ROS1 gene rearrangement:

This is a new molecular subtype of NSCLC with strong recommendation by Updated Molecular Testing Guideline,: " ROS1 testing must be performed on all lung advanced stage adenocarcinoma patients, irrespective of clinical characteristics."[1]

ROS1 is a receptor tyrosine kinase, rearrangement of which leads to dysregulation and inappropriate signaling through ROS1 kinase domain.

Approximately 0.5% - 2% of NSCLC patients carries ROS1 fusion.

FISH analysis is considered to be the gold standard method to detect the ROS1 fusion gene.
Data indicates that tumors harboring ROS1 genetic rearrangement are sensitive to Crizotinib, a ROS1 kinase inhibitor.

MET gene alterations:

In non–small cell lung cancer (NSCLC), aberrant MET signaling can occur through a number of mechanisms that collectively represent a significant proportion of patients.[3]
These include :

- **MET or HGF (hepatocyte growth factor) protein overexpression,**
- **MET gene amplification**
- **MET gene mutation**
- **MET gene fusion/rearrangement**

[1] MET or HGF (hepatocyte growth factor) protein overexpression :
Seen in 35%-72% of the patients. Done by IHC marker.

[2] MET gene mutation:
MET exon 14 mutations found to have response with MET inhibitors such as crizotinib or cabozantinib.
MET exon 14 mutations are described in 3%-4% of NSCLC patients.

[3] MET gene amplification:
MET gene amplifications are found to be present in about 2% to 5% of newly diagnosed adenocarcinomas .

A much greater incidence of MET amplification, ranging from 5% to 22%, has been reported in patients with NSCLC following treatment with erlotinib/gefitinib.

Amplification of MET (and over expression of the protein) is also a common event in brain metastases of NSCLC.

Fluorescence in situ hybridization (FISH)–positive MET status predicts worse survival in patients with advanced NSCLC .

An increased in gene copy numbers by FISH studies, is an independent negative prognostic factor.

MET gene amplification is found to be the preferred biomarkers for MET TKI therapy.

Lung carcinoma panels

Panel	Parameters	MRP	TAT
Lung CA Prima	EGFR (18th, 19th, 20th & 21st) + ALK (by FISH)	12500	8 Days
Lung CA Prima Plus	EGFR + ALK + ROS 1 (by FISH)	15000	8 Days
Lung CA Prima Gold	EGFR + ALK + ROS 1 (by FISH) + PDL1	18000	15 Days
Lung CA Prima Sure	EFGR + ALK + ROS 1 + MET + RET	20000	15 Days
Lung CA Prima Target	EGFR + KRAS + BRAF	15000	8 Days
Lung CA Prima One	EGFR + ALK (by FISH) + PDL1	15000	15 Days

References:
1. 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, Arch Pathol Lab Med—Vol 142, March 2018
2. Non Small Cell Lung Cancer, NCCN Evience Blocks , version 5.2019- june 26.2019
3. Mol Cancer Ther; 16(4) April 2017 , MET in Lung Cancer: Biomarker Selection Based on Scientific Rationale

Head office:
102, Sanoma Plaza, B/s JMC House,
Opp. Parimal Garden,
Ellisbridge, Ahmedabad - 380006
Mobile: +91 9558800100
Phone: 079 4900 6800 / 803-820
Email: info@unipath.in
Website: www.unipath.in

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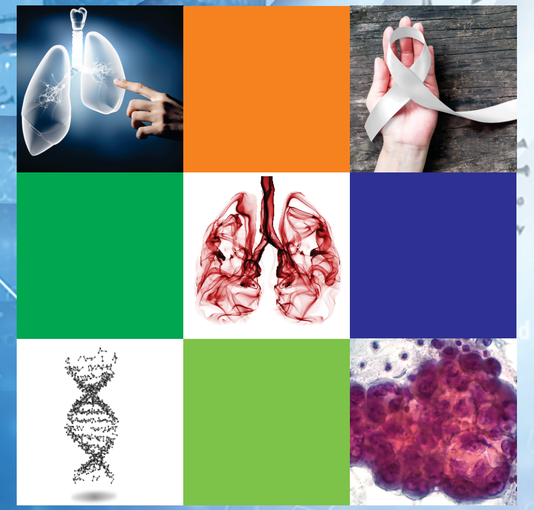
Lung Carcinoma
Profile



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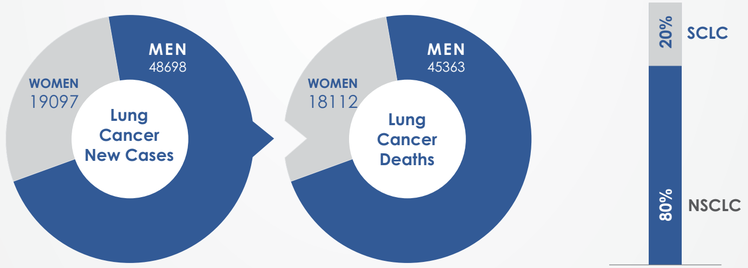
Lung cancer

Lung Cancer is the second most common cancer in men and the fifth most common cancer in both men and women together in India.

Lung cancer in India (Globocan 2018)



More than 80% of all lung cancers belong to the non-small cell type.

The 3 major sub-types of non-small cell lung cancer are
- Adenocarcinoma
- Squamous cell carcinoma
- Large cell carcinoma

Molecular diagnosis in Non Small Cell Lung Cancer (NSCLC):

Testing NSCLC specimens for various genetic alterations is important for identification of proper targeted therapy.

Variety of test methodologies is available for detection of mutations, rearrangements, copy number variations, amplification, etc.

Each method has their own pros and cons.

Methods available are

• IHC • FISH • Sanger Sequencing
• RT PCR • NGS

The genetic alterations described in NSCLC are mutually exclusive. Only 1% - 3% may harbor concurrent alteration.

According to Updated Molecular Testing Guideline recommendations[1], all the lung cancer patients with an advanced stage and with an adenocarcinoma component should go for molecular diagnosis for the selection of lung cancer patients for treatment with targeted therapy.

Genetic alterations :

EGFR Gene Mutation

EGFR (the gene that produces a protein called epidermal growth factor receptor) is abnormal, or mutated. Patients with cancer that has an EGFR mutation generally respond positively to treatment with the drug erlotinib (Tarceva®). If your tumor has an EGFR mutation, your doctor may recommend treatment with this drug.

Detailed molecular testing can tell you if your tumor has particular genetic mutations. Targeted therapies are designed to treat the specific characteristics of the tumor. EGFR inhibitors block the signal from the EGFR gene that encourages growth. These include: afatinib (Gilotrif), erlotinib (Tarceva) and gefitinib (Iressa)

For advanced NSCLC, these drugs can be used alone or with chemotherapy. When chemotherapy isn't working, these drugs can still be used even if you don't have the EGFR mutation. Necitumumab (Portrazza) is another EGFR inhibitor used for advanced squamous cell NSCLC. It's given via intravenous (IV) infusion in combination with chemotherapy.

EGFR T790M

EGFR inhibitors shrink tumors, but these drugs can eventually stop working. When that happens, Clinician may order an additional tumor biopsy to see if the EGFR gene has developed another mutation called T790M. Osimertinib (Tagrisso) drug treats advanced NSCLC involving the T790M mutation.

Another mutation we regularly test for is in a gene called KRAS & BRAF. KRAS is mutated in about 25 percent of patients with non-small cell lung cancer.

BRAF Mutation

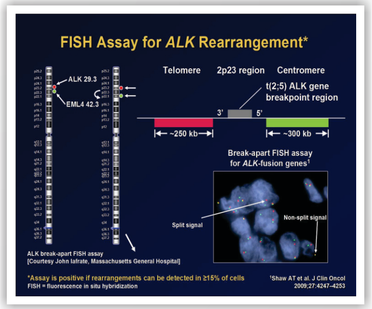
A BRAF mutation V600E occur in 1-2 out of every 100 lung carcinoma (1-2%). commonly people with this mutation smoke or have smoked. Mutation in the BRAF gene causes the BRAF protein (Kinase) to be over reactive. BRAF overacivity causes new cancer cells to form quickly.
BRAF testing is advised for metastatic lung adenocarcinoma, large cell lung carcinoma & unknown subtype.

KRAS Mutations

KRAS is the most common mutation & KRAS mutation prevalence is associated with cigarette smoking. Patients with KRAS mutations appear to have a shorter survival than those with wild-type KRAS; therefore, KRAS mutations are prognostic biomarkers. KRAS mutations do not generally overlap with EGFR mutations, ALK rearrangements, or ROS1 rearrangements. Therefore, KRAS testing may identify patients who may not benefit from further molecular testing.

ALK gene rearrangement :

The ALK gene rearrangement has been reported in 2%-13% of the patients with Non Small Cell Lung Cancer. Most of the patients with ALK gene rearrangement typically have adenocarcinoma, young age and history of minimal to no smoking. ALK rearranged tumors are mutually exclusive to EGFR mutation, ROS1 gene rearrangement and other genetic alterations commonly described in NSCLC.



ALK receptor is a transmembrane protein encoded by ALK gene on the short arm of chromosome 2. The inversion of the part of chromosome 2 leads to rearrangement with the common partner EML4 gene. The EML4-ALK fusion leads to chimeric protein with different clinicopathological subsets. Although a variety of other fusion partners are also identified.

The FDA has approved an ALK inhibitor, Crizotinib (Xalkori) for treatment of ALK positive NSCLC patients and approved a companion diagnostic FISH test. However, recent studies demonstrate improved efficacy of Alectinib over Crizotinib.[2]