1) considering definitive local therapy; 2) continuing osimertinib; or 3) switching to a first-line systemic therapy regimen for metastatic NSCLC (eg, carboplatin plus paclitaxel). There are no data to support using erlotinib (± bevacizumab or ramucirumab), gefitinib, dacomitinib, or afatinib after progression on osimertinib. Doublet chemotherapy options, such as carboplatin plus paclitaxel, are recommended for eligible patients with metastatic NSCLC, genetic variants, and disease progression after first-line targeted therapy.[806] Flare phenomenon may occur in some patients who discontinue ALK, EGFR, METex14, RET, or ROS1 inhibitors. If disease flare occurs, then the appropriate TKIs should be restarted.[836-839] The IMPRESS trial indicated that chemotherapy should be used alone and not be combined with EGFR inhibitors, such as gefitinib, in patients with disease progression on gefitinib.[1160]

For patients with *ALK*–positive metastatic NSCLC and disease progression during or after first-line targeted therapy with alectinib, brigatinib, ceritinib, or lorlatinib, recommended subsequent therapy options depend on whether the progression is asymptomatic or symptomatic and include: 1) considering definitive local therapy (eg, SABR, SRS, surgery); 2) continuing alectinib, brigatinib, ceritinib, or lorlatinib,; 3) switching to lorlatinib for *ALK* G1202R; or 4) switching to a first-line systemic therapy regimen for metastatic NSCLC, such as carboplatin/paclitaxel. The NCCN NSCLC Panel recommends lorlatinib as a subsequent therapy option for select patients with *ALK* G1202R metastatic NSCLC and disease progression after treatment with alectinib, brigatinib, or ceritinib based on clinical trial data.[833] After further progression on subsequent targeted therapy, options include: 1) lorlatinib (if not previously given); or 2) first-line combination chemotherapy options for NSCLC (eg, carboplatin plus paclitaxel) (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).[184,1161] The recommended subsequent

therapy options are slightly different if patients have disease progression after initial targeted therapy with crizotinib.

For patients with *ROS1*-positive metastatic NSCLC and disease progression during or after first-line targeted therapy with ceritinib, crizotinib, or entrectinib, recommended subsequent therapy options depend on whether the progression is asymptomatic or symptomatic and include: 1) considering definitive local therapy (eg, SABR, SRS, surgery); 2) continuing ceritinib, crizotinib, or entrectinib; 3) switching to entrectinib (if previously treated with crizotinib or ceritinib) or lorlatinib (if not previously given); or 4) switching to a first-line systemic therapy regimen for metastatic NSCLC, such as carboplatin plus paclitaxel.

The NCCN NSCLC Panel recommends capmatinib, crizotinib, or tepotinib as subsequent therapy options for select patients with metastatic NSCLC and *MET*ex14 skipping mutations who have not previously received any of these agents (see *Oral TKIs that Inhibit METex14 Skipping Mutations* and *High-Level MET Amplification* in this Discussion). The panel preference stratified the subsequent therapy options for patients with *MET*ex14 skipping mutations and voted that capmatinib or tepotinib are preferred options, whereas crizotinib is useful in certain circumstances.

The NCCN NSCLC Panel recommends pralsetinib, selpercatinib, or cabozantinib as subsequent therapy options for select patients with *RET* rearrangement-positive metastatic NSCLC who have not previously received any of these agents (see *Oral TKIs that Inhibit RET Rearrangements* in this Discussion). The panel preference stratified the subsequent therapy options for patients with *RET*-positive metastatic NSCLC and voted that pralsetinib or selpercatinib are preferred options, whereas cabozantinib is useful in certain circumstances.

The NCCN NSCLC Panel recommends dabrafenib plus trametinib as a subsequent therapy option for select patients with *BRAF* p.V600E-positive

metastatic NSCLC who have not previously received this regimen (see *Oral Agents that Inhibit BRAF Mutations* in this Discussion). Single-agent dabrafenib or vemurafenib are treatment options if the combination of dabrafenib plus trametinib is not tolerated. The panel recommends entrectinib or larotrectinib as subsequent therapy options for select patients with *NTRK1/2/3* fusion-positive metastatic NSCLC who have not previously received any of these agents (see *Oral TKIs that Inhibit NTRK1/2/3 Gene Fusions* in this Discussion). If patients with *BRAF* p.V600E-, *MET*ex14 skipping-, *NTRK1/2/3-, or RET*-positive metastatic NSCLC have disease progression on first-line targeted therapy, then platinum-based doublet therapy options (eg, carboplatin plus paclitaxel) are recommended as subsequent therapy options; note that these platinum-based doublet therapy options are the identical regimens that may be used as first-line combination chemotherapy options for NSCLC, depending on the setting.[806]

Most patients with NSCLC do not have actionable driver mutations [eg, *ALK*, *BRAF* p.V600E, *EGFR, ERBB2 (HER2)*, *KRAS*, *MET*ex14 skipping, *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).[360,364,945,946,958,965]

Data show that overall survival is improved with subsequent therapy with atezolizumab, nivolumab, or pembrolizumab compared with docetaxel.[945,946,965] 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.[938] Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.[1152,1153] When compared with docetaxel, pemetrexed has similar median survival but less toxicity.[1154,1162] Pemetrexed is a recommended subsequent therapy option for eligible patients with metastatic nonsquamous NSCLC.[998] Docetaxel is recommended for patients with wild-type *EGFR* tumors based on two randomized trials comparing erlotinib versus docetaxel.[1163,1164] Patients often have a limited response to subsequent therapy other than ICIs, although chemotherapy may serve a useful palliative role.[1165]

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.[1166] 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).[6,722,723] 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).[1147,1164,1167,1168] 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.[1000] 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 indication by the FDA.[1000] A phase 3 randomized trial compared afatinib with erlotinib as subsequent therapy options for patients with squamous cell NSCLC .[878] 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.[364] 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.[878] 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.[878]

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).[110] 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.[32] 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.[186] 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 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.[162] 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.[317] 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.[935,936]

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.[452,455,767] 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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