Why test for biomarkers in metastatic non-small cell lung cancer (mNSCLC)?

- mNSCLC is not a single disease
- Driver mutations have been identified in up to 50% of mNSCLC and 64% of adenocarcinomas
- These mutations occur in genes that control cellular proliferation, survival, maintenance, and death

Biomarker testing facilitates precision medicine

- Biomarker testing is important for identifying potentially efficacious targeted therapies and avoiding therapies that are unlikely to provide clinical benefit
- Targeted therapy has been shown to decrease tumor burden, decrease symptoms, and dramatically improve the quality of life for patients with specific genetic variants
- Emerging biomarkers and corresponding targeted therapies are expanding the options for patients with mNSCLC

Clinical guidelines recommend broad panel biomarker testing for appropriate patients with mNSCLC

- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) (v3.2022)
  - Perform PD-L1 testing in all patients
  - Perform molecular testing in patients with adenocarcinoma, large-cell carcinoma, and not otherwise specified (EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping, RET)
  - Consider molecular testing in squamous-cell carcinoma (EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping, RET)
  - Testing should be conducted as part of broad, panel-based molecular profiling when feasible
  - Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of EGFR mutations, ALK rearrangements, or ROS1 rearrangements; however, these features should not be used in selecting patients for testing
  - The NCCN Guidelines for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories
- College of American Pathologists, International Association for the Study of Lung Cancer, Association for Molecular Pathology (2018)
  - Offer a comprehensive panel that includes “must test” genes (EGFR, ALK, ROS1) and “recommended” genes (BRAF, MET, RET, ERBB2 [HER2], KRAS) or
  - Offer targeted testing for “must test” genes and offer an expanded panel containing “recommended” genes for patients who are candidates for clinical trials, with possible KRAS testing to exclude testing for “recommended” genes
- Tissue testing is recommended but liquid biopsies can be considered when there is insufficient tissue
  - Formalin-fixed paraffin-embedded specimens are most commonly used but other specimen types may be accepted by testing laboratories
  - Plasma circulating tumor DNA testing (liquid biopsies) can be considered if:
    - Patient is medically unfit for invasive tissue sampling
    - Insufficient material is available at initial diagnosis but follow-up tissue-based analysis is planned if an oncogenic driver is not identified
    - Due to lower sensitivity, liquid biopsies can result in false-negative results
### Established Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Prevalence*</th>
<th>Clinicopathologic Correlates</th>
<th>Approved and Investigational Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALK</strong> fusions†</td>
<td>4% of adenocarcinomas</td>
<td>Adenocarcinomas in never-smokers, younger patients</td>
<td>Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib</td>
</tr>
<tr>
<td><strong>BRAF V600E mutation‡</strong></td>
<td>1%-3%</td>
<td>Smokers, former smokers</td>
<td>Dabrafenib + trametinib</td>
</tr>
<tr>
<td><strong>EGFR</strong> mutations†</td>
<td>15% of adenocarcinomas (US) Up to 62% (Asian populations)</td>
<td>Adenocarcinomas in never-smokers</td>
<td>Afitinib, Dacomitinib, Erlotinib ± ramucirumab, Gefitinib, Osimertinib</td>
</tr>
<tr>
<td><strong>EGFR</strong> exon 20 insertion mutations†</td>
<td>2% 12% of NSCLC with EGFR mutations</td>
<td>Adenocarcinomas</td>
<td>Amivantamab-vmjw, Mobocertinib, Pozotinib</td>
</tr>
<tr>
<td><strong>MET</strong> exon 14 skipping mutations‡</td>
<td>3% of adenocarcinomas 20% of sarcomatoid histology NSCLC</td>
<td>N/A</td>
<td>Capmatinib, Tepotinib</td>
</tr>
<tr>
<td><strong>NTRK</strong> fusions†</td>
<td>&lt;1%</td>
<td>Adenocarcinomas in never-smokers</td>
<td>Entrectinib, Larotrectinib</td>
</tr>
<tr>
<td><strong>PD-L1</strong></td>
<td>24%-60%</td>
<td>Identifies disease most likely to respond to immune checkpoint inhibitors</td>
<td>Atezolizumab, Cemiplimab-rwlc, Nivolumab ± ipilimumab, Pembrolizumab</td>
</tr>
<tr>
<td><strong>RET</strong> fusions†</td>
<td>1%-2% of adenocarcinomas</td>
<td>Adenocarcinomas in never-smokers, younger patients</td>
<td>Cabozantinib, Pralsetinib, Selpercatinib</td>
</tr>
<tr>
<td><strong>ROS1</strong> fusions†</td>
<td>1%-2%</td>
<td>Adenocarcinomas in never-smokers, younger patients</td>
<td>Ceritinib, Crizotinib, Entrectinib, Lorlatinib</td>
</tr>
</tbody>
</table>

### Emerging/Prognostic Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Prevalence†</th>
<th>Clinicopathologic Correlates</th>
<th>Approved and Investigational Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERBB2 (HER2)</strong> mutations†</td>
<td>1%-3%</td>
<td>Adenocarcinomas in never-smokers, women</td>
<td>Ado-trastuzumab emtansine, Fam-trastuzumab, deruxtecan-nxki</td>
</tr>
<tr>
<td><strong>KRAS</strong> G12C mutations†‡</td>
<td>~11% (KRAS mutations: ~33%)</td>
<td>Smokers, former smokers</td>
<td>Adagrasib, JDQ443, Sotorasib</td>
</tr>
<tr>
<td><strong>MET</strong> high-level amplifications†</td>
<td>2%-4% 5%-20% of EGFR-mutated tumors that are EGFR-inhibitor resistant</td>
<td>Associated with secondary resistance to EGFR TKI therapy</td>
<td>Capmatinib, Crizotinib, Tipotinib</td>
</tr>
<tr>
<td><strong>NRG1</strong> fusions†</td>
<td>1%</td>
<td>Adenocarcinomas in never-smokers</td>
<td>Afatinib</td>
</tr>
<tr>
<td><strong>STK11 (LKB1)</strong> mutations†</td>
<td>5%-30%</td>
<td>Prognostic of worse survival with immune checkpoint inhibitors</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Prevalence may vary according to racial background, stage of disease, and treatments received. Unless otherwise noted, percentages represent prevalence in NSCLC.

†In patients with high (≥50%) PD-L1 expression.
References


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