Molecular Testing for Selection of Patients with Lung Cancer for EGFR and ALK Tyrosine Kinase Inhibitors

ASCO Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association of Molecular Pathologists Guideline
Introduction

A growing body of research has demonstrated relationships between specific genomic alterations and response of advanced-stage lung cancer to targeted therapies.

The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) jointly published a guideline in 2013 on molecular testing for the selection of patients with lung cancer for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors.

The guideline addresses which patients and which samples should be tested, when testing should be performed, and which methods should be used.
ASCO Endorsement Process

The ASCO Clinical Practice Guidelines Committee endorsement review process includes:

• a methodological review by ASCO guidelines staff
• a content review by an ad hoc expert panel
• final endorsement approval by ASCO CPGC.

The full ASCO Endorsement methodology supplement can be found at:
www.asco.org/endorsements/lungmarkers

CAP/IASLC/AMP Guideline Methodology can be found at:
http://www.archivesofpathology.org/userimages/ContentEditor/1365017621306/2013-3-26_Supplemental_Digital%20Content.pdf
Clinical Questions

The original guideline addresses five principal questions targeted towards patients with non-small cell lung cancer (NSCLC):

(1) When should molecular testing for NSCLC be performed?
(2) How should $EGFR$ testing be performed?
(3) How should $ALK$ testing be performed?
(4) Should other genes be routinely tested in lung adenocarcinoma?
(5) How should molecular testing of lung adenocarcinomas be implemented and operationalized?
Recommendation Overview

• The major recommendation from the CAP/IASLC/AMP:
  – use testing for EGFR mutations and ALK rearrangements to guide patient selection for therapy with EGFR or ALK inhibitors, respectively, in all patients with advanced-stage lung adenocarcinoma or tumors with an adenocarcinoma component, irrespective of clinical characteristics (smoking history, sex, race, or other clinical factors).

• Also recommended:
  – small tumor samples of other histologies, for which an adenocarcinoma component cannot be excluded because of sampling, can be considered for testing, particularly if clinical criteria are suggestive (eg, younger age, lack of smoking history).
  – Both primary tumors and metastatic lesions are suitable for testing.

• Additional guidance is provided regarding laboratory methods, specimen processing, testing validation, quality assurance, and result reporting in the full guideline:
Recommendation Highlights:

When should molecular testing of lung cancers be performed?

• 1.1a: *EGFR* molecular testing should be used to select patients for *EGFR*-targeted TKI therapy; patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

• 1.1b: *ALK* molecular testing should be used to select patients for *ALK*-targeted TKI therapy; patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

• 1.2: In the setting of lung cancer resection specimens: *EGFR* and *ALK* testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade.
  — In the setting of fully excised lung cancer specimens: *EGFR* and *ALK* testing is not recommended in lung cancers that lack any adenocarcinoma component, such as pure squamous cell carcinomas, pure small-cell carcinomas, or large-cell carcinomas lacking any IHC evidence of adenocarcinoma differentiation.
Recommendation Highlights:

When should molecular testing of lung cancers be performed?

• 1.3: In the setting of more limited lung cancer specimens (biopsies, cytology) in which an adenocarcinoma component cannot be completely excluded, **EGFR** and **ALK** testing may be performed in cases that show squamous or small-cell histology, but clinical criteria (eg, younger age, lack of smoking history) may be useful in selecting a subset of these samples for testing.

• 1.4: To determine **EGFR** and **ALK** status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing.

• 1.5: (Expert consensus) For patients with multiple, apparently separate, primary lung adenocarcinomas, each tumor may be tested, but testing of multiple different areas within a single tumor is not necessary.
Recommendations Highlights:
When should molecular testing of lung cancers be performed?

• 2.1a: *EGFR* mutation testing should be ordered at the time of diagnosis for patients who present with advanced-stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested.

• 2.1b: (Suggestion) *ALK* rearrangement testing should be ordered at the time of diagnosis for patients who present with advanced-stage disease (stage IV according to the 7th edition TNM staging system) and are suitable for therapy, or at time of recurrence or progression in patients who originally presented with lower stage disease but were not previously tested.
Recommendations:
When should molecular testing of lung cancers be performed?

- 2.2a: Expert consensus opinion: *EGFR* testing of tumors at diagnosis from patients who present with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

- 2.2b: Expert consensus opinion: *ALK* testing of tumors at diagnosis from patients who present with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

- 2.3: Recommendation: Tissue should be prioritized for *EGFR* and *ALK* testing.
Other Recommendations: How should EGFR testing be performed?

What is the role of KRAS analysis in selecting patients for targeted therapy with EGFR TKIs?

- 7.1: KRAS mutation testing is not recommended as a sole determinant of EGFR TKI therapy.

Are other molecular markers suitable for testing in lung cancer?

- 10.1a: Testing for EGFR should be prioritized over other molecular markers in lung adenocarcinoma.

- 10.1b: (Suggestion) After EGFR testing, testing for ALK should be prioritized over other proposed molecular markers in lung adenocarcinoma, for which published evidence is insufficient to support testing guideline development at the present time.
Endorsement Recommendation

The ASCO ad hoc guideline review panel endorses the adoption of the CAP/IASLC/AMP guideline.

DISCUSSION POINTS:

The review panel identified three evolving areas that merit additional commentary:

• Advances in ALK testing methodology
• Considerations for selecting appropriate populations for molecular testing
• Emergence of other targetable molecular alterations

Please see the full guideline for additional commentary in these areas.
## ASCO Panel Members

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