Positive Quality Intervention: Larotrectinib (Vitrakvi®) Overview

Description: The purpose of this PQI is to help provide awareness of larotrectinib and educate on management techniques.

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
- Have no satisfactory alternative treatments or that have progressed following treatment

This indication is approved under accelerated approval based on the overall response rate and duration of response.\(^1\) It is important to note that larotrectinib is approved in patients with a NTRK fusion not just an NTRK mutation. NTRK genes, which encode for TRK proteins, can become fused to other genes abnormally, resulting in growth signals that support tumor growth. The efficacy of larotrectinib was studied in three clinical trials that included 55 pediatric and adult patients with solid tumors. Larotrectinib demonstrated a 75% overall response rate across different types of solid tumors, with 73% of responses lasting at least six months, and 39% lasting a year or more at data cutoff. Presented at ESMO 2020, with a data cut-off of July 2019 included 120 additional patients where ORR was 78% and a median PFS of 36.8 months.\(^2\) Tumor types with an NTRK fusion that responded to larotrectinib include soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, lung cancer, primary CNS and cancers with CNS metastasis.\(^3\) In a study determining expected life-years and quality-adjusted life-years (QALYs) a larotrectinib base case found a mean pre-progression QALYs of 5.0 and mean total QALYs of 5.8.\(^4\) Evidence also suggests patients treated with larotrectinib see some degree of benefit with different lines of therapy and performance statuses.\(^5\)

PQI Process:

- Confirm that NTRK fusion was identified on pathology report
  - See Larotrectinib (Vitrakvi®) Genomic Testing Management PQI for more information
- Confirm correct dosing
  - Adults and pediatric patients with BSA ≥ 1 m²: 100 mg orally twice daily with or without food
  - Pediatric patients with BSA < 1 m²: 100 mg/m² orally twice daily with or without food
  - Larotrectinib comes as a capsule (25 mg & 100 mg) and as an oral solution (20 mg/mL)
    - The capsule and oral solution are interchangeable
- Dosing considerations
  - No renal dose adjustments
  - Hepatic impairment prior to initiation
    - Child-Pugh class A: No dose adjustment necessary
    - Child-Pugh class B and C: Reduce initial dose by 50%
  - Co-administration with strong CYP3A4 inhibitors/inducers:
    - If coadministration cannot be avoided,
      - Reduce larotrectinib dose by 50% with inhibitors
      - Double the dose with inducers
      - Upon discontinuation, resume larotrectinib at the original dose after 3-5 elimination half-lives of the CYP3A4 inhibitor/inducer (half-life 2.9 hours)
- Monitoring
  - Monitor LFTs every 2 weeks during the first month of treatment and monthly thereafter

IMORTANT NOTICE: NCODA has developed this Positive Quality Intervention platform. This platform is intended as an educational aid, does not provide individual medical advice, and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication. The materials contained in this platform do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA. NCODA does not ensure the accuracy of the information presented and assumes no liability relating to its accuracy. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. It is the individual’s sole responsibility to seek guidance from a qualified healthcare professional. Updated 1.12.23
Monitor for signs/symptoms of neurotoxicity

- Dose reductions for Grade 3 or Grade 4 toxicity: hold until resolution, then as follows:

<table>
<thead>
<tr>
<th>Dose Modification</th>
<th>Patients with BSA ≥ 1 m²</th>
<th>Patients with BSA &lt; 1 m²</th>
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<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Dose Modification</td>
<td>75 mg orally twice daily</td>
<td>75 mg/m² orally twice daily</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Dose Modification</td>
<td>50 mg orally twice daily</td>
<td>50 mg/m² orally twice daily</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Dose Modification</td>
<td>100 mg orally once daily</td>
<td>25 mg/m² orally twice daily</td>
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- Permanently discontinue for any Grade 3 or 4 Adverse Event that does not resolve within 4 weeks, or any patients unable to tolerate after 3 dose modifications

- Withdrawal pain – Case reports with holding/discontinuation; consider tapering at discontinuation

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) Sheet
  - Do not make up a missed dose within 6 hours of the next scheduled dose
  - If vomiting occurs after taking dose, take the next dose at the scheduled time
  - Store the glass bottle of oral solution in the refrigerator and discard after 90 days of first opening
  - Patients should not eat grapefruit or drink grapefruit juice while taking this medication
  - Females of reproductive potential and patients with female partners of reproductive potential should use effective contraception during and for at least 1 week after the final dose
  - Do not breastfeed during treatment and for 1 week after last dose

- Ensure patients are aware of side effects to monitor at home
  - Patients should report symptoms such as confusion, difficulty speaking, dizziness, coordination problems, tingling, numbness/burning sensation in hands/feet
  - Patients should report symptoms such as loss of appetite, nausea or vomiting, pain in the upper right side of the stomach area

- Oral solution counseling points:
  - Always use the bottle adaptor and oral syringes provided to ensure accurate measurement
    - 1 mL and 5 mL syringes are provided * Do not use a household teaspoon*
    - Each syringe may be used over a 7-day period and replaced thereafter
  - Place the tip of the oral syringe into the mouth against the side of the cheek and slowly squirt
  - Remain in the upright position for a few minutes following dose administration
  - If spit up, do not give another dose; wait until the next scheduled dose
  - Always place the child-resistant cap back on the bottle *Do NOT remove the bottle adaptor*
  - Clean the oral syringes by removing the plunger from the barrel and rinse with warm water

- Patient Assistance: NCODA Financial Assistance Tool

References:

1. VITRAKVI® (larotrectinib) [package insert].