Written By: Elizabeth Ledbetter, PharmD
Institution: Indiana Health University

Larotrectinib (Vitrakvi®) Overview

Description: The purpose of this PQI is to provide education around larotrectinib patient management.

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

Most common adverse reactions (≥ 20%):

- Increased: AST, ALT, alkaline phosphatase
- Decreased: albumin, leukocytes, lymphocytes, neutrophils, red blood cells, serum calcium
- Musculoskeletal pain, fatigue, vomiting, cough, constipation, pyrexia, diarrhea, nausea, abdominal pain, dizziness, and rash

PQI Process:

- Confirm that *NTRK* fusion was identified on pathology report
  - Larotrectinib is approved in patients with a *NTRK fusion* not just an *NTRK mutation*.
  - See **Larotrectinib (Vitrakvi®) Genomic Testing Management** PQI for more information
- Confirm correct dosing
  - Adults and pediatric patients with BSA ≥ 1 m^2: 100 mg orally twice daily with or without food
  - Pediatric patients with BSA < 1 m^2: 100 mg/m^2 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%
  - Coadministration with strong CYP3A4 inhibitors/inducers:
    - If coadministration cannot be avoided,
      - Reduce larotrectinib dose by 50% with strong CYP3A4 inhibitors
      - Double the larotrectinib dose with moderate to strong CYP3A4 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
  - Obtain liver function tests (ALT, AST, ALP and bilirubin) before initiation of treatment and every 2 weeks during the first 2 months of treatment, then monthly thereafter or as

clinically indicated
    - Monitor for signs/symptoms of neurotoxicity including dizziness, cognitive impairment, mood disorders, and sleep disturbances
- For Grade 3 or Grade 4 toxicity, hold larotrectinib until adverse reaction resolves or improves to baseline or Grade 1. Resume treatment at the next dosage modification if resolution occurs within 4 weeks.

Table 1 Recommended Larotrectinib Dosage Reductions for Adverse Reactions

Dose Modification	Patients with BSA ≥ 1 m^2	Patients with BSA < 1 m^2
1st Dose Modification	75 mg orally twice daily	75 mg/m^2 orally twice daily
2nd Dose Modification	50 mg orally twice daily	50 mg/m^2 orally twice daily
3rd Dose Modification	100 mg orally once daily	25 mg/m^2 orally twice daily

- 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[11]
- Dosage modifications for hepatotoxicity

Table 2 Recommended Larotrectinib Dosage Modifications for Hepatotoxicity

Severity	Dosage Modification
AST or ALT ≥ 5 x ULN with bilirubin ≤ 2 x ULN	• Withhold treatment until recovery to ≤ Grade 1 or return to baseline • Resume larotrectinib at the next lower dose level • Permanently discontinue if a Grade 4 AST and/or ALT elevation occurs after resuming larotrectinib
AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	Permanently discontinue lartotrectinib

Patient-Centered Activities:

- Provide larotrectinib Patient Education Sheet (PES)
    - 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].
2. McDermott R, et al. Survival benefits of larotrectinib in an integrated dataset of patients with TRK fusion cancer. Presented at ESMO Virtual Congress 2020, Annals of Oncology (2020) 31 (suppl_4): S1034-S1051.
3. Drilon AE, et al. Activity of larotrectinib in TRK fusion cancer patients with brain metastases or primary central nervous system tumors. J of Clin Onc 37, no. 15_suppl.
4. Roth JA, Carlson JJ, Xia F, et al. The Potential Long-Term Comparative Effectiveness of Larotrectinib and Entrectinib for Second-Line Treatment of TRK Fusion-Positive Metastatic Lung Cancer. J Managed Care & Specialty Pharmacy 2020 26:8, 981-986.
5. Drilon AE, et al. Larotrectinib in TRK fusion cancer patients: Outcomes by prior therapy and performance status [abstract]. In: Proceedings of the Annual Meeting of the American Association for Cancer Research 2020; 2020 Apr 27-28 and Jun 22-24. Philadelphia (PA): AACR; Cancer Res 2020;80(16 Suppl):Abstract nr CT199.