Excerpt from Needs Assessment

Molecular Testing in Lung Cancer

Target Audience

This activity is intended for oncologists, pathologists, surgeons, and clinical geneticists.

Goal Statement

The goal of this activity is to increase understanding of the updated 2018 American Society of Clinical Oncology (ASCO)-endorsed guidelines[1] and recommendations for molecular testing in lung cancer patients for treatment with targeted tyrosine kinase inhibitors (TKIs).

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

1. Describe the most recent updates in the ASCO-endorsed clinical practice guidelines for molecular testing for patient selection in lung cancer
2. Summarize the clinical significance of molecular testing
3. Identify the patient population for whom molecular testing is recommended
4. List the genes to be tested and the methods for conducting molecular testing
5. Recognize the importance of incorporating reflex testing by pathologists

Background

Lung cancer is the leading cause of cancer death in the United States, with over 200,000 estimated new diagnoses of lung cancer in 2017.[2] Lung adenocarcinoma, which accounts for almost half of all lung cancers, is the most common subtype.[3] As adenocarcinoma may be asymptomatic in early stages, most patients present with advanced or distantly metastatic disease at diagnosis. Advanced lung cancer patients have a poor prognosis, with a median survival of 1 year.[3-4] Moreover, less than 5% of patients with advanced or metastatic lung cancer live past 5 years.[3]

Advances in our understanding of lung cancer biology and molecular testing methods have helped identify key driver mutations that can be used to inform clinical practice. Mutations in the kinase domain of the epidermal growth factor receptor (EGFR) in tumors of TKI-responsive lung cancer patients were first described in 2004.[5-6] Since then, more molecular alterations have been discovered in lung tumors, especially in lung adenocarcinoma. The use of targeted TKI therapy in patients harboring clinically relevant molecular alterations has become the standard of care for patients with lung cancer.

The first edition of the Association for the College of American Pathologists (CAP)/Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP) joint guideline for molecular testing to guide the selection of patients with lung cancer for treatment with TKIs based on *EGFR* and anaplastic lymphoma kinase (*ALK*) alterations was published in 2013.[7] ASCO endorsed the 2013 guideline and included recommendations for selecting patients for testing, test sample specifications, and testing methodology.[8] The CAP/IASLC/AMP updated the guidelines on molecular testing for selection of patients with lung cancer for treatment with targeted TKIs. The 2017 updates were based on the advances in the past few years since the publication of the first joint guideline. ASCO critically appraised and endorsed the revised guidelines in February 2018.[1] It is essential that oncologists and clinical geneticists understand the most recent ASCO-endorsed guidelines and their applications in clinical practice.

Gap #1: Clinicians may not be aware of the most recent updates to the ASCO-endorsed guidelines for molecular testing for patient selection in lung cancer.

The 2018 ASCO-endorsed guidelines for molecular testing in lung cancer

The new recommendations in the 2018 ASCO-endorsed guideline addressed the following aspects of molecular testing in lung cancer.

Genes recommended for testing in lung cancer patients

The CAP, IASLC, and AMP suggest 3 genes—*EGFR*, *ALK*, and *ROS1*—constitute the minimum set of genes that must be offered by all labs that provide genomic testing services for lung cancers. The ASCO panel recommends proto-oncogene receptor tyrosine kinase ROS1 testing be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics. The ASCO panel suggests that ROS1 immunohistochemistry (IHC) may be used as a screening test for advanced lung adenocarcinoma patients but that positive ROS1 IHC results should be confirmed using cytogenetic or molecular methods. These recommendations were based on the efficacy with which *ROS1*-involving structural rearrangements can be treated with targeted inhibitors.[9-18]

ASCO further recommends that *BRAF* testing should be performed on all advanced lung adenocarcinoma patients, irrespective of clinical characteristics. ASCO does not recommend *RET*, *ERBB2* (*HER2*), *KRAS*, or *MET* molecular testing as routine stand-alone assays outside the context of clinical trials. However, the CAP/IASLC/AMP[19] and ASCO[1] do deem it appropriate to include *RET*, *ERBB2* (*HER2*), *KRA*S, or *MET* as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, *BRAF*, and *ROS1* testing is negative and if there is sufficient material available for testing.

Molecular testing methods

For *ALK* testing, ASCO stated in the updated guidelines that IHC is an equivalent alternative to fluorescent in situ hybridization (FISH). Also, multiplexed genetic sequencing panels are noted as the preferred choice, where available, over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, *BRAF*, and *ROS1*.

Molecular testing for lung cancers without an adenocarcinoma component

ASCO suggests the use of molecular biomarker testing in tumors with either an adenocarcinoma component, non-squamous, non–small-cell histology, or in those with any non-small-cell histology when clinical features indicate a higher probability of an oncogenic driver, such as young age (<50 years) and light or absent tobacco exposure. The 2017 CAP/IASLC/AMP panel notes that strict reliance upon adenocarcinoma histology may occasionally exclude some patients without a definitive diagnosis of adenocarcinoma, who may yet benefit from targeted therapy. This may be true especially for small biopsies that partially sample a larger tumor.

Testing in patients who have relapsed on targeted therapy

In patients with lung adenocarcinoma who harbor sensitizing *EGFR* mutations and have progressed after treatment with an EGFR-targeted TKI, physicians must use *EGFR* T790M mutational testing when selecting patients for third-generation EGFR-targeted therapy.[1] Assays capable of detecting *EGFR* T790M mutations in as little as 5% viable cells are recommended for testing in patients with secondary clinical resistance to EGFR-targeted TKIs.

The T790M mutation in the same *EGFR* allele that harbors the original sensitizing mutation is a major mechanism of secondary clinical resistance to the EGFR-directed TKIs, erlotinib and gefitinib.[20-21] *EGFR* T790M blocks TKI-mediated inhibition of EGFR. Third-generation EGFR TKIs, such as osimertinib, are active in the presence of *EGFR* T790M mutation. Furthermore, in cases where rare responses have been reported to third-generation inhibitors in *EGFR* T790M–negative disease, other resistance mechanisms such as MET or ERBB2 amplification may be present.[21] In the latter case, the resistant tumors may be more effectively targeted by other agents. Therefore, knowledge of the T790M mutation status can guide appropriate therapy decisions in cases with secondary clinical resistance to an EGFR inhibitor.

Testing for circulating cell-free DNA (cfDNA)

The guideline has no recommendations for use of cfDNA testing, due to insufficient evidence. They note that, in some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify *EGFR* mutations.

Learning Objective: Describe the most recent updates in the ASCO-endorsed clinical practice guidelines for molecular testing for selecting lung cancer patients for TKI therapy.

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