Positive Quality Intervention: Larotrectinib (Vitrakvi®) Genomic Testing Management

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

Background: Larotrectinib is indicated for the treatment of adult and pediatric patients with solid tumors that:
- Have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation
- Are metastatic or where surgical resection is likely to result in severe morbidity, and
- Have no satisfactory alternative treatments or that have progressed following treatment

This indication is approved under accelerated approval based on overall response rate and duration of response.¹ As a key oncogenic driver, NTRK gene fusions are found in many types of solid tumors. Note that NTRK gene fusion is separate from general NTRK gene mutation. Within adult patients NTRK gene fusion frequency displays in estimated amounts such as the select tumors below:²

- Lung: 0.2%-3.3%
- GI Cancers: 0.7%-3.6%
- Thyroid: 2.4%-12%
- Sarcoma: 1%
- Glioblastoma: 1.2%
- Mammary Analogue Secretory Carcinoma: up to 100%

In October 2020, the FDA approved the next generation sequencing based FoundationONE CDx test (F1CDx) as a companion diagnostic for NTRK1, NTRK2, and NTRK3 in DNA or RNA isolated from tumor tissue from eligible patients. F1CDx is a next generation sequencing (NGS) based in-vitro diagnostic device capable of detecting several mutations along with NTRK gene fusions.³

PQI Process:
- NTRK genomic testing should be performed upon diagnosis and at progression
- Consider the following testing methods when planning for NTRK genomic testing
  - NGS (Next generation sequencing)⁴ *preferred*
    - Utilize FoundationONE CDx test as available
    - Confirm the NGS assay used has the capacity to detect NTRK gene fusions (See Supplemental Information)
    - Ensure gene fusion testing of NTRK1, NTRK2, and NTRK3 are included in the panel order
    - It is important to note that if DNA does not detect NTRK, then the sample should be re-sequenced using RNA to ensure proper detection of NTRK
  - IHC (Immunohistochemistry)
    - Can be used as a screening diagnostic, however, sensitivity/specificity has been questioned
    - Following TRK IHC positive result, confirmation of NTRK gen fusion would be required for initiation of larotrectinib
  - FISH (fluorescence in situ hybridization)
    - Note that multiple tests would need to be run in order to detect NTRK gene fusions at multiple locations
    - Suited for tumor histologies that are pathognomonic for the ETV6-NTRK3 fusion such as Infantile Fibrosarcoma, secretory breast cancer, and MASC

Patient-Centered Activities:
- Provide education to patients regarding genetic testing and what to expect
- Prepare care team for timely turnaround time of testing results

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• Refer to Larotrectinib (Vitrakvi®) Overview PQI for more information on medication management and provide Oral Chemotherapy Education (OCE) sheet

Supplemental Information:
The following NGS testing laboratories are confirmed to detect all 3 NTRK gene fusions
• Caris Life Sciences
• Foundation Medicine
• Integrated Oncology (LabCorp)/OmniSeq
• NAVICAN
• NeoGenomics Laboratories
• Paradigm Diagnostics
• PathGroup
• Tempus

References: