Molecular In My Pocket…

ONCOLOGY: *Molecular Biomarkers of Lung Cancer*

What to test:

Tumor Stage – Advanced-stage (stages IIIb and IV) or recurrent lung cancer. Consideration of testing early-stage patients (based on institutional policy)**.**

Histology – Adenocarcinomas or mixed cancers with adenocarcinoma components; consideration of testing non-adenocarcinoma histology in small samples that may not be representative, or in the appropriate clinical setting (never/light smokers, age < 50 years).

Materials – Formalin-fixed paraffin-embedded tissue (FFPE); fresh, frozen, or alcohol-fixed tissue; any type of cytology specimen with adequate cellularity. Macro/microdissection encouraged for tumor enrichment*

Biomarker	Specific Alterations	Indications	Result Interpretation Significance	Assays Techniques*
Must Test				
EGFR	Exons 18-21 (most common, L858R; exon 19 in frame deletions)	Consideration of therapy with EGFR-targeted tyrosine kinase inhibitors	Responsiveness to EGFR-targeted TKIs	NGS, PCR-based assays
	Exon 20 insertions	Consideration of therapy with EGFR-targeted tyrosine kinase inhibitors	Primary resistance to EGFR-targeted TKI therapy	
	T790M	Progression after treatment with early generation EGFR-targeted tyrosine kinase therapy	Consideration of third-generation EGFR-targeted therapy (osimertinib)	
ALK	ALK rearrangements	Consideration of therapy with targeted inhibitors	Predicts response to crizotinib, alectinib	FISH, IHC, NGS
ROS1	ROS1 rearrangements	Consideration of therapy with targeted inhibitors	Predicts response to crizotinib	FISH, RT-PCR, NGS; IHC as a screening with subsequent FISH or molecular confirmation of positive IHC results
BRAF**	p.V600E	Consideration of therapy with targeted BRAF inhibitors	Predicts response to BRAF inhibitors (dabrafenib-trametinib)	NGS, PCR-based assays
Expanded Panel, if Adequate Material Available				
RET	RET rearrangements	Consideration for a clinical trial with RET targeted therapy	Predicts response to inhibitors of RET-kinase	FISH, NGS
***ERBB2* (HER2)**	ERBB2 (HER2) mutations (most common, in frame insertion, exon 20 and substitutions at codon S310) & amplifications	Consideration for a clinical trial with ERBB2 (HER2)-targeted therapy	Predicts response to ERBB2-targeted therapy (afatanib, TDM1)	NGS
MET	Exon 14 skipping Amplifications	Consideration for a clinical trial with targeted therapy	Predicts response to crizotinib Secondary resistance to EGRF-targeted TKI therapy	FISH (for amplification), NGS, RT-PCR
KRAS***	Codon 12, 13, 61, and 146	Consideration for a clinical trial with targeted therapy	Diminished likelihood of another targetable oncogenic alteration	NGS, PCR-based assays

Use of Cell-Free Plasma DNA*				
EGFR	Exons 18-21 (most common, L858R; exon 19 in frame deletions)	If tissue is limited or insufficient for testing	Responsiveness to EGFR-targeted TKIs	Cell-free DNA assays (NGS, ddPCR)
	T790M	Progression after treatment with early generation EGFR-targeted tyrosine kinase inhibitor	Consideration of third-generation EGFR-targeted therapy (osimertinib)	

Abbreviations:

NGS	next generation sequencing	*IHC*	immunohistochemistry
FISH	fluorescent in situ hybridization	*TKI*	tyrosine kinase inhibitor
ddPCR	digital droplet PCR		

* Analytic methods should be able to detect mutation in a sample with 20% or more malignant cell content

** Per NCCN guidelines, BRAF inhibitors are recommended as first line therapy for BRAF-mutant lung cancer

*** Single-gene *KRAS* test may be performed to exclude patients with *KRAS*-mutant cancer from expanded panel in sequential testing algorithm

****Testing of tumor sample is recommended if plasma result is negative

Where to test: Testing should be performed in the laboratories that are certified under clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform high complexity (molecular pathology) testing.

***References*:**

1. Lindeman, N. I., *et al*. (2018). Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. https://jmd.amjpathol.org/article/S1525-1578(17)30590-1/fulltext
2. Lindeman, N. I., *et al*. (2013). Molecular Testing Guideline for the Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and Association for Molecular Pathology. (*JMD* 2013;15(4)).
3. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 6.2018 – August 2018; NCCN.org. accessed 8/20/2017

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