ROS1 Gene Rearrangements

- Oncogenic gene fusions involving the ROS1 receptor tyrosine kinase have recently been identified in up to 1-2% of NSCLC.\(^1,2\)
- ROS1 gene rearrangements define a distinct molecular subset of NSCLC that are most often mutually exclusive from EGFR mutations, KRAS mutations, and ALK rearrangements.\(^2,3\)
- ROS1 gene rearrangements are associated with adenocarcinoma, light/never smokers, and young patients (<50 years).\(^2,4\)
- In recent clinical studies, patients with advanced NSCLC harboring ROS1 rearrangements derived great benefit from crizotinib (XALKORI\(^\text{®}\)) treatment.\(^1,4\)

Data from a recent report from American Society of Clinical Oncology showed antitumor activity of crizotinib in patients with ROS1 gene rearrangements:\(^4\)

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>ROS1-Positive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>1</td>
</tr>
<tr>
<td>Partial Response</td>
<td>6</td>
</tr>
<tr>
<td>ORR*</td>
<td>54% (7/13)</td>
</tr>
<tr>
<td>DCR**</td>
<td>85% (11/13)</td>
</tr>
</tbody>
</table>

* Overall Response Rate = complete and partial response
** Disease Control Rate at 8 weeks

RET Gene Rearrangements

- Recently, RET gene rearrangements have been identified in 1-2% of lung adenocarcinoma.\(^3,5\)
- RET gene rearrangements define a distinct molecular subset of NSCLC that are most often mutually exclusive from EGFR mutations, KRAS mutations, ALK and ROS1 rearrangements.\(^3,5\)
- RET gene rearrangements are associated with adenocarcinoma, light/never smokers, and younger patients.\(^3\)
- In recent clinical studies, inhibition of RET was seen with multiple kinase inhibitors in RET overexpressing cells.\(^6\)
  The evaluation of RET gene rearrangements could be applicable in clinical practice to detect NSCLC patients that may be responsive to RET inhibitors like sunitinib, sorafenib or vandetanib.\(^5,6\)
Methodology for ROS1 and RET Gene Rearrangements:

Fluorescence in situ hybridization (FISH) probes optimized to breakpoint(s) involved in translocations of the ROS1 gene (region 6q22) and RET gene (region 10q11).

Specimen Requirement Options:

Fixed Paraffin Block with Corresponding H&E:
- Tissue should be well-fixed in formalin; if a different fixative is used it should be noted on the requisition.
- Store specimen at room temperature.
- Use cold pack for transport in warmer weather. Be sure cold pack is not in direct contact with specimen during transport.

Unstained Slides:
- Send all slides within 6 weeks of cutting.
- Minimum of 5 slides for FISH testing (each test)
- Pre-cut slides from paraffin block in 5 micron sections and mount on poly-Hysine-coated or plus (+) slides.
- Air dry. Do not oven dry.
- Store specimens at room temperature.

CPT Code(s): 88271(2), 88275, 88291

REFERENCES