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Positive Quality Intervention: Selpercatinib (Retevmo®) Genomic Testing Management

Description: This PQI is developed to provide guidance to genomic testing with respect to selpercatinib.

Background: *RET*-altered cancers include both *RET* fusions and *RET* mutations. Both alterations involve activating *RET* signaling pathways that promote unwanted cell proliferation in cancers. NCCN guidelines for NSCLC include a Category 2A recommendation for *RET* testing as part of broad molecular profiling in routine clinical practice. In multiple guidelines, *RET* testing is considered as part of a larger initial panel or secondary single analyte test following negative results for other genetic variants such as EGFR, ALK, and ROS1. Molecular testing within *RET*-mutated medullary thyroid cancer (MTC) is applicable as approximately 50% of patients with sporadic MTC have somatic *RET* mutations. In American Thyroid Association, NCCN, and ESMO guidelines, *RET* testing should be considered within the MTC space. Next generation sequencing (NGS) analyzes DNA and/or RNA when detecting *RET*. This method requires a small amount of tissue for multiplex testing for many common and rare cancer-related biomarkers. Tissue testing is often considered as *RET* alteration may not be found in the blood through liquid biopsy and up to 30% of *RET* alterations can be missed if only ctDNA is tested. There are multiple testing methods for *RET* that will help determine patient eligibility for selpercatinib, noting that indicated tumor types are associated with specific alterations (Review Supplemental Information section for approved indications).

***RET* alteration to test**	**Associated tumor type(s)**
RET-fusion	NSCLC, Thyroid
RET-mutation	MTC

*FDA-approved companion diagnostic tests for RET-fusion and RET-mutation alterations in plasma or other solid tumors other than NSCLC and MTC are not currently available

PQI Process:

- Consider the following preferred testing methods when planning for *RET* genomic testing:
  - Perform NGS when applicable
    - Account for 2-4 weeks for test completion
    - Both DNA and RNA-based NGS testing methods are appropriate and care team should discuss the general advantages and disadvantages of both
      - RNA-based NGS is able to reveal unbiased fusion information and there are no intron coverage issues [1,2]
  - Reverse Transcription-PCR
    - Quick and relatively inexpensive; test completion with 1-2 days
    - PCR testing is designed predominantly for fusions and *RET* fusion frequency is underestimated
  - FISH
    - High rate of false positive/false negative
    - Should only be considered in rare circumstances (eg., if NGS/RT-PCR are not available)

Patient-Centered Activities:

- Provide education to patients regarding genetic testing and what to expect
- Provide testing schedule to patient
- Refer to **Selpercatinib (Retevmo®) Management** PQI and Oral Chemotherapy Education (OCE) Sheet
- Patient Assistance: NCODA Financial Assistance Tool

Supplementary Information:

Selpercatinib is a kinase inhibitor indicated for the treatment of

- Adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC)*
- Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy*
- Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)*

*Approved under accelerated approval based on overall response rate and duration of response[3]

References:

1. Garinet S, Laurent-Puig P, Blons H, Oudart JB. Current and future molecular testing in NSCLC, what can we expect from new sequencing technologies? *J Clin Med*.
2. Drilon A, Wang L, Arcila ME, et al. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. *Clin Cancer Res.* 2015;21(16):3631-3639
3. RETEVMO® [package insert]. Lilly USA, LLC, Indianapolis, IN.