NCCN Guidelines® Insights
Non–Small Cell Lung Cancer, Version 5.2018
Featured Updates to the NCCN Guidelines

David S. Ettinger, MD[1,*]; Dara L. Aisner, MD, PhD[2,*]; Douglas E. Wood, MD[3]; Wallace Akerley, MD[4]; Jessica Bauman, MD[5]; Joe Y. Chang, MD, PhD[6]; Lucian R. Chirieac, MD[7]; Thomas A. D'Amico, MD[8]; Thomas J. Dilling, MD, MS[9]; Michael Dobelbower, MD, PhD[10]; Ramaswamy Govindan, MD[11]; Matthew A. Gubens, MD, MS[12]; Mark Hennon, MD[13]; Leora Horn, MD, MSc[14]; Rudy P. Lackner, MD[15]; Michael Lanuti, MD[16]; Ticiana A. Leal, MD[17]; Rogerio Lilenbaum, MD[18]; Jules Lin, MD[19]; Billy W. Loo Jr, MD, PhD[20]; Renato Martins, MD, MPH[3]; Gregory A. Otterson, MD[21]; Sandip P. Patel, MD[22]; Karen Reckamp, MD, MS[23]; Gregory J. Riely, MD, PhD[24]; Steven E. Schild, MD[25]; Theresa A. Shapiro, MD, PhD[1]; James Stevenson, MD[26]; Scott J. Swanson, MD[7]; Kurt Tauer, MD[27]; Stephen C. Yang, MD[1]; Kristina Gregory, RN, MSN, OCN[28,*]; and Miranda Hughes, PhD[28,*]

Abstract

The NCCN Guidelines for Non–Small Cell Lung Cancer (NSCLC) address all aspects of management for NSCLC. These NCCN Guidelines Insights focus on recent updates to the targeted therapy and immunotherapy sections in the NCCN Guidelines. For the 2018 update, a new section on biomarkers was added.

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[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [2]University of Colorado Cancer Center; [3]University of Washington/Seattle Cancer Care Alliance; [4]Huntsman Cancer Institute at the University of Utah; [5]Fox Chase Cancer Center; [6]The University of Texas MD Anderson Cancer Center; [7]Dana-Farber/Brigham and Women's Cancer Center; [8]Duke Cancer Institute; [9]Moffitt Cancer Center; [10]University of Alabama at Birmingham Comprehensive Cancer Center; [11]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [12]UCSF Helen Diller Family Comprehensive Cancer Center; [13]Roswell Park Comprehensive Cancer Center; [14]Vanderbilt-Ingram Cancer Center; [15]Fred & Pamela Buffett Cancer Center; [16]Massachusetts General Hospital Cancer Center; [17]University of Wisconsin Carbone Cancer Center; [18]Yale Cancer Center/Smilow Cancer Hospital; [19]University of Michigan Rogel Cancer Center; [20]Stanford Cancer Institute; [21]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [22]UC San Diego Moores Cancer Center; [23]City of Hope Comprehensive Cancer Center; [24]Memorial Sloan Kettering Cancer Center; [25]Mayo Clinic Cancer Center; [26]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [27]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; and [28]National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

Please Note

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Release date: July 10, 2018; Expiration date: July 10, 2019

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Non–Small Cell Lung Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Non–Small Cell Lung Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:
Kerrin M. Rosenthal, MA; Kimberly Callan, MS; Genevieve Emberger Hartzman, MA; Erin Hesler; Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Karen Kanefield; and Kathy Smith.

Individuals Who Provided Content Development and/or Authorship Assistance:

David S. Ettinger, MD, Panel Chair, has disclosed that he has served as a scientific advisor for AbbVie Inc., BeyondSpring Pharmaceuticals, Inc., Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Eli Lilly and Company, Genentech, Inc., and Guardant Health, Inc.; and that he has received grant/research support from Golden Biotech, Inc.
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Miranda Hughes, PhD, Oncology Scientist/Senior Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

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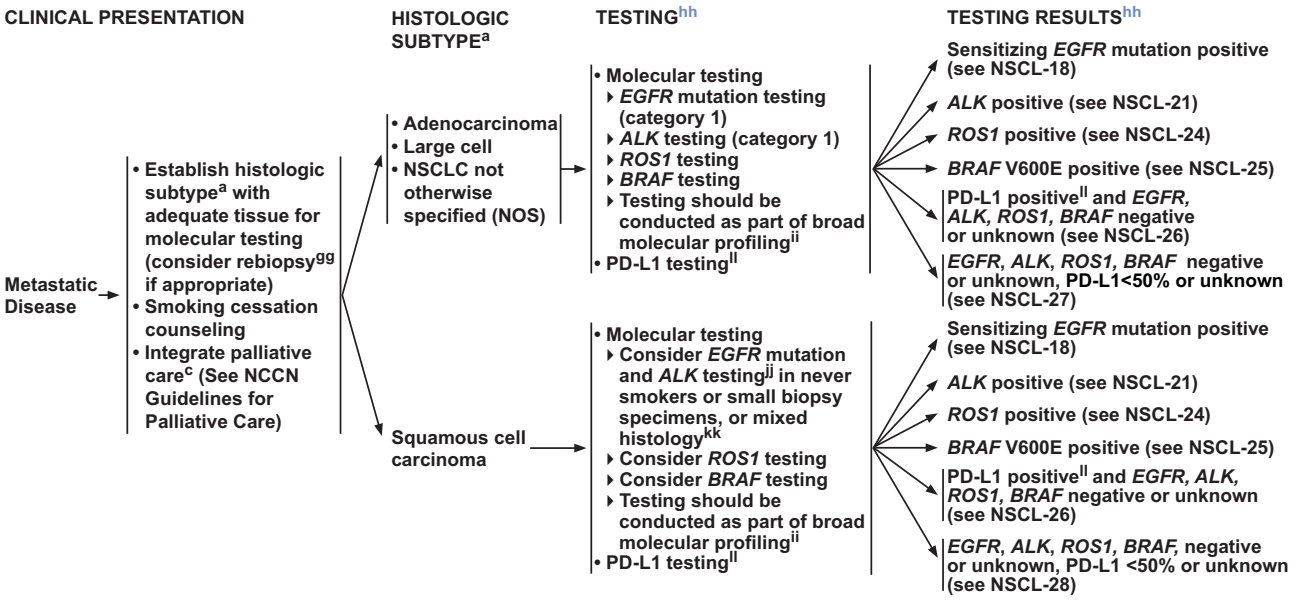


[a]See Principles of Pathologic Review (NSCL-A).
[c]Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.
[gg]If repeat biopsy is not feasible, plasma biopsy should be considered.
[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[ii]The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients with Genetic Alterations (NSCL-H).
[jj]In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIC). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.
[kk]Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.
[ll]PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.

NSCL-17

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 noted.

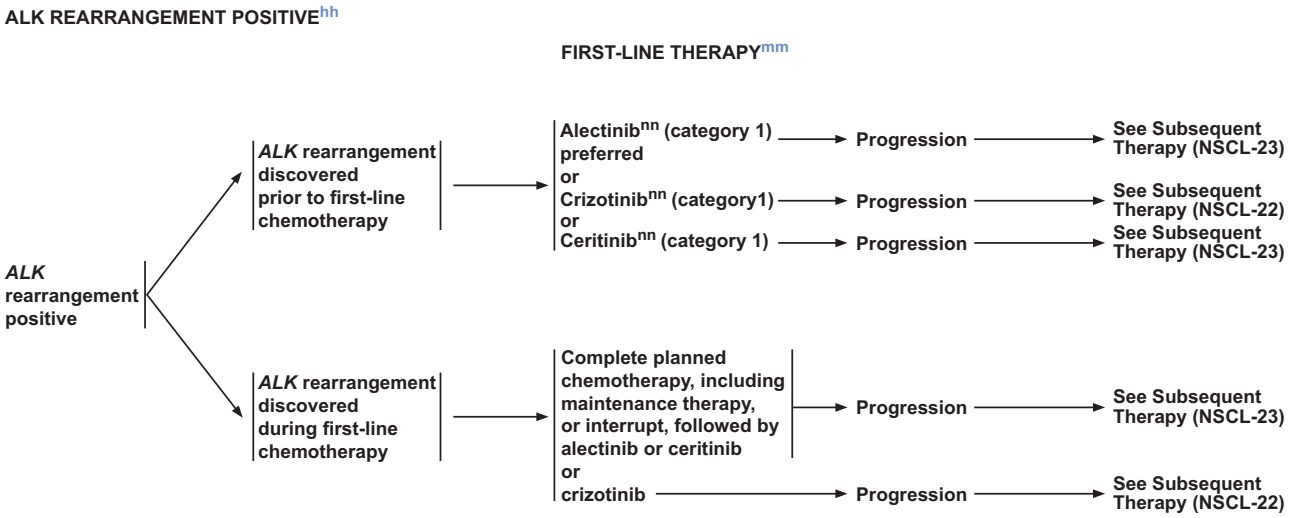
Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Lung cancer is the leading cause of cancer death in the United States.[1] In 2018, an estimated 234,030 new cases of lung and bronchial cancer will be diagnosed and 154,050 deaths will occur.[2,3] However, quality of life and progression-free survival (PFS) have improved for patients with advanced non–small cell lung cancer (NSCLC) who have specific predictive biomarkers and receive targeted therapy or immunotherapy compared with those receiving chemotherapy.[4–9] These NCCN Guidelines Insights focus on recent updates in targeted therapy and immunotherapy for patients with advanced NSCLC. For a list of the 2018 updates, see the complete version of the NCCN Guidelines for NSCLC (available at NCCN.org). The NCCN Guidelines for NSCLC address all aspects of disease management.

Biomarkers

A *predictive* biomarker is correlated with therapeutic efficacy based on the mechanism of action between



[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn]For performance status 0-4.

the therapy and the biomarker. A *prognostic* biomarker is indicative of patient survival independent of treatment received, because the biomarker is an indicator of the innate tumor aggressiveness. For the 2018 update, a new section was added to the NCCN Guidelines that discusses key established biomarkers and appropriate testing methods to identify them (see NSCL-G, pages 815–818).[10]

Key established predictive biomarkers include *ALK* rearrangements, *ROS1* rearrangements, sensitizing *EGFR* mutations, *BRAF* V600E point mutations, and PD-L1 expression levels (see NSCL-G, pages 815–818, and "Established Biomarkers," following section). The NCCN panel recommends testing for these key established biomarkers in patients with advanced NSCLC before initial treatment, because effective targeted therapy or immunotherapy is available. The panel strongly advises broader molecular profiling to assess for emerging biomarkers (see NSCL-17, page 809, and "Emerging Biomarkers," page 816).

Established Biomarkers

ALK Rearrangements: Approximately 5% of patients with NSCLC have *ALK* rearrangements; these patients tend to have adenocarcinoma histology and be never-smokers or light smokers.[11,12] The NCCN panel recommends testing for *ALK* rearrangements (category 1 recommendation) based on the efficacy of alectinib, crizotinib, and ceritinib (see NSCL-17, page 809). Two tests have been FDA-approved for stand-alone testing or rapid prescreening: (1) a fluorescence in situ hybridization (FISH) diagnostic test, and (2) an immunohistochemistry assay.[13–22] Next-generation sequencing (NGS) can be used if the platform has been appropriately designed and validated.[23–27]

Initial ALK-Directed Therapy: Alectinib is an oral tyrosine kinase inhibitor (TKI) that inhibits *ALK* rearrangements.[28] A phase III randomized trial (ALEX) assessed first-line therapy with alectinib versus crizotinib in 303 patients with *ALK*-positive

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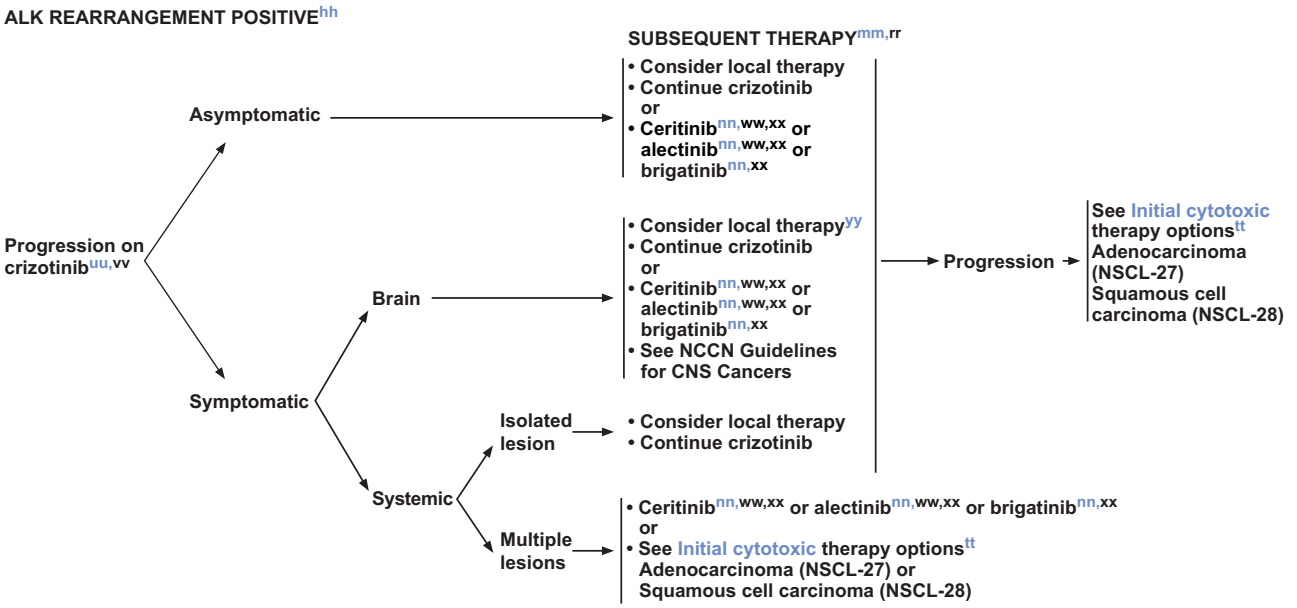


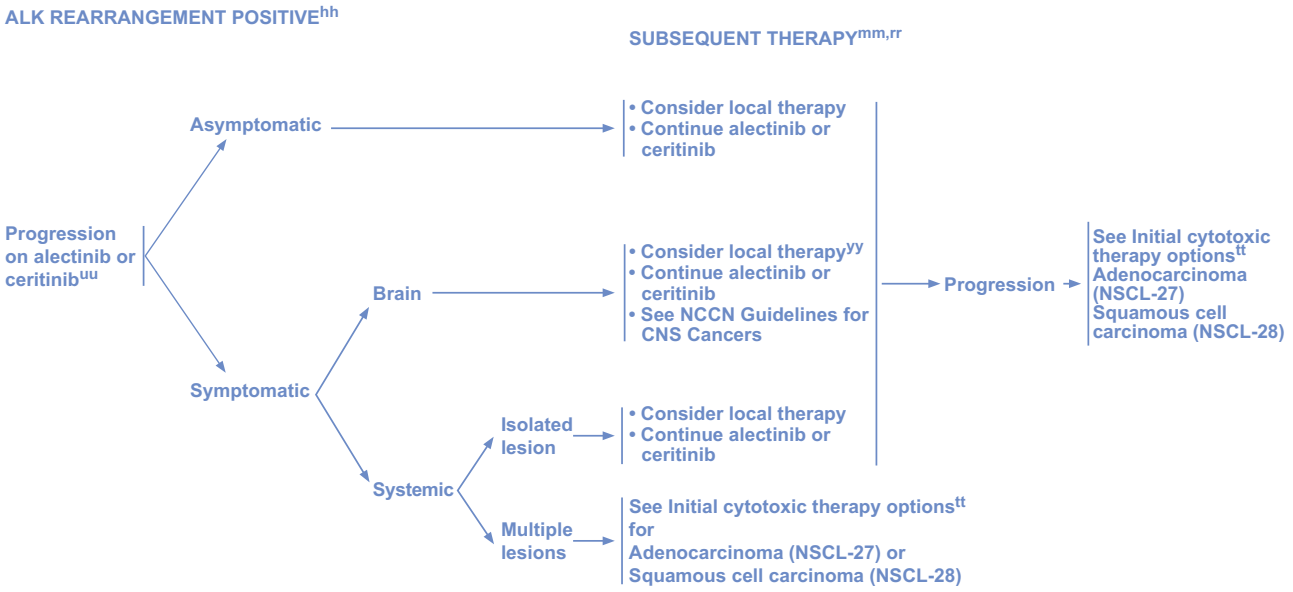
[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn]For performance status 0-4.
[rr]For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.
[tt]The data in the second-line setting suggest that immunotherapy is less effective, irrespective of PD-L1 expression, in tumors with an actionable mutation.
[uu]Beware of flare phenomenon in subset of patients who discontinue ALK inhibitor. If disease flare occurs, restart ALK inhibitor.
[vv]Patients who are intolerant to crizotinib may be switched to ceritinib, alectinib, or brigatinib.
[ww]If not previously given.
[xx]Ceritinib, alectinib, or brigatinib are treatment options for patients with ALK-positive metastatic NSCLC that has progressed on crizotinib.
[yy]If considering WBRT, consider switching ALK inhibitor before using WBRT.

NSCL-22

advanced NSCLC, including those with asymptomatic central nervous system (CNS) disease.[28] Disease progression or death occurred in fewer patients receiving alectinib (41% [62/152]; median follow-up of 18.6 months) compared with crizotinib (68% [102/151]; median follow-up of 17.6 months). The hazard ratio (HR) was 0.47 (95% CI, 0.34–0.65; *P*<.001) for disease progression or death. PFS was significantly increased with alectinib versus crizotinib: the 12-month event-free survival was 68.4% (95% CI, 61.0–75.9) compared with 48.7% (95% CI, 40.4–56.9), respectively. Median PFS was 25.7 months (95% CI, 19.9 months vs not available) for alectinib compared with 10.4 months (95% CI, 7.7–14.6 months) for crizotinib based on updated results. Fewer patients receiving alectinib had CNS progression (12%; 18/152) versus those receiving crizotinib (45%; 68/151), and response rates were 83% (126/152) versus 75% (114/151) (*P*=.09), respectively. Patients receiving alectinib had fewer grade 3 to 5 adverse events (AEs) compared with crizotinib (41% [63/152] vs 50% [75/151], respectively), although patients received alectinib for a longer duration than crizotinib (median, 17.9 vs 10.7 months). Two treatment-related deaths were reported for crizotinib, and none were reported for alectinib.

A phase III randomized trial (J-ALEX) assessed first-line therapy with alectinib versus crizotinib in 207 Japanese patients with *ALK*-positive advanced NSCLC, with results similar to the ALEX trial.[5] The NCCN panel recommends alectinib as a preferred first-line treatment (category 1) for *ALK*-positive metastatic NSCLC based on these clinical trials and FDA approval (see NSCL-21, page 810). Two other ALK inhibitors, crizotinib and ceritinib, are also recommended (category 1 for both) by the panel for first-line therapy in patients with *ALK*-positive NSCLC based on clinical trial data and FDA approvals.[6,29,30]

Subsequent Therapy: Patients typically experience disease progression after initial therapy with



[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[rr]For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.
[tt]The data in the second-line setting suggest that immunotherapy is less effective, irrespective of PD-L1 expression, in tumors with an actionable mutation.
[uu]Beware of flare phenomenon in subset of patients who discontinue ALK inhibitor. If disease flare occurs, restart ALK inhibitor.
[yy]If considering WBRT, consider switching ALK inhibitor before using WBRT.

NSCL-23

alectinib, crizotinib, or ceritinib; second-line or beyond (ie, subsequent) therapy recommendations depend on the mechanism of resistance to therapy (see NSCL-22 and NSCL-23, pages 811 and 812). For patients who experience progression on first-line crizotinib, subsequent therapy for *ALK*-positive NSCLC includes alectinib, ceritinib, or brigatinib; continuing crizotinib is also an option, depending on the type of progression (see NSCL-22, page 811).[31–35] For patients who experience progression on first-line alectinib or ceritinib, recommended subsequent therapy for *ALK*-positive NSCLC includes the initial cytotoxic chemotherapy regimens (eg, carboplatin/pemetrexed for nonsquamous NSCLC) used for first-line treatment in patients without genetic alterations, depending on type of progression (see NSCL-23, above).[36,37] Molecular testing of a biopsy to review the resistance mechanism in this scenario may be beneficial to determine the role of other ALK inhibitors. Continuing alectinib or ceritinib may also be appropriate for some patients who experience progression on alectinib or ceritinib (see NSCL-23, above).[38] In tumors with an actionable mutation, such as *ALK* rearrangements, immunotherapy appears to be less effective (regardless of PD-L1 expression levels) based on data in the second-line setting.[39–42] Ongoing studies are assessing the role of individual *ALK* kinase domain mutations in selecting subsequent therapy.[43,44]

ROS1 Rearrangements: Although ROS1 is a distinct receptor tyrosine kinase, it is very similar to ALK.[45,46] *ROS1* rearrangements occur in approximately 1% to 2% of patients with NSCLC, and occur more frequently in younger women (median age, 50 years) with adenocarcinoma who are never-smokers and in those negative for *EGFR* and *KRAS* mutations and *ALK* rearrangements.[46–49] The NCCN Guidelines Panel recommends *ROS1* testing based on the efficacy of crizotinib and ceritinib (see NSCL-17 and NSCL-24, pages 809 and 813).[46,50,51] Testing for *ROS1* rearrangements may be performed using FISH (see

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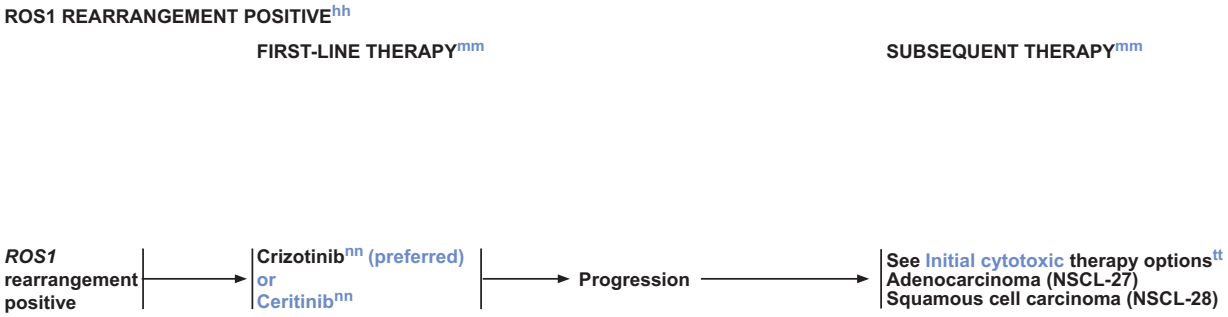


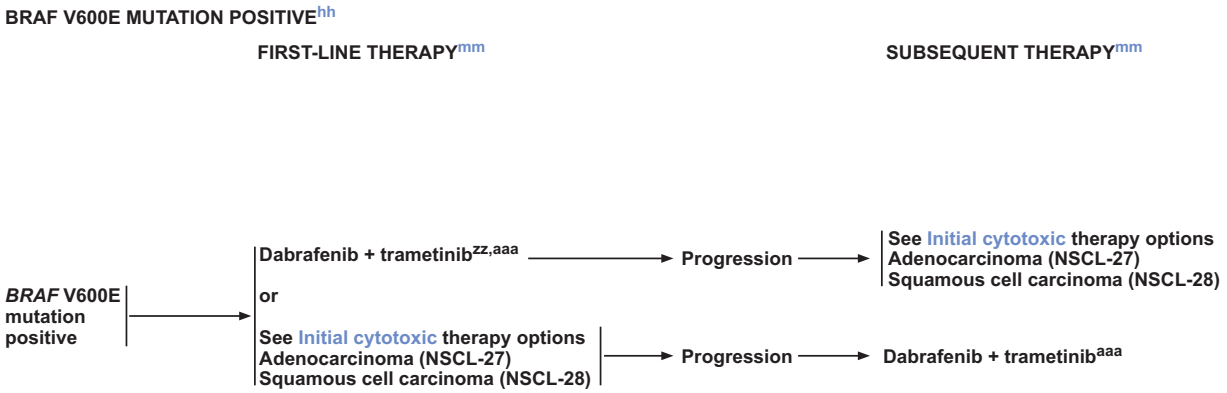
[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn]For performance status 0-4.
[tt]The data in the second-line setting suggest that immunotherapy is less effective, irrespective of PD-L1 expression, in tumors with an actionable mutation.

NSCL-24

NSCL-G, pages 815–818).[13,48,52–54] NGS can also be used if the platform has been appropriately designed and validated.[23–27,46] Immunohistochemistry testing for ROS1 requires confirmation of all positives due to a low specificity of the testing methodology. A single companion diagnostic test has been FDA-approved for *ROS1* rearrangements; however, clinicians may use any appropriately validated test.[51]

First-Line Therapy: Crizotinib inhibits *ROS1* rearrangements and is FDA-approved for patients with locally advanced or metastatic *ROS1*-positive NSCLC.[6,29,50,55–59] Crizotinib is very effective for patients with *ROS1* rearrangements, yielding response rates of approximately 70% to 80%, including complete responses (CRs).[46,50,51] In 50 patients with *ROS1*-positive advanced NSCLC, crizotinib yielded an objective response rate of 72% (95% CI, 58–84), with 3 CRs and 33 partial responses (PRs).[46] The median duration of response was 17.6 months (95% CI, 14.5 months to not reached), and the median PFS was 19.2 months (95% CI, 14.4 months to not reached). Another study assessed crizotinib in 30 patients with *ROS1*-positive stage IV NSCLC.[50] There were 5 CRs (overall response rate [ORR], 80%; disease control rate, 86.7%), and 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. For the 2018 guideline update, the NCCN panel voted that crizotinib is the preferred agent for patients with *ROS1*-positive NSCLC based on trial data and the FDA approval (see NSCL-24, above).

Ceritinib is an oral TKI that inhibits *ROS1* rearrangements.[60] A phase II trial assessed ceritinib as first-line therapy in patients (n=28 evaluable) with *ROS1*-positive NSCLC.[60] One CR and 19 PRs (ORR, 62%; 95% CI, 45%–77%) were reported. PFS was 19.3 months (95% CI, 1–37 months) for crizotinib-naïve patients and 9.3 months (95% CI, 0–22 months) for all patients; median overall sur-



[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[zz]At this point, there are no published data on the progression-free survival (PFS) of patients treated in the first-line setting.
[aaa]Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated.

vival (OS) was 24 months (95% CI, 5–43 months). For the 2018 update, the NCCN panel recommends ceritinib (category 2A) for patients with *ROS1*-positive advanced NSCLC based on this trial, although it is not currently FDA-approved for this indication.

Subsequent Therapy: For patients with *ROS1*-positive NSCLC who progress on first-line crizotinib or ceritinib, the panel recommends the initial cytotoxic chemotherapy regimens (eg, carboplatin/pemetrexed for nonsquamous NSCLC) used for first-line treatment of NSCLC in patients without genetic alterations or a clinical trial (see NSCL-24, page 813). Alectinib and ceritinib are not recommended in patients with *ROS1*-positive NSCLC whose disease becomes resistant to crizotinib, because no trial data suggest that these agents would be effective in this setting.[46] In patients with biomarkers who have progressed on targeted therapy, immunotherapy appears to be less effective (regardless of PD-L1 expression levels).[39–42] Ongoing studies are assessing new agents for patients with *ROS1*-positive NSCLC whose disease becomes resistant to crizotinib.[61–64]

BRAF V600E Mutations: BRAF is a serine/threonine kinase that is part of the MAP/ERK signaling pathway. *BRAF* V600E is the most common of the *BRAF* point mutations, occurring in 1% to 2% of patients with lung adenocarcinoma who are typically current or former smokers.[65–67] *BRAF* mutations typically do not overlap with *EGFR* mutations or *ALK* rearrangements.[65,68] The NCCN panel recommends testing for *BRAF* mutations based on data showing the efficacy of dabrafenib/trametinib (see NSCL-17, page 809).[65,68] Real-time PCR, Sanger sequencing, and NGS are the most commonly used methods to assess for *BRAF* mutations (see NSCL-G, pages 815–818).

Dabrafenib and trametinib inhibit kinases in the RAS/RAF/MEK/ERK pathway.[65,68] Dabrafenib inhibits *BRAF* harboring V600E mutations; trametinib inhibits MEK 1/2, which is downstream of BRAF signaling. A phase II trial assessed first-line

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

Molecular Diagnostic Studies in Non-Small Cell Lung Cancer

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

Continued

combination therapy with dabrafenib/trametinib for 36 patients with metastatic NSCLC and *BRAF* V600E mutations.[69] The ORR was 64% (n=23; 95% CI, 46–79) with 2 CRs, and median PFS was 10.9 months (95% CI, 7.0–16.6 months). Many patients (69%; n=25) had ≥1 grade 3 or 4 AEs. Serious AEs included increased alanine aminotransferase level (14%; n=5), pyrexia (11%; n=4), increased aspartate aminotransferase level (8%; n=3), and decreased ejection fraction (8%; n=3).

A phase II study assessed subsequent therapy with the dabrafenib/trametinib regimen in 57 patients with advanced NSCLC and *BRAF* V600E mutations whose disease had progressed on chemotherapy.[65,70] The response rate was 63% (n=36) with dabrafenib/trametinib; PFS was 9.7 months (95% CI, 6.9–19.6). Serious AEs occurred in 56% of patients (n=32), including pyrexia, anemia, confusional state, hemoptysis, hypercalcemia, and cutaneous squamous cell carcinoma. Common grade 3 to 4 AEs included neutropenia in 9% (n=5), hyponatremia in 7% (n=4), and anemia in 5% (n=3). Four patients died of retroperitoneal hemorrhage, subarachnoid hemorrhage, respiratory distress, or severe disease progression. Preliminary updated data showed that patients receiving dabrafenib/trametinib had a median OS of 18.2 months (95% CI, 14.3 months to not estimable).[71]

Based on these trials and the FDA approval, the NCCN Guidelines Panel recommends first-line or subsequent therapy with dabrafenib/trametinib in patients with metastatic NSCLC and *BRAF* V600E mutations (see NSCL-25, page 814).[69,71,72] First-line or subsequent chemotherapy regimens are also recommended options using the same initial cytotoxic regimens recommended for patients without genetic alterations (eg, carboplatin/pemetrexed for nonsquamous disease). Single-agent therapy with dabrafenib or vemurafenib is also an option for patients with *BRAF* V600E mutations who cannot tolerate combination therapy with dabrafenib/trametinib.[68,71,73]

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- Molecular Targets for Analysis
  - In general, the mutations/alterations described below are seen in a non-overlapping fashion, although between 1%–3% of NSCLC may harbor concurrent alterations.
  - *EGFR* (Epidermal Growth Factor Receptor) Gene Mutations: EGFR is a receptor tyrosine kinase normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies.
    - The most commonly described mutations in *EGFR* (exon 19 deletions, p.L858R point mutation in exon 21) are associated with responsiveness to EGFR tyrosine kinase inhibitor (TKI) therapy; most recent data indicate that tumors that do not harbor a sensitizing *EGFR* mutation should not be treated with EGFR TKI in any line of therapy.
    - Many of the less commonly observed alterations in EGFR, which cumulatively account for ~10% of *EGFR*-mutated NSCLC (ie, exon 19 insertions, p.L861Q, p.G719X, p.S768I) are also associated with responsiveness to EGFR TKI therapy, although the number of studied patients is lower.
    - Some mutations in *EGFR* are associated with lack of responsiveness to EGFR TKI therapy, including most *EGFR* exon 20 insertions, and p.T790M.
      - Most *EGFR* exon 20 insertion mutations predict resistance to clinically achievable levels of TKIs.
      - The exception is a rare *EGFR* exon 20 insertion variant, p.A763_Y764insFQEA, which is associated with responsiveness to EGFR TKI therapy. Therefore, knowledge of an *EGFR* exon 20 insertion must be included in the specific sequence alteration.
      - The finding of p.T790M is most commonly associated with relapse following initial therapy with EGFR TKI, which is a known mechanism of resistance. If identified prior to TKI exposure, genetic counseling should be considered, because germline p.T790M is associated with familial lung cancer predisposition and additional testing is warranted.
    - As use of NGS testing increases, additional *EGFR* variants are increasingly identified; however, the clinical implications of individual alterations are unlikely to be well established.
    - Some clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with the presence of an *EGFR* mutation; however, these features should not be utilized in selecting patients for testing.
    - Testing Methodologies: Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS are the most commonly deployed methodologies for examining *EGFR* mutation status.
  - *ALK* (Anaplastic Lymphoma Kinase) Gene Rearrangements: ALK is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the ALK kinase domain.
    - The most common fusion partner seen with ALK is echinoderm microtubule-associated protein-like 4 (EML4), although a variety of other fusion partners have been identified.
    - The presence of an *ALK* rearrangement is associated with responsiveness to ALK TKIs, with recent studies demonstrating improved efficacy of alectinib over crizotinib in the first-line setting.
    - Some clinicopathologic features—such as smoking status and histology have been associated with the presence of an *ALK* rearrangement; however, these features should not be utilized in selecting patients for testing.
    - Testing Methodologies: FISH break-apart probe methodology was the first methodology deployed widely. IHC can be deployed as an effective screening strategy. FDA-approved IHC (ALK [D5F3] CDx Assay) can be utilized as a stand-alone test, not requiring confirmation by FISH, although secondary confirmation is encouraged. Numerous NGS methodologies can detect *ALK* fusions, and targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners.

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Emerging Biomarkers

The NCCN Guidelines recommend broad-based molecular testing to assess for rare driver mutations for which effective drugs may be available (even if not yet FDA-approved for lung cancer), or to counsel patients regarding the availability of clinical trials in addition to assessing for established biomarkers. Emerging rare driver mutations include *HER2* mutations (ie, *ERBB2* mutations), *RET* rearrangements, high-level *MET* amplification, or *MET* exon 14 skipping mutations (see "Emerging Targeted Agents for Patients With Genetic Alterations" in the complete version of the NCCN Guidelines [NSCL-H]). Clinical trials are currently in progress for other emerging biomarkers; for example, new targeted agents are being assessed for effectiveness in patients with *NTRK* fusions.[74,75]

Immunotherapy

The NCCN panel recommends first-line pembrolizumab/carboplatin (or cisplatin)/pemetrexed (category 1) for patients with advanced nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or NSCLC not otherwise specified based on data from phase II and III trials and on the FDA approval (pembrolizumab/carboplatin/pemetrexed).[76,77] Pembrolizumab/chemotherapy is recommended for patients without (or unknown) genetic alterations whose PD-L1 levels are <50% or unknown. Most patients received pembrolizumab/carboplatin/pemetrexed (72%; n=445), but some received pembrolizumab/cisplatin/pemetrexed (28%; n=171); patients did not have *EGFR* mutations or *ALK* rearrangements. The estimated OS rate at 1 year was 69.2% (95% CI, 64.1–73.8) for pembrolizumab/chemotherapy versus 49.4% (95% CI, 42.1–56.2) for chemotherapy alone (HR for death, 0.49; 95% CI, 0.38–0.64; $P<.001$) after a median follow-up of 10.5 months. OS was improved regardless of PD-L1 expression levels, although most patients (63%) had levels of ≥1%. Median PFS was 8.8 months (95% CI, 7.6–9.2 months) for pembrolizumab/chemotherapy

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- ***ROS1*** **(ROS proto-oncogene 1) Gene Rearrangements: ROS1 is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the ROS1 kinase domain.**
  - **Numerous fusion partners are seen with *ROS1*, and common fusion partners include: CD74, SLC34A2, CCDC6, and FIG.**
  - **The presence of a *ROS1* rearrangement is associated with responsiveness to oral ROS1 TKIs.**
  - **Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of a *ROS1* rearrangement; however, these features should not be utilized in selecting patients for testing.**
  - **Testing Methodologies: FISH break-apart probe methodology can be deployed; however, it may under-detect the FIG-ROS1 variant. IHC approaches can be deployed; however, IHC for *ROS1* fusions has low specificity, and follow-up confirmatory testing is a necessary component of utilizing ROS1 IHC as a screening modality. Numerous NGS methodologies can detect *ROS1* fusions, and targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners (which may lead to under-detection of *ROS1* fusion events).**
- ***BRAF*** **(B-Raf proto-oncogene) point mutations: BRAF is a serine/threonine kinase that is part of the canonical MAP/ERK signaling pathway. Activating mutations in BRAF result in unregulated signaling through the MAP/ERK pathway.**
  - **Mutations in *BRAF* can be seen in NSCLC. The presence of a specific mutation resulting in a change in amino acid position 600 (p.V600E) has been associated with responsiveness to combined therapy with oral inhibitors of BRAF and MEK.**
  - **Note that other mutations in *BRAF* are observed in NSCLC, and the impact of those mutations on therapy selection is not well understood at this time.**
  - **Testing Methodologies: Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS are the most commonly deployed methodologies for examining *BRAF* mutation status. While an anti-BRAF p.V600E-specific monoclonal antibody is commercially available, and some studies have examined utilizing this approach, it should only be deployed after extensive validation.**
- ***KRAS*** **(KRAS proto-oncogene) point mutations: KRAS is a G-protein with intrinsic GTPase activity, and activating mutations result in unregulated signaling through the MAP/ERK pathway.**
  - **Mutations in *KRAS* are most commonly seen at codon 12, although other mutations can be seen in NSCLC.**
  - **The presence of a *KRAS* mutation is prognostic of poor survival when compared to patients with tumors without *KRAS* mutation.**
  - **Mutations in *KRAS* have been associated with reduced responsiveness to EGFR TKI therapy.**
  - **Owing to the low probability of overlapping targetable alterations, the presence of a mutation in *KRAS* may identify patients who will not benefit from further molecular testing.**

- **Testing in the Setting of Progression on Targeted Therapy:**
  - **For many of the above listed analytes, there is growing recognition of the molecular mechanisms of resistance to therapy. Re-testing of a sample that is actively progressing while exposed to targeted therapy can shed light on appropriate next therapeutic steps:**
    - **For patients with an underlying *EGFR* sensitizing mutation who have been treated with EGFR TKI, minimum appropriate testing includes high-sensitivity evaluation for p.T790M; when there is no evidence of p.T790M, testing for alternate mechanisms of resistance (*MET* amplification, *ERBB2* amplification) may be used to direct patients for additional therapies The presence of p.T790M can direct patients to third-generation EGFR TKI therapy.**

Continued

versus 4.9 months (95% CI, 4.7–5.5 months) for chemotherapy alone (HR for disease progression or death, 0.52; 95% CI, 0.43–0.64; *P*<.001), and the response rate was 47.6% (95% CI, 42.6–52.5) versus 18.9% (95% CI, 13.8–25.0), respectively. Grade ≥3 AEs occurred at a similar rate in both arms (67.2% vs 65.8% for chemotherapy).

For the 2018 update, the NCCN panel added a recommendation for atezolizumab/carboplatin/paclitaxel/bevacizumab (category 1) as first-line therapy for patients with metastatic nonsquamous NSCLC based on results of a recent phase III randomized trial (IMpower150).[78] This regimen is recommended for patients whose PD-L1 levels are <50% or unknown. Maintenance therapy with atezolizumab, bevacizumab, or both is also recommended (category 1). Patients with *EGFR* mutations or *ALK* rearrangements who had experienced disease progression on (or were intolerant of) prior TKI were enrolled in this trial. Median OS was 19.2 months (95% CI, 17.0–23.8) in the atezolizumab arm compared with 14.7 months (95% CI, 13.3–16.9) in the control arm of carboplatin/paclitaxel/bevacizumab; the HR for death was 0.78 (95% CI, 0.64–0.96; *P*=.02). PFS was increased in the atezolizumab arm versus chemotherapy/bevacizumab (8.3 vs 6.8 months; HR, 0.62; 95% CI, 0.52–0.74; *P*<.001).

The NCCN panel also added a first-line therapy recommendation (category 2A) for carboplatin/paclitaxel (or nab-paclitaxel)/pembrolizumab for patients with metastatic squamous cell NSCLC based on preliminary data from the phase III KEYNOTE-407 trial.[79] This pembrolizumab/chemotherapy regimen is recommended for patients whose PD-L1 levels are <50% or unknown. Maintenance therapy with pembrolizumab is also a recommended option (category 2A). Patients receiving pembrolizumab/chemotherapy had an overall response rate of 58.4% compared with 35.0% in those receiving chemotherapy alone (*P*=.0004).

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- Testing in the Setting of Progression on Targeted Therapy (continued)
  - Assays for the detection of *EGFR* p.T790M should be designed to have an analytic sensitivity of a minimum of 5% allelic fraction. The original sensitizing mutation can be utilized as an internal control in many assays to determine whether a p.T790M is within the range of detection if present as a sub-clonal event.
  - ◊ For patients with underlying *ALK* rearrangement who have been treated with ALK TKI, it is unclear whether identification of specific tyrosine kinase domain mutation can identify appropriate next steps in therapy, although some preliminary data suggest that specific kinase domain mutations can impact next line of therapy.
- IHC for Biomarker Selection in NSCLC:
  - PD-L1 (Programmed Death Ligand 1): PD-L1 is a co-regulatory molecule that can be expressed on tumor cells and inhibit T-cell–mediated cell death. T-cells express PD-1, a negative regulator, which binds to ligands including PD-L1 (CD274) or PD-L2 (CD273). In the presence of PD-L1, T-cell activity is suppressed.
    - ◊ Checkpoint inhibitor antibodies block the PD-1 and PD-L1 interaction, thereby improving the antitumor effects of endogenous T cells.
    - ◊ IHC for PD-L1 can be utilized to identify disease most likely to respond to first-line immunotherapy.
      - Various antibody clones have been developed for IHC analysis of PD-L1 expression, and while several show relative equivalence, some do not.
      - Interpretation of PD-L1 IHC is typically focused on the proportion of tumor cells expressing membranous staining at any level and therefore is a linear variable.
      - The FDA-approved IHC assay for PD-L1 utilizes a cutoff of 50% tumor proportion score for first-line and 1% tumor proportion score for second-line therapy with pembrolizumab.
      - The definition of positive and negative testing is dependent on the individual antibody and platform deployed, which may be unique to each checkpoint inhibitor therapy. The potential for multiple different assays for PD-L1 has raised concern among both pathologists and oncologists.
  - *ALK* fusions: IHC assays for ALK can serve as a screening modality for further ALK testing, and can alternatively be used as a stand-alone test to determine eligibility for ALK TKI. An FDA-approved IHC assay for ALK is available.
  - *ROS1* fusions: IHC assays for ROS1 should only be deployed as a screening modality for further ROS1 testing, because the specificity of a positive result is low. Positive ROS1 IHC should not be utilized to select patients for TKI therapy without additional confirmatory testing. Currently there is not an FDA-approved IHC assay for ROS1.
  - *BRAF* p.V600E mutations: An antibody specific to the p.V600E mutation is available. Some studies have examined utilization of this antibody in cases of NSCLC; however, optimization of this antibody may be tumor-specific and care should be exercised when using this approach.
  - *EGFR* mutations: Limited mutation-specific antibodies are available for EGFR. While these antibodies have good specificity, the sensitivity is lacking, and it is not recommended to use *EGFR* mutation-specific antibodies except in circumstances of extremely limited tissue, because many sensitizing *EGFR* mutations are not detected with this approach.

Summary

The NCCN Guidelines for NSCLC address all aspects of disease management. These NCCN Guidelines Insights focus on recent updates to targeted therapy for patients with advanced NSCLC who have *ALK* or *ROS1* rearrangements or *BRAF* V600E mutations. For the 2018 guideline update, the panel recommends crizotinib as a preferred agent for patients with *ROS1* rearrangements. The panel also recommends ceritinib (category 2A) for patients with *ROS1*-positive advanced NSCLC. A new section was added that describes key established biomarkers and appropriate testing to identify patients with these biomarkers. The NCCN panel also revised the recommendation for pembrolizumab/carboplatin (or cisplatin)/pemetrexed to category 1 (from category 2A) based on recent trial data.[78,79] In addition, the following regimens are now recommended: (1) atezolizumab/carboplatin/paclitaxel/bevacizumab (category 1) as first-line therapy for patients with metastatic nonsquamous NSCLC; and (2) pembrolizumab/carboplatin/paclitaxel (or nab-paclitaxel) (category 2A) as first-line therapy for patients with metastatic squamous cell carcinoma.

For a list of all 2018 updates, see the complete NCCN Guidelines for NSCLC (available at NCCN.org).

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Non–Small Cell Lung Cancer, Version 5.2018

Instructions for Completion

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Posttest Questions

1. Before selecting initial therapy for metastatic NSCLC, the NCCN Guidelines recommend testing for which of the following biomarkers:
   a. *ALK* rearrangements
   b. *EGFR* mutations
   c. PD-1 and PD-L1 expression levels
   d. *ROS1* rearrangements
   e. *BRAF* V600E point mutations
      i. a and b
      ii. a, b, and c
      iii. a, b, c, and d
      iv. a, b, c, d, and e

2. Which of the following agents is recommended as preferred therapy for patients with metastatic NSCLC and *ROS1* rearrangements in the NCCN Guidelines based on clinical trial data and FDA approval?
   a. Ceritinib
   b. Crizotinib
   c. Brigatinib
   d. Alectinib

3. Which of the following agents is recommended as preferred therapy for patients with metastatic NSCLC and *ALK* rearrangements in the NCCN Guidelines based on clinical trial data and FDA approval?
   a. Ceritinib
   b. Crizotinib
   c. Brigatinib
   d. Alectinib