NCCN: Continuing Education

Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Release date: March 10, 2021; Expiration date: March 10, 2022

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 is as scientific advisor for BeyondSpring Pharmaceuticals and Takeda Pharmaceuticals North America, Inc.

Miranda Hughes, PhD, Oncology Scientist/Senior Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Non–Small Cell Lung Cancer, Version 2.2021

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Clinical Practice Guidelines in Oncology (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 NCCN Guidelines regarding targeted therapies, immunotherapies, and their respective biomarkers.

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*Provided content development and/or authorship assistance.

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.

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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 of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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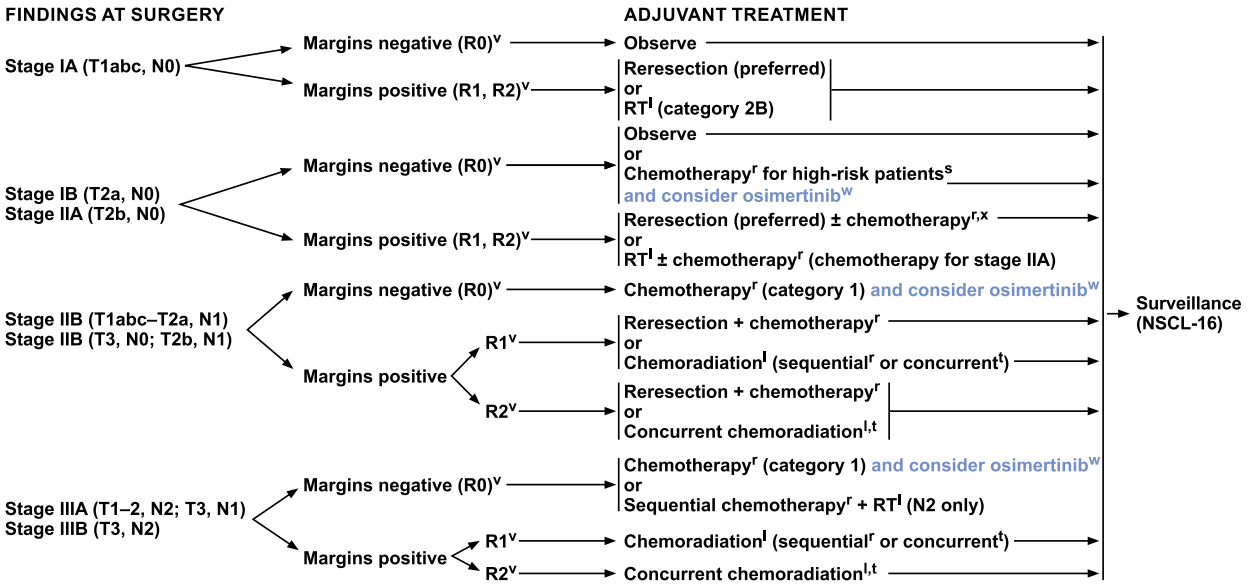

l See Principles of Radiation Therapy (NSCL-C).
r See Systemic Therapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).
s Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.
t See Concurrent Chemoradiation Regimens (NSCL-F).
v R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
w For patients with *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
x Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

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NSCL-4

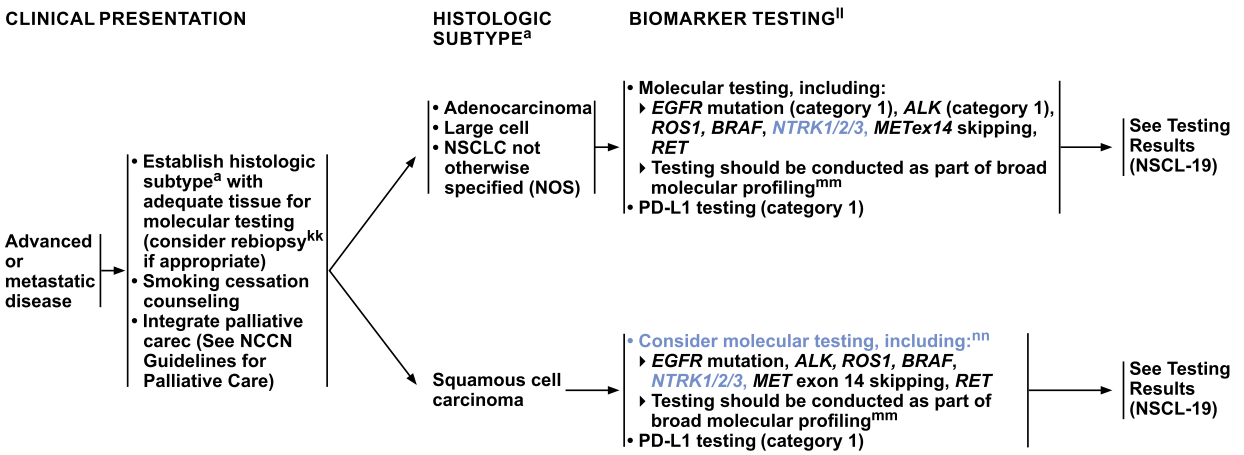
Overview

Lung cancer is the leading cause of cancer death in the United States.[1] In 2021, an estimated 235,760 new cases (119,100 in men and 116,660 in women) of lung and bronchial cancer will be diagnosed, and 131,880 deaths (69,410 in men and 62,470 in women) are estimated to occur.[1] Only 26% of all patients with non–small cell lung cancer (NSCLC) are alive ≥5 years after diagnosis.[2] The 5-year relative survival rate for metastatic disease is approximately 6% when patients receive historic cytotoxic chemotherapy regimens.[2] However, certain patients with metastatic NSCLC who are eligible for newer targeted therapies or immunotherapies are now surviving longer, with 5-year survival rates ranging from 15% to 50%, depending on the biomarker.[3–13]

These NCCN Guidelines Insights focus on recent updates in targeted therapies, immunotherapies, and their respective biomarkers for eligible patients with NSCLC. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC address all aspects of management for NSCLC. For the 2020 and 2021 updates, several new targeted therapies (or new indications for therapies), including capmatinib, lorlatinib, pralsetinib, selpercatinib, and fam-trastuzumab deruxtecan, are now recommended in the NCCN Guidelines for eligible patients with metastatic NSCLC who have certain actionable biomarkers.[14–20] These NCCN Guidelines Insights detail the reasons behind the recent revisions and provide a valuable resource for busy healthcare providers who need to quickly learn about the recent recommendations to improve outcomes for their patients with metastatic NSCLC. Unless otherwise indicated, all NCCN recommendations are category 2A (the complete version of these guidelines is available at NCCN.org).

Biomarkers

A *predictive* (also known as *actionable*) biomarker has a corresponding specific targeted therapy(ies) that has been shown to improve outcomes in patients with the predictive biomarker (eg, *ALK* rearrangements are targeted by alectinib, brigatinib, lorlatinib, and other ALK inhibitors). A *prognostic* biomarker is indicative of patient survival independent of the treatment received, because the biomarker is an indicator of the innate tumor aggressiveness (eg, *KRAS* mutations). In the NCCN Guidelines, key established predictive molecular biomarkers include *ALK* rearrangements, *BRAF* V600E point



[a] See Principles of Pathologic Review (NSCL-A).
[c] Temel JS, et al. N Engl J Med 2010;363:733-742.
[kk] If there is insufficient tissue to allow testing for all of *EGFR*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET, and RET,* repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
[mm] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Biomarkers to Identify Patients for Therapies (NSCL-I).
[nn] 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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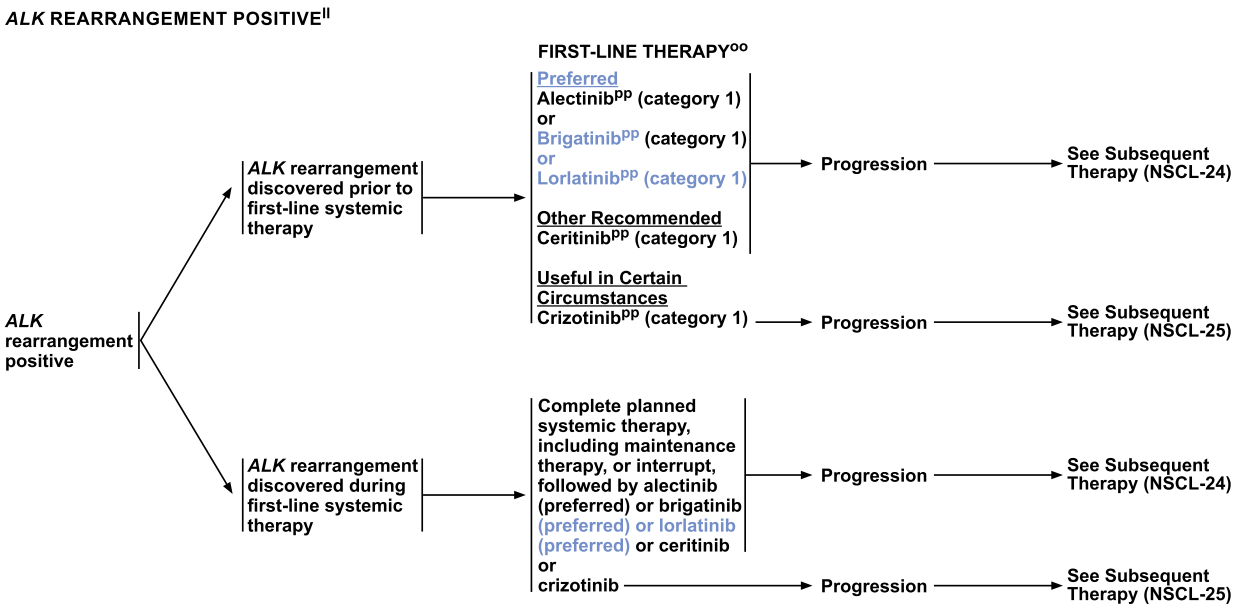
NSCL-18

mutations, sensitizing *EGFR* mutations, *METex14* skipping mutations, *NTRK1/2/3* gene fusions, *RET* rearrangements, and *ROS1* rearrangements; PD-L1 expression is a key established immune biomarker (see NSCL-18, page 257). The NCCN NSCLC Panel recommends testing for these key established predictive biomarkers after patients have been diagnosed with metastatic NSCLC and ideally before initial treatment, because effective targeted therapy or immunotherapy is available depending on biomarker test results.[14]

Emerging predictive biomarkers also have corresponding specific targeted therapies, but fewer data are available to support use of these targeted therapies compared with the targeted therapies for the key established predictive biomarkers (see NSCL-I, page 264). Several emerging biomarkers have become established biomarkers in the NCCN Guidelines after more clinical trial data were published for their corresponding targeted therapies. For example, *METex14* skipping mutations and *RET* rearrangements were moved from the emerging biomarkers section to the established biomarker section of the algorithm for the 2020 update (see NSCL-18, page 257).[14,16–18] For the version 1.2021 (v1.2021) update, the panel clarified that biomarker testing is recommended in certain patients with metastatic (stage IV) disease, including M1a, M1b, and M1c. The panel also recommends considering biomarker testing for *EGFR* mutations in surgical tissue or biopsies from patients with completely resected stage IB–IIIA NSCLC to determine whether adjuvant osimertinib can be considered for these patients (see NSCL-4, page 256, and next section).[14,21]

Molecular Biomarkers

The panel recommends molecular testing using a validated test(s) that assesses a minimum of the following potential genetic variants: *ALK* rearrangements (category 1), *BRAF* mutations, *EGFR* mutations (category 1), *METex14* skipping mutations, *NTRK1/2/3* gene fusions, *RET* rearrangements, and *ROS1* rearrangements.[14] Both FDA-approved companion diagnostics and laboratory-developed test platforms are available to evaluate for these and other analytes. The NCCN Guidelines for NSCLC provide recommendations for specific biomarkers that should be assessed in patients who have been diagnosed with NSCLC, and recommend testing techniques for the key established biomarkers, but do not endorse any specific commercially available biomarker assays. For the 2020 update, the panel recommends that molecular testing be performed via a broad, panel-based



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

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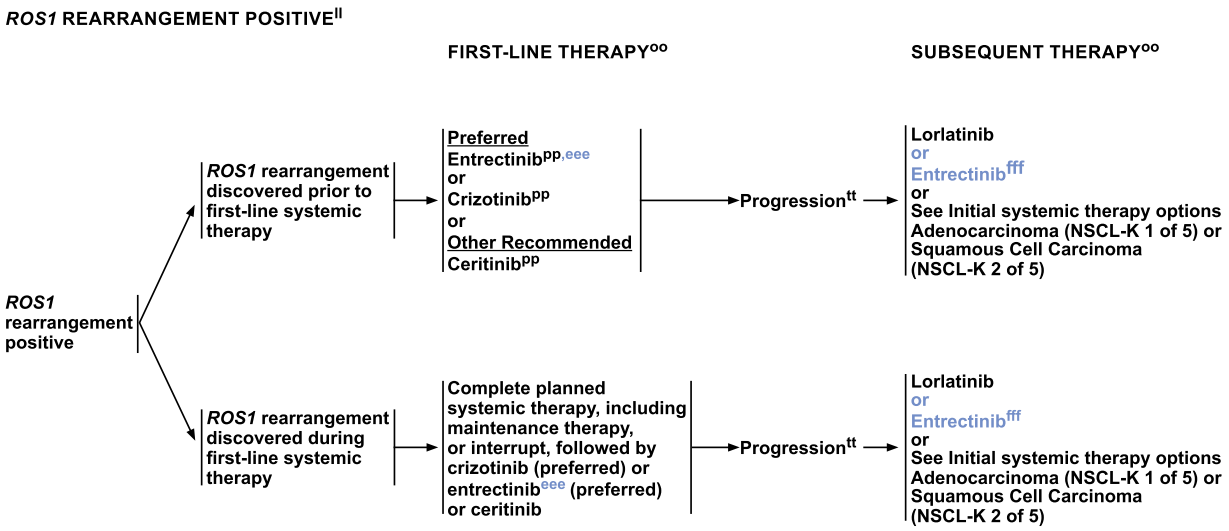
NSCL-23

approach, most typically performed by next-generation sequencing (NGS), so that testing is done for all of the actionable biomarkers at the same time, including the established and emerging biomarkers. This testing technique helps ensure that there is sufficient tissue to test for all of the actionable biomarkers. However, some gene fusions are difficult to detect using DNA-based NGS. For patients who, in broad panel testing, do not have identifiable driver oncogenes (especially never smokers), RNA-based NGS should be considered, if not already performed, to maximize detection of fusion events.[22]

ALK, *EGFR*, *BRAF*, *METex14*, *NTRK1/2/3*, *RET*, and *ROS1* status should be known before deciding whether to use either targeted therapy or immunotherapy with or without chemotherapy regimens. If it is not feasible to perform molecular testing, then patients are treated as though they do not have driver oncogenes.[23–27] Note that the panel recommends that testing for PD-L1 expression levels, which is an immune biomarker, be performed using an immunohistochemistry test that is an FDA companion diagnostic or has been shown to have equivalent performance to an approved companion diagnostic.[28,29] The immunohistochemical evaluation of PD-L1 that guides use of pembrolizumab is based on tumor proportion score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity.

For the 2021 and 2020 updates, new content was added for *EGFR* mutations and *NTRK1/2/3* gene fusions; recommended testing techniques were added for *METex14* skipping mutations, *NTRK1/2/3* gene fusions, and *RET* fusions (see NSCL-H 2 and 4, pages 263 and 264)[14]; and content was revised for the key established biomarkers, such as *EGFR* mutations, and for the emerging biomarkers, such as tumor mutational burden (TMB) (see NSCL-18 and NSCL-I, pages 257 and 264). For the v1.2021 update, the panel decided that routine molecular testing should be considered in all patients with metastatic NSCLC squamous cell carcinoma (see NSCL-18, page 257).[14] Therefore, characteristics—such as smoking status, small biopsy specimens, and mixed histology—should no longer be used when considering whether to perform biomarker testing on patients with metastatic NSCLC squamous cell carcinoma. This decision is based on recent data showing that patients with metastatic squamous cell carcinoma also have actionable biomarkers, such as *EGFR* mutations, although at a lower incidence than those with metastatic NSCLC adenocarcinoma.[23,30–32] The cumulative incidence



[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] See Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[pp] For performance status 0–4.
[tt] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[eee] Entrectinib may be better for patients with brain metastases.
[fff] Entrectinib is primarily for patients with CNS progression after crizotinib.

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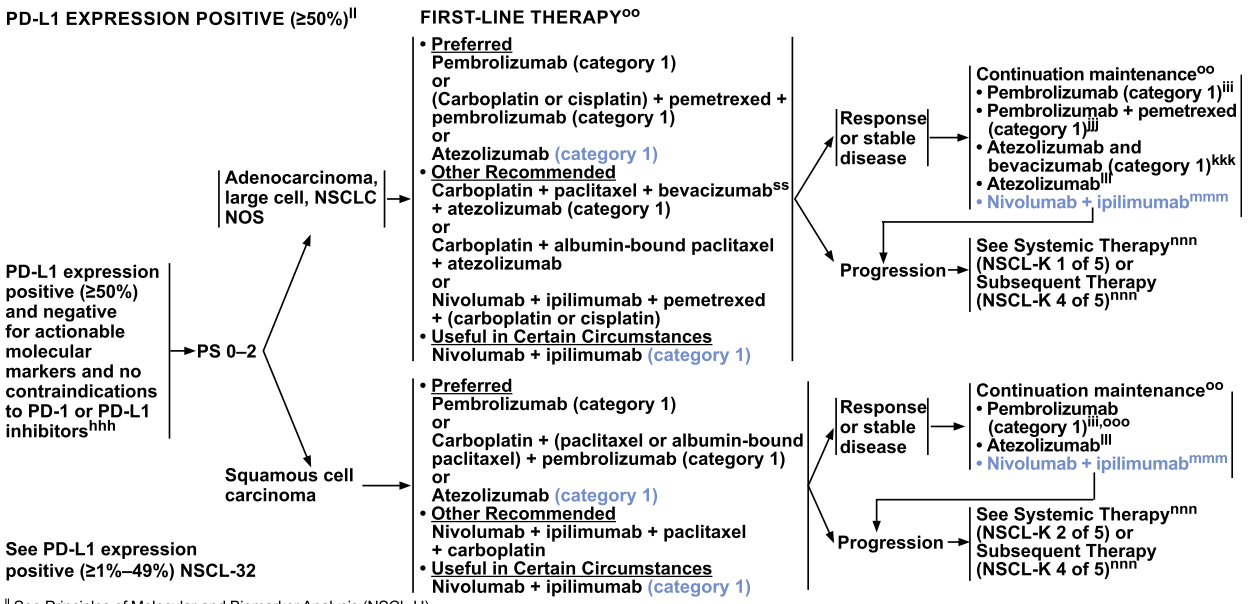
NSCL-26

of actionable alterations in tumors carrying a diagnosis of metastatic squamous cell carcinoma is sufficient to justify consideration of molecular testing. The panel now feels that molecular testing should be considered in patients with metastatic squamous cell carcinoma based on the effectiveness of targeted therapies.[23,32] The panel also clarified that *NTRK1/2/3* gene fusions are established predictive molecular biomarkers for the 2021 update. Typically, the key established molecular biomarkers do not overlap; most patients with actionable mutations only have one actionable mutation.[23,32] Although *KRAS* mutations are not actionable at this time, inclusion on panel-based testing is informative, because it generally excludes the presence of an actionable alteration.

Immunotherapy with or without chemotherapy is recommended for patients who do not have actionable molecular biomarkers. If patients have both a molecular biomarker and high PD-L1 expression levels, targeted therapy is usually recommended over immunotherapy with or without chemotherapy based on data showing that targeted therapy yields higher response rates compared with immunotherapy in the first-line setting, targeted therapy is better tolerated, and most patients with an actionable molecular biomarker will only have a modest or slight response to immunotherapy.[23–27] Response rates for immunotherapy are lower in patients with *EGFR* and *ALK* variants; however, pembrolizumab with or without chemotherapy may be considered for a heavy smoker with PD-L1 levels of 100% and a *BRAF* V600E mutation.

Recent data show that certain patients with completely resected early-stage NSCLC who have sensitizing *EGFR* mutations have longer duration of disease-free survival if they receive adjuvant osimertinib versus placebo.[21] ADAURA, a phase III randomized trial in 682 patients, showed that 90% (95% CI, 84%–93%) of patients with stage II–IIIA NSCLC receiving osimertinib were alive and disease-free at 24 months compared with 44% (95% CI, 37%–51%) receiving placebo (HR, 0.17; 99.06% CI, 0.11–0.26; $P<.001$).[21] Disease-free survival was also improved in patients who received adjuvant chemotherapy before osimertinib compared with placebo. Nine patients in the osimertinib group and 20 in the placebo group died. It will be interesting to see whether patients with other actionable molecular biomarkers, such as *ALK* rearrangements, also have improved survival with targeted agents in the same setting. For the v1.2021 update, the panel recommends considering adjuvant osimertinib for patients with completely resected *EGFR* mutation–positive stage



[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] See Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[ss] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[hhh] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit. If there are contraindications, refer to NSCL-K 1 of 5 (adenocarcinoma) or NSCL-K 2 of 5 (squamous cell carcinoma).
[iii] If pembrolizumab monotherapy given.
[jjj] If pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
[kkk] If atezolizumab/carboplatin/paclitaxel/bevacizumab given.
[lll] If atezolizumab/carboplatin/albumin-bound paclitaxel or atezolizumab given (category 1 following atezolizumab alone).
[mmm] If nivolumab + ipilimumab ± chemotherapy given (category 1 following nivolumab + ipilimumab).
[nnn] 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."
[ooo] If pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) given.

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NSCL-31

IIB–IIIA and high-risk stage IB–IIA NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum chemotherapy based on FDA approval and clinical trial results (see NSCL-E, page 261).[21] High-risk features are described in the algorithm (see NSCL-4, page 256).

For the version 2.2021 (v2.2021) update, the panel now recommends lorlatinib (category 1) as another preferred first-line therapy option for patients with *ALK* rearrangement–positive metastatic NSCLC (see NSCL-23, page 258).[15] The panel revised the preference stratification for brigatinib (category 1) to a preferred first-line therapy option for patients with *ALK* rearrangement–positive metastatic NSCLC in the v1.2021 update (see NSCL-23, page 258).[33,34] The panel clarified that entrectinib may be better for patients with *ROS1* rearrangement–positive metastatic NSCLC who have brain metastases, and entrectinib is now recommended as a subsequent therapy option for patients with *ROS1*-positive disease who have CNS progression after crizotinib (see NSCL-26, page 259).[35,36] Entrectinib was designed to cross the blood–brain barrier.[35] However, entrectinib is less effective for certain resistant *ROS1* variants.[35] For the v1.2021 update, the panel added capmatinib as a treatment option for patients with high-level *MET* amplification, which is an emerging biomarker (see NSCL-I, page 264).[16] The panel also added fam-trastuzumab deruxtecan as a treatment option for patients with *ERBB2* (*HER2*) mutation–positive metastatic NSCLC, which is another emerging biomarker (see NSCL-I, page 264).[19] The panel deleted single-agent dabrafenib as a treatment option for patients with *BRAF* V600E mutation–positive metastatic NSCLC who cannot tolerate combination therapy with dabrafenib + trametinib; single-agent vemurafenib remains an option in this setting.[37,38] Although less toxic, dabrafenib monotherapy is less effective than combination therapy with dabrafenib + trametinib.[39]

For the 2020 updates, the panel added selpercatinib and pralsetinib as preferred first-line therapy options for patients with *RET* rearrangement–positive metastatic NSCLC.[17,18] Selpercatinib and pralsetinib are also recommended as preferred subsequent therapy options in this setting if RET inhibitors have not been previously given as first-line therapy. The panel also added capmatinib as a preferred first-line therapy option for patients with *METex14* skipping mutations.[16] Likewise, capmatinib is also recommended as a preferred subsequent therapy option in this setting if MET inhibitors have not been previously given as first-line therapy.

SYSTEMIC THERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

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

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

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

Useful in Certain Circumstances

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

All regimens can be used for sequential chemotherapy/RT.

Previous Adjuvant Chemotherapy or Ineligible for Platinum-Based Chemotherapy
- **Osimertinib 80 mg daily**[10]
  - **Consider osimertinib for patients with completely resected Stage IB–IIIA *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.**

[1] Kreuter M, Vansteenkiste J, Fishcer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. Ann Oncol 2013;24:986-992.
[2] Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012;30:3516-3524.
[3] Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-3024.
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[5] Arriagada R, Bergman B, Dunant A, et al. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. N Engl J Med 2004;350:351-360.
[6] Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-727.
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NSCL-E

Immune Biomarkers

Several immune biomarkers, including PD-L1 expression levels and TMB, have been assessed in clinical trials to see if they are useful for predicting whether patients with metastatic NSCLC will respond to various immunotherapy regimens, such as single-agent pembrolizumab or nivolumab + ipilimumab.[40–43] The response rate to immune checkpoint inhibitors varies depending on the regimen and setting. The highest response rates occur in patients with PD-L1 levels ≥50% in the first-line setting and no actionable molecular biomarkers (approximately 40% response rate to single-agent immunotherapy; approximately 60% to chemoimmunotherapy).[40,41,44–46] However, only approximately 30% of patients with metastatic NSCLC have PD-L1 levels ≥50%.[44,47] Although PD-L1 expression level is widely used as an immune biomarker, it is not an ideal biomarker because some patients with low PD-L1 expression levels respond to immunotherapy and others with high levels do not respond to immunotherapy.[48,49] PD-L1 expression levels are useful for deciding whether to use single-agent immunotherapy or combination immunotherapy.

TMB is an approximate measure of the total number of somatic mutations.[50] Theoretically, high TMB levels will correlate with high neoantigen levels that will activate an antitumor immune response.[48] TMB levels are typically high in patients with NSCLC who are smokers or former smokers. Low TMB is more commonly detected in never-smokers.[22,51] Preliminary data for progression-free survival from CheckMate 227, a phase III 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.[42] However, updated data from this trial showed that overall survival was improved with nivolumab + ipilimumab regardless of TMB or PD-L1 expression levels.[43] 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.[42,43,52,53] KEYNOTE-158, a phase II trial, assessed TMB levels in patients with solid tumors who received pembrolizumab as second-line therapy; however, none of the patients had NSCLC.[54] TMB does not identify patients who will respond to chemotherapy; therefore, it has limited value for assessing combination immunotherapy + chemotherapy regimens.[48] TMB is also

CONCURRENT CHEMORADIATION REGIMENS

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

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

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

[€] For patients with superior sulcus tumors, the recommendation is for 2 cycles concurrent with radiation therapy and 2 more cycles after surgery. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25:313-318.

[*] Regimens can be used as preoperative/adjuvant chemotherapy/RT.
[†] Regimens can be used as definitive concurrent chemotherapy/RT.
[‡] For eligible patients, durvalumab may be used after noted concurrent chemo/RT regimens.
[§] If using durvalumab, an additional 2 cycles of chemotherapy is not recommended, if patients have not received full-dose chemotherapy concurrently with RT.

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NSCL-F

not an ideal immune biomarker, because some patients with low levels experience a response to immunotherapy and others with high levels do not.[48]

In addition to the lack of clinical data to support use of TMB as an immune biomarker, there are technical problems with measuring TMB,[50] including lack of agreement on the definition of a cutoff for designating high TMB levels and lack of standardization of TMB measurements across laboratories.[50] 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. For the v1.2021 update, the panel decided to remove 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 NSCL-I, page 264).[14,43,50] Currently, the NCCN Guidelines do not recommend measurement of TMB levels before deciding whether to use nivolumab + ipilimumab combined with or without chemotherapy or to use other immune checkpoint inhibitors, such as pembrolizumab.[14]

For the v1.2021 update, the panel added a recommendation (category 2A) for consolidation immunotherapy with single-agent durvalumab for patients with unresectable stage II NSCLC who have not experienced disease progression after definitive concurrent chemoradiation. Previously, the durvalumab recommendation had been restricted to patients with unresectable stage III NSCLC (category 1) (see NSCL-F, page 262).[55] The panel also revised the recommendation for atezolizumab monotherapy to category 1 (from category 2A) as a preferred treatment option for patients with PD-L1 expression levels of ≥50% and negative for actionable biomarkers (see NSCL-31, page 260).[45] The recommendation for nivolumab + ipilimumab was also revised to category 1 (from category 2A) for patients with PD-L1 expression levels of ≥1% and negative for actionable biomarkers (see NSCL-31, page 260).

Summary

These NCCN Guidelines Insights focus on recent updates in targeted therapies, immunotherapies, and their respective biomarkers for eligible patients with NSCLC. For a list of the recent updates, see the complete version of these guidelines at NCCN.org. The NCCN Guidelines for

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.**
    - **Consider adding molecular testing for *EGFR* mutation to be performed on diagnostic biopsy or post-surgical resection sample to ensure the *EGFR* mutation results are available for adjuvant treatment decisions for patients with stage IB to IIIA NSCLC.**
    - **Many of the less commonly observed alterations in EGFR, which cumulatively account for ~10% of *EGFR*-mutation positive NSCLC (ie, *exon 19* insertions, *p.L861Q, p.G719X, p.S768I*) are also associated with responsiveness to EGFR TKI therapy, although the number of studied patients is lower.**
    - ***EGFR exon 20 (EGFRex20)* mutations are a heterogeneous group, some of which are responsive to targeted therapy and that require detailed knowledge of the specific alteration.**
      - ***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 *p.T790M* is observed in the absence of prior EGFR TKI therapy, genetic counseling and possible germline genetic testing is warranted.**
      - **Most other *EGFRex20* alterations are a diverse group of in-frame duplication or insertion mutations.**
        - **These are generally associated with lack of response to EGFR TKI therapy, with select exceptions:**
          ***p.A763_Y764insFQEA* is associated with sensitivity to TKI therapy**
          ***p. A763_Y764insLQEA* may be associated with sensitivity to TKI therapy**
        - **For this reason, the specific sequence of *EGFRex20* insertion mutations is important, and some assays will identify the presence of an *EGFRex20* insertion without specifying the sequence. In this scenario, additional testing to further clarify the *EGFRex20* insertion is indicated.**
    - **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.**

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NSCLC address all aspects of management for NSCLC. For the 2020 and 2021 updates, several new targeted therapies or new indications for therapies, including capmatinib, lorlatinib, pralsetinib, selpercatinib, and fam-trastuzumab deruxtecan, are now recommended in the NCCN Guidelines for eligible patients with metastatic NSCLC who have certain actionable biomarkers.[14,16–20] For the v2.2021 update, the panel now recommends lorlatinib (category 1) as another preferred first-line therapy option for patients with *ALK* rearrangement–positive metastatic NSCLC.[15] For the v1.2021 update, the panel recommends considering adjuvant osimertinib for patients with completely resected *EGFR* mutation–positive stage IIB–IIIA and high-risk stage IB–IIA NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum chemotherapy.[14,21]

The panel revised the preference stratification for brigatinib (category 1) to a preferred first-line therapy option for patients with *ALK* rearrangement–positive metastatic NSCLC.[33,34] The panel clarified that entrectinib may be better for patients with *ROS1* rearrangement–positive metastatic NSCLC who have brain metastases; entrectinib is recommended as a subsequent therapy option for patients with *ROS1*-positive disease who have central nervous system progression after crizotinib.[35,36] For the v1.2021 update, the panel decided that routine molecular biomarker testing should be considered in all patients with metastatic NSCLC squamous cell carcinoma; *EGFR* mutation biomarker testing can also be considered for patients with completely resected stage IB–IIIA NSCLC.[14,21,30,31] Content was revised for the key established biomarkers, such as *EGFR* mutations. TMB, which is an immune biomarker, was deleted from the NCCN Guidelines based on clinical trial data, concerns about variable TMB measurements, and other issues.[14,43,50] TMB was previously listed as an emerging biomarker. Currently, the NCCN Guidelines do not recommend measurement of TMB levels before deciding on the use of nivolumab + ipilimumab combined with or without chemotherapy or the use of other immune checkpoint inhibitors, such as pembrolizumab.[14]

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PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- Molecular Targets for Analysis (continued)
  - *MET* (mesenchymal-epithelial transition) *exon 14 (METex14)* skipping variants: MET is a receptor tyrosine kinase. A mutation that results in loss of *exon 14* can occur in NSCLC. Loss of *METex14* leads to dysregulation and inappropriate signaling.
    - The presence of *METex14* skipping mutation is associated with responsiveness to oral MET TKIs.
    - A broad range of molecular alterations lead to *METex14* skipping.
    - Testing Methodologies: NGS-based testing is the primary method for detection of *METex14* skipping events, with RNA-based NGS demonstrating improvement in 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.
  - ***NTRK1/2/3* (neurotrophic tyrosine receptor kinase) gene fusions**
    - ***NTRK1/2/3* are tyrosine receptor kinases that are rarely rearranged in NSCLC as well as in other tumor types, resulting in dysregulation and inappropriate signaling.**
    - **Numerous fusion partners have been identified.**
    - **To date, no specific clinicopathologic features, other than absence of other driver alterations, have been identified in association with these fusions.**
    - Point mutations in *NTRK1/2/3* are generally non-activating and have not been studied in association with targeted therapy.
    - **Testing Methodologies: Various methodologies can be used to detect *NTRK1/2/3* gene fusions, including: FISH, IHC, PCR, and NGS; false negatives may occur. IHC methods are complicated by baseline expression in some tissues. FISH testing may require at least 3 probe sets for full analysis. NGS testing can detect a broad range of alterations. DNA-based NGS may under-detect *NTRK1* and *NTRK3* fusions.**
- In the event that a complete assessment for all biomarkers cannot be reasonably accomplished prior to initiation of therapy, consider repeat panel testing or selected biomarker testing at progression on first-line therapy if a lesion can be accessed for sampling and testing.
- **Testing in the Setting of Progression on Targeted Therapy:**
  - **For many of the above listed analytes, there is growing recognition of the molecular mechanisms of resistance to therapy. Re-testing of a sample from a tumor that is actively progressing while exposed to targeted therapy can shed light on appropriate next therapeutic steps:**
    - **For patients with an underlying *EGFR* sensitizing mutation who have been treated with EGFR TKI, minimum appropriate testing includes high-sensitivity evaluation for *p.T790M*; when there is no evidence of *p.T790M*, testing for alternate mechanisms of resistance (*MET* amplification, *ERBB2* amplification) may be used to direct patients for additional therapies. The presence of *p.T790M* can direct patients to third-generation EGFR TKI therapy.**
      - **Assays for the detection of *EGFR p.T790M* should be designed to have an analytic sensitivity of a minimum of 5% allelic fraction. The original sensitizing mutation can be utilized as an internal control in many assays to determine whether a *p.T790M* is within the range of detection if present as a sub-clonal event.**
    - **For patients with underlying *ALK* rearrangement who have been treated with ALK TKI, it is unclear whether identification of specific tyrosine kinase domain mutation can identify appropriate next steps in therapy, although some preliminary data suggest that specific kinase domain mutations can impact next line of therapy.**

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EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

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

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