NCCN Guidelines® Insights

Non–Small Cell Lung Cancer, Version 6.2015

Featured Updates to the NCCN Guidelines

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Abstract

These NCCN Guidelines Insights focus on recent updates to the 2015 NCCN Guidelines for Non–Small Cell Lung Cancer (NSCLC). Appropriate targeted therapy is very effective in patients with advanced NSCLC who have specific genetic alterations. Therefore, it is important to test tumor tissue from patients with advanced NSCLC to determine whether they have genetic alterations that make them candidates for specific targeted therapies. These NCCN Guidelines Insights describe the different testing methods currently available for determining whether patients have genetic alterations in the 2 most commonly actionable genetic alterations, notably anaplastic lymphoma kinase *(ALK)* gene rearrangements and sensitizing epidermal growth factor receptor *(EGFR)* mutations. (J Natl Compr Canc Netw 2015;13:515–524)

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Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to 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 NCCN Guideline Panel discussion, including the literature reviewed.**

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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

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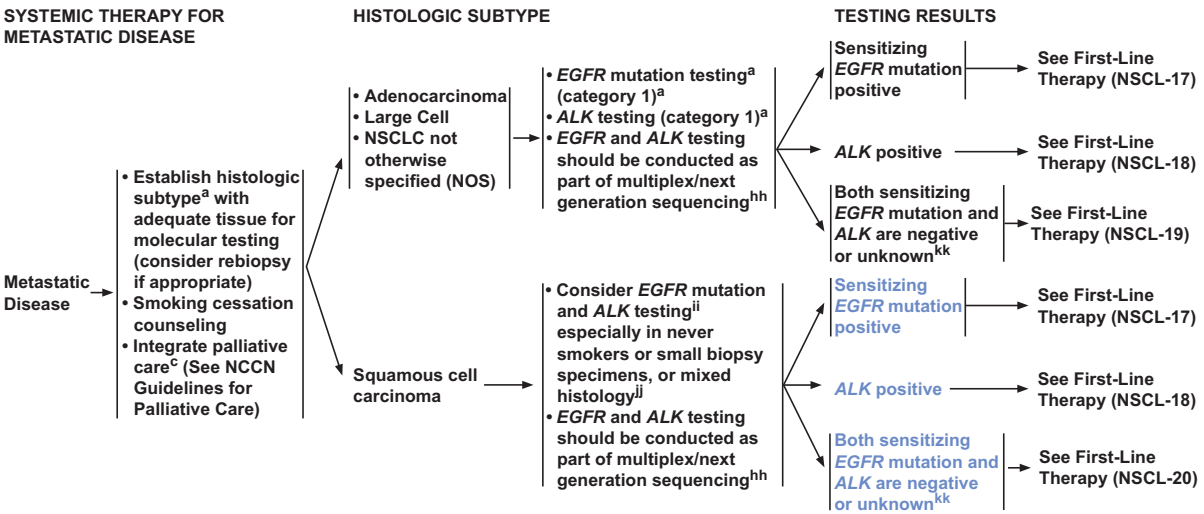
Non–Small Cell Lung Cancer, Version 6.2015



[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.
[hh]The NCCN NSCLC Guidelines Panel strongly endorses 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).
[ii]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 (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.
[jj]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.
[kk]Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

NSCL-16

NCCN Categories of Evidence and Consensus

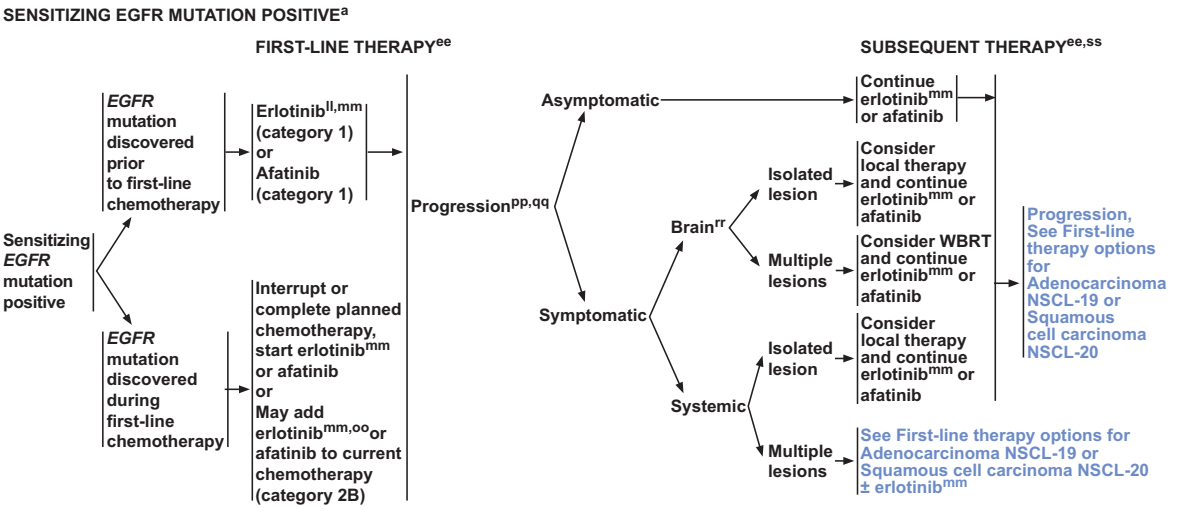
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

In 2015, an estimated 221,200 new cases (115,610 in men and 105,590 in women) of lung and bronchial cancer will be diagnosed, and 158,040 deaths (86,380 in men and 71,660 in women) are estimated to occur in the United States.[1] Currently, most lung cancer is diagnosed clinically when patients present with symptoms such as persistent cough, pain, and weight loss. Unfortunately, most patients are diagnosed when they already have advanced-stage disease. Even for earlier-stage disease, the relapse rate after radical therapy is significant. Taking into account all stages at diagnosis, the 5-year survival rate for lung cancer is only 16.8%.[2,3] The 5-year survival rate for those with stage IV disease at diagnosis is much lower (≈2%). However, for select patients with advanced lung cancer, the advent of targeted therapies has had a profound effect on the ability to control the disease, palliate symptoms, and potentially prolong life



[a]See Principles of Pathologic Review (NSCL-A).
[ee]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ll]For performance status 0-4.
[mm]In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[oo]Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who are never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol 2012;30:2063-2069.
[pp]Prior to changing therapy, a biopsy is reasonable to determine mechanism of acquired resistance.
[qq]Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[rr]Consider pulse erlotinib for carcinomatosis meningitis.
[ss]Afatinib appears to have some efficacy in patients who progressed on EGFR therapy. Miller VA, Hirsh V, Cadrenal J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-38.

NSCL-17

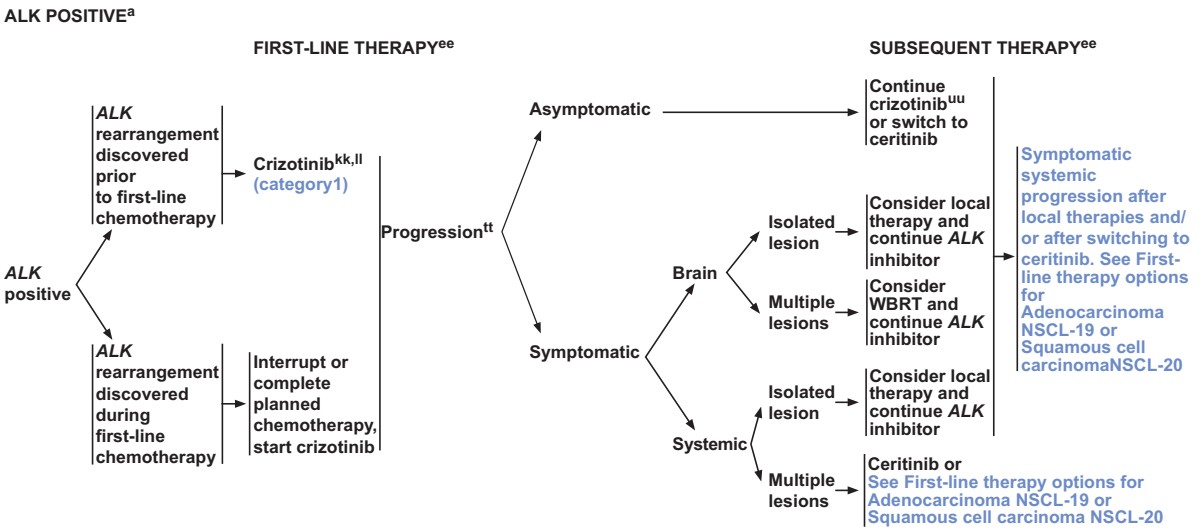
for patients with the specific molecular aberrations in their tumors that make them sensitive to these therapies.[4–19] Therefore, it is important to perform molecular testing on tumor tissue from patients with advanced non–small cell lung cancer (NSCLC) to determine whether they have genetic alterations and thus are candidates for targeted therapy. These NCCN Guidelines Insights describe the different testing methods currently available for determining whether patients have 2 of the most common actionable genetic alterations: anaplastic lymphoma kinase (*ALK*) gene rearrangements and sensitizing epidermal growth factor receptor (*EGFR*) mutations. The complete version of the NCCN Guidelines addresses all aspects of management for NSCLC, including screening, diagnosis, evaluation, staging, treatment, surveillance, and therapy for recurrence and metastasis. The NCCN Guidelines for NSCLC are updated at least once a year by the NCCN Panel; the 2015 updated version marks 20 years of their publication.[20]

Genetic Alterations

Targeted therapy is potentially very effective in select patients with advanced NSCLC harboring genetic alterations. The 2 best characterized examples to date represent patients with either *ALK* gene rearrangements or sensitizing *EGFR* mutations in their tumors.[4–6,8–12] Patients whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations are usually highly sensitive to EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy.[6,11,12] Patients whose tumors have *ALK* gene rearrangements are usually highly sensitive to ALK inhibitors.[4,5,8–10] Other actionable molecular abnormalities continue to be discovered and explored, including *BRAF* mutations and *ROS1* and *RET* rearrangements.[7,21–25]

Sensitizing *EGFR* mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients[26]; they include (in addition to the L858R and exon 19 deletions) other, rarer, drug-sensitive *EGFR* mutations, such as those

Non–Small Cell Lung Cancer, Version 6.2015



[a]See Principles of Pathologic Review (NSCL-A).
[ee]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[kk]Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in *ROS1*-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.
[ll]For performance status 0-4.
[tt]Patients who are intolerant to crizotinib may be switched to ceritinib.
[uu]For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

NSCL-18

at exon 21 (L861Q) and exon 18 (G719X).[27] Clinical characteristics associated with the presence of an *EGFR* mutation include adenocarcinoma, little or no smoking history, female sex, and East Asian ancestry.[6,11,28] Some *EGFR* mutations are activating, but resistant to standard EGFR TKIs, most notably exon 20 insertion mutations (with the exception of the rare FQEA exon 20 insertion, which is TKI-sensitive).[29–33] Most patients treated with the first- or second-generation EGFR TKIs (eg, erlotinib, gefitinib, afatinib) will develop disease progression approximately 1 year after initiating therapy. These patients have developed acquired resistance, associated with the selection of additional biological changes within the tumor. The most common of these changes is the T790M mutation, occurring in 50% to 60% of patients with *EGFR* mutations, because of the development of an exon 20 point mutation in cis with the original sensitizing mutation in the *EGFR*.[34–39] The presence of the T790M mutation in the TKI-naïve state has also been described in 2 separate contexts. First, highly sensitive sequencing techniques may be able to detect low-level clones harboring T790M that are later selected out by EGFR-TKI therapy. Because these clones may be present in only a small fraction of cells, the patient may still derive clinical benefit from the initial TKI therapy, although the progression-free survival may be shorter.[40] Second, families with germline T790M have been rarely described, wherein the development of lung cancer seems to depend on the development of a second, more classical L858R or exon 19 deletion.[41,42] In these families, because T790M is, by definition, present in all cells in the cancer (and in the host), first- or second-generation TKIs have little efficacy.[34–40,43]

Approximately 2% to 7% of patients with NSCLC have *ALK* gene rearrangements.[4,44–46] *EML4*

is the most common fusion partner with *ALK*, leading to at least 13 different variants, but other fusion partners with *ALK* have been reported.[46] Patients with *ALK* rearrangements usually have adenocarcinoma histology and little or no smoking history.[47] Most driver oncogenes tend to be mutually exclusive with other driver oncogenes. For example, *ALK* rearrangements tend to be mutually exclusive with other common driver mutations, such as *EGFR* or *KRAS* mutations, and vice versa.[48,49] Consequently, clinical enrichment (eg, only assessing patients with adenocarcinomas who are never/light smokers and/or those known to be wild-type for other common oncogenes) can be used to significantly increase the frequency of detecting either *ALK* rearrangements or sensitizing *EGFR* mutations in the tested population. However, because many exceptions to the classical phenotype exist, clinical enrichment may miss patients with *ALK* rearrangements or *EGFR* mutations who do not meet the classical phenotype.[48,50–53] Currently, crizotinib is the only ALK TKI approved for the treatment of patients with *ALK*-positive NSCLC who are ALK TKI–naïve. Similar to those treated with an EGFR TKI, patients treated with an ALK TKI will develop acquired resistance to therapy. However, the different mechanisms of acquired resistance to ALK TKIs seem to be more complex than the EGFR story. Ceritinib is a second-generation ALK inhibitor that is approved in the post-crizotinib setting and shows activity in approximately 60% of cases.[7]

Molecular Testing

The NCCN Guidelines for NSCLC recommend molecular testing for *ALK* gene rearrangements and *EGFR* mutations (category 1) in patients with advanced adenocarcinoma so that these patients can receive effective first-line treatment with targeted agents, such as crizotinib for *ALK*-positive disease or erlotinib or afatinib for sensitizing *EGFR* mutation–positive disease (see NSCL-16, NSCL-17, and NSCL-18, pages 517–519).[46,54–56] In patients with squamous cell carcinoma, in which these abnormalities are rarer, molecular testing for *ALK* gene rearrangements and sensitizing *EGFR* mutations can be considered, especially when the biopsy specimen is small and a mixed histology tumor cannot be ruled out, and/or in a patient with other significant risk factors such as minimal smoking history. Both erlotinib and afatinib are FDA-approved for first-line use in patients with proven sensitizing *EGFR* mutations; gefitinib and icotinib are also EGFR TKIs that are licensed in other countries.[57] *EGFR*, *KRAS*, and *ALK* genetic alterations do not usually overlap[49]; *KRAS* mutations are the most common mutation in lung adenocarcinomas. Although *KRAS* mutations are not currently considered directly actionable, upfront *KRAS* testing has been proposed as a sequential approach to determine which patients (ie, those positive for *KRAS* mutations) may not require additional molecular diagnostic testing.[46,55,58] However, sequential testing has also been criticized because it slows down the determination of actionable abnormalities and therefore decreases the ability of patients to be treated in the first-line setting. Moreover, sequential testing may deplete samples, necessitating additional biopsies to provide tissue for molecular testing in patients with lung cancer whose tumors are not easily accessible and therefore only small specimens are available.

DNA mutational analysis to detect *EGFR* mutations is the preferred method for determining whether patients are eligible for EGFR-TKI therapy[46,59–61]; immunohistochemistry (IHC) and EGFR copy number analysis are not recommended as a means of determining who should receive EGFR-TKI therapy.[46] Various DNA mutation detection assays can be used to determine the *EGFR* mutation status in tumor cells.[46] Direct sequencing of DNA corresponding to exons 18 to 21 of the *EGFR* gene is a reasonable approach; however, more-sensitive methods are available.[60,62–65] The joint College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/ASCO guidelines suggest that the methodology should detect all actionable mutations occurring with a frequency of 1% or more among *EGFR* mutations.[46] Mutation-specific screening assays for detecting multiple biomarkers simultaneously, such as the Sequenom MassARRAY system and SNaPshot Multiplex System, have been developed that can detect more than 50 point mutations, including a range of different sensitizing and resistant *EGFR* mutations.[66,67] *ALK* gene rearrangements can be detected using the dual probe "break-apart" fluorescence in situ hybridization (FISH) assay, which has been approved by the FDA for detecting *ALK* rearrangements and is a prerequisite before treatment with crizotinib.[46,68] However, several other assays can be used, including IHC for *ALK* or reverse

transcriptase–polymerase chain reaction (RT-PCR) for specific fusion transcripts.[45,68] Multiple studies have explored IHC for *ALK*; however, the antibody used, antigen retrieval technique, staining technique, scoring system, and cutpoint for determining positivity are not yet standardized. Some studies suggest that IHC can be used to screen for *ALK* rearrangements, either alone or as part of a sequential screen, reserving FISH analysis to confirm or deny some or all IHC-positive cases. However, until a specific widespread IHC methodology is validated, it is not yet possible to recommend IHC (not otherwise specified) for *ALK* screening.[44–46,69–76]

Serial testing of genes, such as *KRAS*, *EGFR*, and *ALK*, is likely to miss other potentially actionable targets and to deplete the scant tissue material. Next-generation sequencing (NGS; ie, massive parallel sequencing) can identify a very large number of genetic abnormalities at the same time. Comprehensive analysis of the whole genome, whole exome, and/or transcriptome sequencing using NGS technology has significantly advanced the understanding of the molecular pathogenesis of cancer. However, conducting these assays in the clinic routinely poses several challenges, including the complexity of bioinformatics, high cost, and a long turnaround time. Instead, targeted NGS using a panel of cancer-related genes allows unbiased variant detection using a single platform. It is now feasible to conduct these assays using formalin-fixed paraffin-embedded specimens. However, it is important to recognize that NGS requires quality control as much as any other diagnostic technique; because NGS is primer-dependent, the panel of genes and abnormalities detected with NGS will vary depending on the makeup of the NGS panel. For example, some panels can detect both mutations and gene rearrangements, and copy number variation, but they are not uniformly present in all NGS assays being conducted either commercially or in institutional laboratories.[77–80] The NCCN Guidelines Panel strongly endorses broader molecular profiling using either multiplex mutational analyses and FISH or appropriate NGS panels to minimize delay and tissue requirements (and thus increase both efficiency and cost-effectiveness when compared with doing multiple separate analyses) and to identify other actionable driver abnormalities beyond *ALK* and *EGFR* to ensure that patients receive the most appropriate treatment.[55] Patients found to have novel oncogenes with molecular profiling may be eligible for clinical trials of targeted agents that are being explored for their activity in these subtypes of disease.

Summary

These NCCN Guidelines Insights focus on recent updates to the 2015 NCCN Guidelines for NSCLC. Targeted therapy is very effective in select patients with advanced NSCLC who have specific genetic alterations. Therefore, it is important to test tumor tissue for these genetic alterations in patients with advanced NSCLC to determine whether they are candidates for targeted therapy. These NCCN Guidelines Insights describe the different testing methods currently available for determining whether patients have genetic alterations in the 2 most common actionable abnormalities, notably *ALK* gene rearrangements and sensitizing *EGFR* mutations.

The NCCN Guidelines for NSCLC recommend molecular testing for *ALK* gene rearrangements and *EGFR* mutations (category 1) in patients with advanced adenocarcinoma so that these patients can receive effective first-line treatment with targeted agents, such as erlotinib or afatinib for *EGFR*-sensitizing mutations, or crizotinib for *ALK*-rearranged disease (see NSCL-16, NSCL-17, and NSCL-18, pages 517–519).[46,54–56] In patients with squamous cell carcinoma, in which these abnormalities are much rarer, molecular testing for *ALK* gene rearrangements and sensitizing *EGFR* mutations can be considered, especially in patients with a small biopsy specimen in which a mixed histology component may be missed or in those who have other risk factors, such as minimal smoking history. DNA mutational analysis for sensitizing *EGFR* mutations is the preferred method to determine eligibility for EGFR-TKI therapy.[46,59–61] Direct sequencing of DNA corresponding to exons 18 to 21 of the *EGFR* gene is a reasonable approach; however, more-sensitive mutation-specific methods are available.[60,62–65] *ALK* gene rearrangements can be detected using dual-probe "break-apart" FISH assay.[46] Studies suggest that other assays, such as RT-PCR or IHC, can also be used to screen for *ALK* rearrangements. However, because multiple different techniques exist for IHC, until a specific widespread *ALK* IHC technique is validated, it is not yet possible to recommend IHC for *ALK* screening. Multiplex molecular test-

ing may be possible for actionable mutations and for gene rearrangements, depending on the techniques and platforms used. Multiplex molecular testing offers potential advantages by minimizing delays and tissue requirements, potentially increasing both efficiency and cost-effectiveness, and identifying rarer but still potentially actionable abnormalities in other driver oncogenes that would make patients candidates for enrollment onto clinical trials.

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Non–Small Cell Lung Cancer, Version 6.2015

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Posttest Questions

1. Which of the following is true about sensitizing *EGFR* mutations?
   1. The tumors are sensitive to erlotinib.
   2. The tumors are sensitive to bevacizumab.
   3. The tumors are sensitive to afatinib.
   4. The tumors are sensitive to crizotinib and ceritinib.

   Choose one answer:
   a. 1 and 3
   b. 2 and 3
   c. 2 and 4
   d. 1 and 4
2. True or False: *ALK* rearrangements tend to be mutually exclusive with other common driver mutations, such as *EGFR* or *KRAS* mutations, and vice versa.
3. A 65-year-old woman has adenocarcinoma with a sensitizing *EGFR* mutation. She has been treated with TKIs for 1 year but recently her tumors have progressed. Which of the following is a possible mechanism for her progression?
   a. She has developed acquired resistance due to a FQEA exon 20 insertion mutation.
   b. She has developed acquired resistance due to a T790M mutation.
   c. She has developed acquired resistance due to an EGFR exon 19 deletion.
   d. She has developed acquired resistance due to an EGFR exon 21 L858R mutation.