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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 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 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

- Monitor for signs/symptoms of neurotoxicity
- Dose reductions for Grade 3 or Grade 4 toxicity; hold until resolution, then as follows:

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]

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].
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.