

## NCCN Guidelines® Insights

Non–Small Cell Lung Cancer,  
Version 6.2015

## Featured Updates to the NCCN Guidelines

David S. Ettinger, MD<sup>1,\*</sup>; Douglas E. Wood, MD<sup>2</sup>; Wallace Akerley, MD<sup>3</sup>; Lyudmila A. Bazhenova, MD<sup>4</sup>; Hossein Borghaei, DO, MS<sup>5</sup>; David Ross Camidge, MD, PhD<sup>6,\*</sup>; Richard T. Cheney, MD<sup>7</sup>; Lucian R. Chirieac, MD<sup>8</sup>; Thomas A. D'Amico, MD<sup>9</sup>; Todd L. Demmy, MD<sup>7</sup>; Thomas J. Dilling, MD<sup>10</sup>; M. Chris Dobelbower, MD, PhD<sup>11</sup>; Ramaswamy Govindan, MD<sup>12,\*</sup>; Frederic W. Grannis Jr, MD<sup>13</sup>; Leora Horn, MD, MSc<sup>14,\*</sup>; Thierry M. Jahan, MD<sup>15</sup>; Ritsuko Komaki, MD<sup>16</sup>; Lee M. Krug, MD<sup>17</sup>; Rudy P. Lackner, MD<sup>18</sup>; Michael Lanuti, MD<sup>19</sup>; Rogerio Lilenbaum, MD<sup>20</sup>; Jules Lin, MD<sup>21</sup>; Billy W. Loo Jr, MD, PhD<sup>22</sup>; Renato Martins, MD, MPH<sup>23</sup>; Gregory A. Otterson, MD<sup>24</sup>; Jyoti D. Patel, MD<sup>25</sup>; Katherine M. Pisters, MD<sup>16</sup>; Karen Reckamp, MD, MS<sup>13</sup>; Gregory J. Riely, MD, PhD<sup>17</sup>; Eric Rohren, MD, PhD<sup>16</sup>; Steven E. Schild, MD<sup>26</sup>; Theresa A. Shapiro, MD, PhD<sup>1</sup>; Scott J. Swanson, MD<sup>8</sup>; Kurt Tauer, MD<sup>27</sup>; Stephen C. Yang, MD<sup>1</sup>; Kristina Gregory, RN, MSN<sup>28,\*</sup>; and Miranda Hughes, PhD<sup>28,\*</sup>

## 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)

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

\*Provided content development and/or authorship assistance.

## 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.**

These NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding the content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their applications or use in any way.

**The full and most current version of these NCCN Guidelines are available at [NCCN.org](http://NCCN.org).**

© National Comprehensive Cancer Network, Inc. 2015, All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN.

## Non–Small Cell Lung Cancer, Version 6.2015

**NCCN: Continuing Education****Accreditation Statement**

This activity is designated to meet the educational needs of physicians, nurses, and pharmacists involved in the management of patients with cancer. There is no fee for this article. The National Comprehensive Cancer Network (NCCN) is accredited by the ACCME to provide continuing medical education for physicians. NCCN designates this journal-based CE activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NCCN is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

NCCN designates this educational activity for a maximum of 1.0 contact hour. Accreditation as a provider refers to recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity. Kristina M. Gregory, RN, MSN, OCN, is our nurse planner for this educational activity.



National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. NCCN designates this continuing education activity for 1.0 contact hour(s) (0.1 CEUs) of continuing education credit in states that recognize ACPE accredited providers. This is a knowledge-based activity. UAN: 0836-00015-006-H01-P

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at <http://education.nccn.org/node/65998>; and 4) view/print certificate.

Release date: May 13, 2015; Expiration date: May 13, 2016

**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****Editor:**

**Kerrin M. Green, MA**, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*, has disclosed that she has no relevant financial relationships.

**CE Planners:**

**Deborah J. Moonan, RN, BSN**, Director, Continuing Education, NCCN, has disclosed that she has no relevant financial relationships.

**Ann Gianola, MA**, Manager, Continuing Education Accreditation & Program Operations, NCCN, has disclosed that she has no relevant financial relationships.

**Kristina M. Gregory, RN, MSN, OCN**, Vice President, Clinical Information Operations, NCCN, has disclosed that she has no relevant financial relationships.

**Rashmi Kumar, PhD**, Senior Manager, Clinical Content, NCCN, has disclosed that she has no relevant financial relationships.

**Individuals Who Provided Content Development and/or Authorship Assistance:**

**David S. Ettinger, MD**, Panel Chair, has disclosed that he is a scientific advisor for AMAG, ARIAD Pharmaceuticals, Inc., Biodesix, Boehringer Ingelheim GmbH, Eisai Inc., Eli Lilly and Company, Genentech, Inc., Gilead Sciences, Inc., and Helsinn Pharmaceuticals, and receives consultant fees/honoraria from Bristol-Myers Squibb Company.

**David Ross Camidge, MD, PhD**, Panel Member, has disclosed that he is a scientific advisor for Astex, Eli Lilly and Company, Genentech, Inc., Immunogen, IndiPharm, Novartis Pharmaceuticals Corporation, and Roche Laboratories, Inc., and receives consultant fees/honoraria from ARIAD Pharmaceuticals, Inc. and Boehringer Ingelheim GmbH; and he receives grant/research support from ARIAD Pharmaceuticals, Inc.

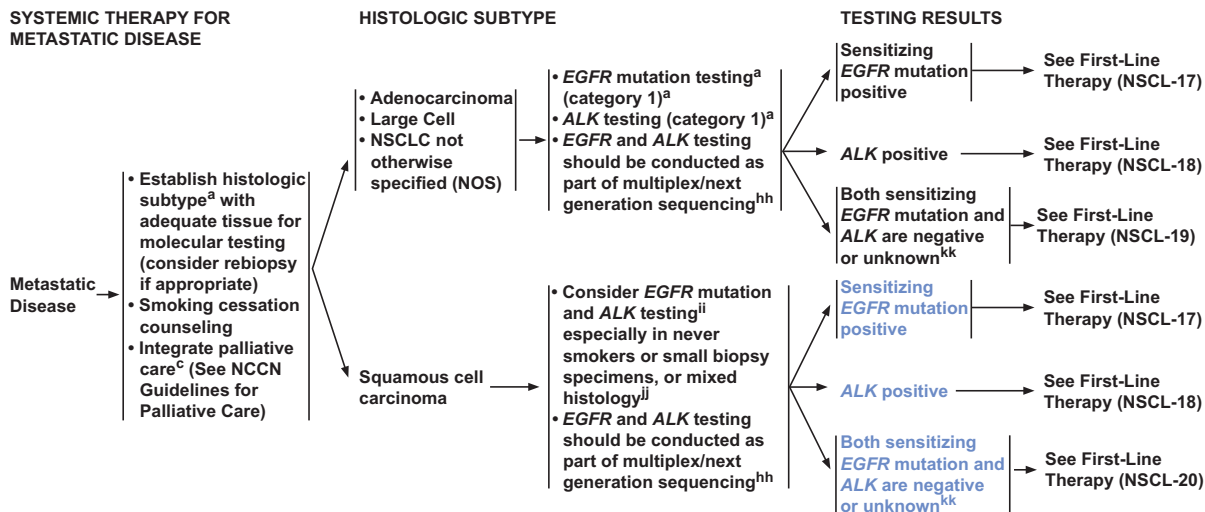
**Ramaswamy Govindan, MD**, Panel Member, has disclosed that he receives consultant fees/honoraria from Bayer HealthCare, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Covidien AG, GlaxoSmithKline, Mallinckrodt, Merck & Co., Inc., Pfizer Inc., and Roche Genentech.

**Leora Horn, MD, MSc**, Panel Member, has disclosed that she receives grant/research support from Astellas Pharma US, Inc. and consultant fees/honoraria from Genentech, Inc. and Merck & Co, Inc., and is a scientific advisory for Bayer HealthCare and Xcovery.

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

Supported by an educational grant from Eisai; a contribution from Exelixis Inc.; educational grants from Bristol-Myers Squibb, Genentech BioOncology, Merck, Novartis Oncology, Novocure; and by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

# Non-Small Cell Lung Cancer, Version 6.2015



<sup>a</sup>See Principles of Pathologic Review (NSCL-A).  
<sup>c</sup>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.  
<sup>h</sup>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).  
<sup>i</sup>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, Bharna G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). *Curr Protoc Hum Genet* 2008;chapter 10:unit 10.11.  
<sup>j</sup>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.  
<sup>k</sup>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.

Version 6.2015 © National Comprehensive Cancer Network, Inc. 2015. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

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.

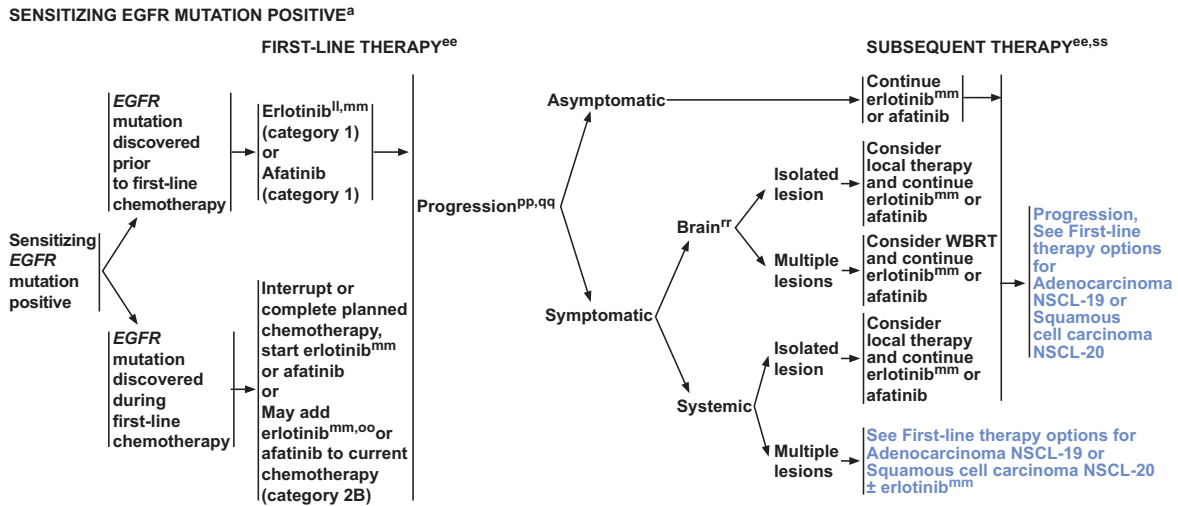
**All recommendations are category 2A unless otherwise noted.**

**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.<sup>1</sup> 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%.<sup>2,3</sup> 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

## Non–Small Cell Lung Cancer, Version 6.2015



<sup>a</sup>See Principles of Pathologic Review (NSCL-A).

<sup>ee</sup>See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

<sup>ll</sup>For performance status 0-4.

<sup>mm</sup>In areas of the world where gefitinib is available, it may be used in place of erlotinib.

<sup>oo</sup>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.

<sup>pp</sup>Prior to changing therapy, a biopsy is reasonable to determine mechanism of acquired resistance.

<sup>qq</sup>Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

<sup>rr</sup>Consider pulse erlotinib for carcinomatosis meningitis.

<sup>ss</sup>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.

Version 6.2015 © National Comprehensive Cancer Network, Inc. 2015. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NSCL-17

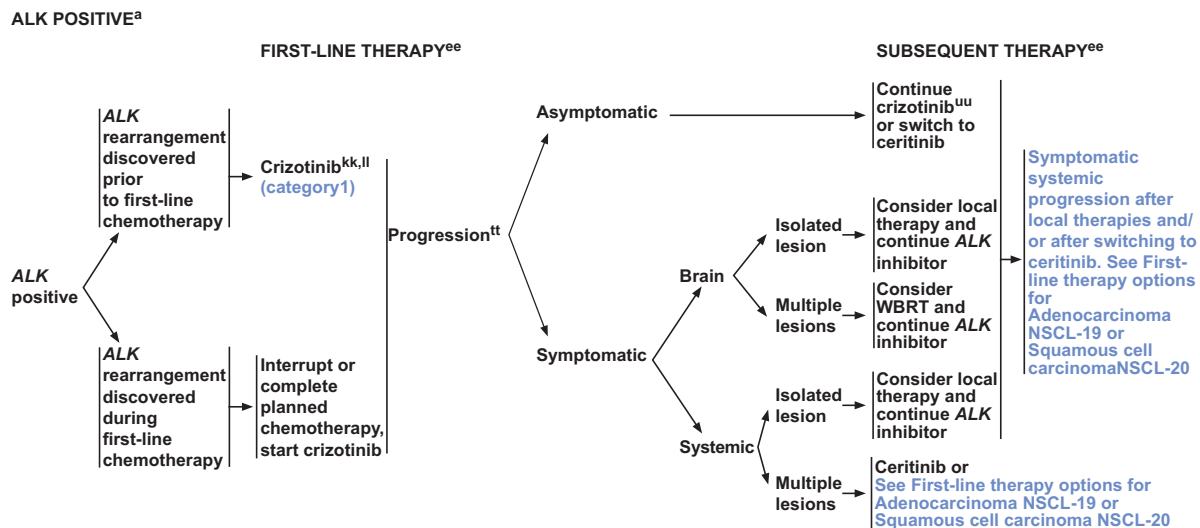
for patients with the specific molecular aberrations in their tumors that make them sensitive to these therapies.<sup>4-19</sup> Therefore, it is important to perform molecular testing on tumor tissue from patients with advanced non–small cell lung cancer (NSCLC) to determine whether they have genetic 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.<sup>20</sup>

## 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.<sup>4-6,8-12</sup> 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.<sup>6,11,12</sup> Patients whose tumors have *ALK* gene rearrangements are usually highly sensitive to *ALK* inhibitors.<sup>4,5,8-10</sup> Other actionable molecular abnormalities continue to be discovered and explored, including *BRAF* mutations and *ROS1* and *RET* rearrangements.<sup>7,21-25</sup>

Sensitizing *EGFR* mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients<sup>26</sup>; 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



<sup>a</sup>See Principles of Pathologic Review (NSCL-A).

<sup>ee</sup>See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

<sup>kk</sup>Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-H, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

<sup>ll</sup>For performance status 0-4.

<sup>tt</sup>Patients who are intolerant to crizotinib may be switched to ceritinib.

<sup>uu</sup>For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

Version 6.2015 © National Comprehensive Cancer Network, Inc. 2015. All rights reserved. The NCCN Guidelines<sup>®</sup> and this illustration may not be reproduced in any form without the express written permission of NCCN<sup>®</sup>.

NSCL-18

at exon 21 (L861Q) and exon 18 (G719X).<sup>27</sup> Clinical characteristics associated with the presence of an *EGFR* mutation include adenocarcinoma, little or no smoking history, female sex, and East Asian ancestry.<sup>6,11,28</sup> 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).<sup>29–33</sup> 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*.<sup>34–39</sup> 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.<sup>40</sup> 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.<sup>41,42</sup> 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.<sup>34–40,43</sup>

Approximately 2% to 7% of patients with NSCLC have *ALK* gene rearrangements.<sup>4,44–46</sup> *EML4*

## Non–Small Cell Lung Cancer, Version 6.2015

is the most common fusion partner with *ALK*, leading to at least 13 different variants, but other fusion partners with *ALK* have been reported.<sup>46</sup> Patients with *ALK* rearrangements usually have adenocarcinoma histology and little or no smoking history.<sup>47</sup> 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.<sup>48,49</sup> 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.<sup>48,50–53</sup> 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.<sup>7</sup>

### 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).<sup>46,54–56</sup> 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 erlo-

tinib 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.<sup>57</sup> *EGFR*, *KRAS*, and *ALK* genetic alterations do not usually overlap<sup>49</sup>; *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.<sup>46,55,58</sup> 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<sup>46,59–61</sup>; immunohistochemistry (IHC) and *EGFR* copy number analysis are not recommended as a means of determining who should receive *EGFR*-TKI therapy.<sup>46</sup> Various DNA mutation detection assays can be used to determine the *EGFR* mutation status in tumor cells.<sup>46</sup> Direct sequencing of DNA corresponding to exons 18 to 21 of the *EGFR* gene is a reasonable approach; however, more-sensitive methods are available.<sup>60,62–65</sup> 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.<sup>46</sup> 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.<sup>66,67</sup> *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.<sup>46,68</sup> However, several other assays can be used, including IHC for *ALK* or reverse

## Non–Small Cell Lung Cancer, Version 6.2015

transcriptase–polymerase chain reaction (RT-PCR) for specific fusion transcripts.<sup>45,68</sup> 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.<sup>44–46,69–76</sup>

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.<sup>77–80</sup> 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.<sup>55</sup> 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).<sup>46,54–56</sup> 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.<sup>46,59–61</sup> 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.<sup>60,62–65</sup> *ALK* gene rearrangements can be detected using dual-probe “break-apart” FISH assay.<sup>46</sup> 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-

## Non–Small Cell Lung Cancer, Version 6.2015

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.

## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5–29.
2. Howlander N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2011, based on November 2013 SEER data submission, posted to the SEER web site, April 2014. Bethesda, MD: National Cancer Institute; 2014. Available at: [http://seer.cancer.gov/csr/1975\\_2011/](http://seer.cancer.gov/csr/1975_2011/). Accessed April 21, 2015.
3. SEER Cancer Statistics Factsheets: Lung and Bronchus Cancer. Bethesda, MD: National Cancer Institute. Available at: <http://seer.cancer.gov/statfacts/html/lungb.html>. Accessed April 21, 2015.
4. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363:1693–1703.
5. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 2012;13:1011–1019.
6. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–246.
7. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;370:1189–1197.
8. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014;371:2167–2177.
9. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013;368:2385–2394.
10. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol* 2011;12:1004–1012.
11. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
12. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015;16:141–151.
13. Aberle DR, Abtin F, Brown K. Computed tomography screening for lung cancer: has it finally arrived? Implications of the national lung screening trial. *J Clin Oncol* 2013;31:1002–1008.
14. Reck M, Heigener DF, Mok T, et al. Management of non-small-cell lung cancer: recent developments. *Lancet* 2013;382:709–719.
15. Forde PM, Ettinger DS. Targeted therapy for non-small-cell lung cancer: past, present and future. *Expert Rev Anticancer Ther* 2013;13:745–758.
16. Ettinger DS. Ten years of progress in non-small cell lung cancer. *J Natl Compr Canc Netw* 2012;10:292–295.
17. Johnson DH, Schiller JH, Bunn PA Jr. Recent clinical advances in lung cancer management. *J Clin Oncol* 2014;32:973–982.
18. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
19. Wood DE, Kazerooni E, Baum SL, et al. Lung cancer screening, version 1.2015. *J Natl Compr Canc Netw* 2015;13:23–34.
20. Ettinger DS, Cox JD, Ginsberg RJ, et al. NCCN non-small-cell lung cancer practice guidelines. The National Comprehensive Cancer Network. *Oncology (Williston Park)* 1996;10:81–111.
21. Mazieres J, Zalcman G, Crino L, et al. crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. *J Clin Oncol* 2015;33:992–999.
22. Villaruz LC, Socinski MA, Abberbock S, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. *Cancer* 2015;121:448–456.
23. Peters S, Michielin O, Zimmermann S. Dramatic response induced by vemurafenib in a BRAF V600E-mutated lung adenocarcinoma. *J Clin Oncol* 2013;31:e341–344.
24. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol* 2012;30:863–870.
25. Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov* 2013;3:630–635.
26. Li C, Fang R, Sun Y, et al. Spectrum of oncogenic driver mutations in lung adenocarcinomas from East Asian never smokers. *PLoS One* 2011;6:e28204.
27. Riely GJ, Politi KA, Miller VA, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. *Clin Cancer Res* 2006;12:7232–7241.
28. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol* 2011;29:2866–2874.
29. Arcila ME, Nafa K, Chaff JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol Cancer Ther* 2013;12:220–229.
30. Oxnard GR, Lo PC, Nishino M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. *J Thorac Oncol* 2013;8:179–184.
31. Lund-Iversen M, Kleinberg L, Fjellbirkeland L, et al. Clinicopathological characteristics of 11 NSCLC patients with EGFR-exon 20 mutations. *J Thorac Oncol* 2012;7:1471–1473.
32. Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. *Lancet Oncol* 2012;13:e23–31.
33. Yasuda H, Park E, Yun CH, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. *Sci Transl Med* 2013;5:216ra177.
34. Finlay MR, Anderton M, Ashton S, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. *J Med Chem* 2014;57:8249–8267.
35. Yu HA, Arcila ME, Rekhman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013;19:2240–2247.
36. Gainor JF, Shaw AT. Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer. *J Clin Oncol* 2013;31:3987–3996.
37. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med* 2005;2:e73.
38. Kosaka T, Yatabe Y, Endoh H, et al. Analysis of epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer and acquired resistance to gefitinib. *Clin Cancer Res* 2006;12:5764–5769.
39. Onitsuka T, Uramoto H, Nose N, et al. Acquired resistance to gefitinib: the contribution of mechanisms other than the T790M, MET, and HGF status. *Lung Cancer* 2010;68:198–203.
40. Rosell R, Molina MA, Costa C, et al. Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations. *Clin Cancer Res* 2011;17:1160–1168.
41. Yu HA, Arcila ME, Harlan Fleischut M, et al. Germline EGFR T790M mutation found in multiple members of a familial cohort. *J Thorac Oncol* 2014;9:554–558.
42. Oxnard GR, Miller VA, Robson ME, et al. Screening for germline EGFR T790M mutations through lung cancer genotyping. *J Thorac Oncol* 2012;7:1049–1052.



## Non–Small Cell Lung Cancer, Version 6.2015

43. Gazdar A, Robinson L, Oliver D, et al. Hereditary lung cancer syndrome targets never smokers with germline EGFR gene T790M mutations. *J Thorac Oncol* 2014;9:456–463.
44. Wynes MW, Sholl LM, Dietel M, et al. An international interpretation study using the ALK IHC antibody D5F3 and a sensitive detection kit demonstrates high concordance between ALK IHC and ALK FISH and between evaluators. *J Thorac Oncol* 2014;9:631–638.
45. Ali G, Proietti A, Pelliccioni S, et al. ALK rearrangement in a large series of consecutive non-small cell lung cancers: comparison between a new immunohistochemical approach and fluorescence in situ hybridization for the screening of patients eligible for crizotinib treatment. *Arch Pathol Lab Med* 2014;138:1449–1458.
46. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013;8:823–859.
47. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009;27:4247–4253.
48. Camidge DR, Kono SA, Flacco A, et al. Optimizing the detection of lung cancer patients harboring anaplastic lymphoma kinase (ALK) gene rearrangements potentially suitable for ALK inhibitor treatment. *Clin Cancer Res* 2010;16:5581–5590.
49. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA* 2014;311:1998–2006.
50. D'Angelo SP, Pietanza MC, Johnson ML, et al. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. *J Clin Oncol* 2011;29:2066–2070.
51. Atherly AJ, Camidge DR. The cost-effectiveness of screening lung cancer patients for targeted drug sensitivity markers. *Br J Cancer* 2012;106:1100–1106.
52. Weickhardt AJ, Camidge DR. The therapeutic potential of anaplastic lymphoma kinase inhibitors in lung cancer: rationale and clinical evidence. *Clin Invest* 2011;1:1119–1126.
53. Dogan S, Shen R, Ang DC, et al. Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. *Clin Cancer Res* 2012;18:6169–6177.
54. Besse B, Adjei A, Baas P, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. *Ann Oncol* 2014;25:1475–1484.
55. Kerr KM, Bubendorf L, Edelman MJ, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. *Ann Oncol* 2014;25:1681–1690.
56. Leigh NB, Rekhtman N, Biermann WA, et al. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: american society of clinical oncology endorsement of the college of american pathologists/international association for the study of lung cancer/association for molecular pathology guideline. *J Clin Oncol* 2014;32:3673–3679.
57. Shi Y, Zhang L, Liu X, et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. *Lancet Oncol* 2013;14:953–961.
58. Roberts PJ, Stinchcombe TE. KRAS mutation: should we test for it, and does it matter? *J Clin Oncol* 2013;31:1112–1121.
59. Han SW, Kim TY, Jeon YK, et al. Optimization of patient selection for gefitinib in non-small cell lung cancer by combined analysis of epidermal growth factor receptor mutation, K-ras mutation, and Akt phosphorylation. *Clin Cancer Res* 2006;12:2538–2544.
60. Dacic S. EGFR assays in lung cancer. *Adv Anat Pathol* 2008;15:241–247.
61. Sholl LM, Xiao Y, Joshi V, et al. EGFR mutation is a better predictor of response to tyrosine kinase inhibitors in non-small cell lung carcinoma than FISH, CISH, and immunohistochemistry. *Am J Clin Pathol* 2010;133:922–934.
62. Eberhard DA, Giaccone G, Johnson BE, Non-Small-Cell Lung Cancer Working Group. Biomarkers of response to epidermal growth factor receptor inhibitors in Non-Small-Cell Lung Cancer Working Group: standardization for use in the clinical trial setting. *J Clin Oncol* 2008;26:983–994.
63. Pao W, Ladanyi M. Epidermal growth factor receptor mutation testing in lung cancer: searching for the ideal method. *Clin Cancer Res* 2007;13:4954–4955.
64. Hirsch FR, Bunn PA Jr. EGFR testing in lung cancer is ready for prime time. *Lancet Oncol* 2009;10:432–433.
65. Shepherd FA, Tsao MS. Epidermal growth factor receptor biomarkers in non-small-cell lung cancer: a riddle, wrapped in a mystery, inside an enigma. *J Clin Oncol* 2010;28:903–905.
66. Lovly CM, Horn L. Molecular profiling of lung cancer. *My Cancer Genome* Web site. Available at: <http://www.mycancergenome.org/content/disease/lung-cancer> (updated February 6, 2015). Accessed April 21, 2015.
67. Dias-Santagata D, Akhavanfard S, David SS, et al. Rapid targeted mutational analysis of human tumours: a clinical platform to guide personalized cancer medicine. *EMBO Mol Med* 2010;2:146–158.
68. Weickhardt AJ, Aisner DL, Franklin WA, et al. Diagnostic assays for identification of anaplastic lymphoma kinase-positive non-small cell lung cancer. *Cancer* 2013;119:1467–1477.
69. Thunnissen E, Bubendorf L, Dietel M, et al. EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations. *Virchows Arch* 2012;461:245–257.
70. Kim H, Yoo SB, Choe JY, et al. Detection of ALK gene rearrangement in non-small cell lung cancer: a comparison of fluorescence in situ hybridization and chromogenic in situ hybridization with correlation of ALK protein expression. *J Thorac Oncol* 2011;6:1359–1366.
71. Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. *Clin Cancer Res* 2009;15:5216–5223.
72. Mino-Kenudson M, Chirieac LR, Law K, et al. A novel, highly sensitive antibody allows for the routine detection of ALK-rearranged lung adenocarcinomas by standard immunohistochemistry. *Clin Cancer Res* 2010;16:1561–1571.
73. von Laffert M, Warth A, Penzel R, et al. Multicenter immunohistochemical ALK-testing of non-small-cell lung cancer shows high concordance after harmonization of techniques and interpretation criteria. *J Thorac Oncol* 2014;9:1685–1692.
74. Zhou J, Zhao J, Sun K, et al. Accurate and economical detection of ALK positive lung adenocarcinoma with semiquantitative immunohistochemical screening. *PLoS One* 2014;9:e92828.
75. Minca EC, Portier BP, Wang Z, et al. ALK status testing in non-small cell lung carcinoma: correlation between ultrasensitive IHC and FISH. *J Mol Diagn* 2013;15:341–346.
76. Shaw AT, Solomon B, Kenudson MM. Crizotinib and testing for ALK. *J Natl Compr Canc Netw* 2011;9:1335–1341.
77. Cardarella S, Ortiz TM, Joshi VA, et al. The introduction of systematic genomic testing for patients with non-small-cell lung cancer. *J Thorac Oncol* 2012;7:1767–1774.
78. Li T, Kung HJ, Mack PC, Gandara DR. Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies. *J Clin Oncol* 2013;31:1039–1049.
79. Planchard D. Identification of driver mutations in lung cancer: first step in personalized cancer. *Target Oncol* 2013;8:3–14.
80. Hagemann IS, Devarakonda S, Lockwood CM, et al. Clinical next-generation sequencing in patients with non-small cell lung cancer. *Cancer* 2015;121:631–639.

## Non–Small Cell Lung Cancer, Version 6.2015

### Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at <http://education.nccn.org/node/65998>; and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-

choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on “New Member? Sign up here” link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.

### 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.