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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

- 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:

1. VITRAKVI® [package insert]. Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ.
2. Sigal, D. S., Bhangoo, M. S., Hermel, J. A., Pavlick, D. C., Frampton, G., Miller, V. A., Ross, J. S., & Ali, S. M. Comprehensive genomic profiling identifies novel NTRK fusions in neuroendocrine tumors. Retrieved September 23, 2021, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6254675/.
3. Food and Drug Administration. FDA Approves Companion Diagnostic to identify NTRK fusions in solid tumors for Vitrakvi®. https://www.fda.gov/drugs/fda-approves-companion-diagnostic-identify-ntrk-fusions-solid-tumors-vitrakvi.
4. Vitrakvi®. Testing For Oncologists. https://www.hcp.vitrakvi-us.com/testing-for-oncologists/#oncolog-ngs-testing.