National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

Positive Quality Intervention: Larotrectinib Overview

Description: The purpose of this PQI is to help provide awareness of larotrectinib (Vitrakvi) 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, 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] 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[8]. 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[9]. In a study determining expected life-years and quality-adjusted life-years (QALYs) a larotrectinib base case found a mean preprogression QALYs of 5.0 and mean total QALYs of 5.8.[7] Evidence also suggests patients treated with larotrectinib see some degree of benefit with different lines of therapy and performance statuses[10].

PQI Process:

- Confirm that *NTRK* fusion was identified on pathology report
- Confirm correct dosing
  - Adults as well as pediatric patients with BSA ≥ 1 m^2: 100 mg twice daily with or without food
  - Pediatric patients with BSA < 1 m^2: 100 mg/m^2 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%

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PQI Process Continued:

- Coadministration with strong CYP3A4 inhibitors/inducers:
  - If coadministration cannot be avoided, reduce larotrectinib dose by 50% with inhibitors and double the dose with inducers. Upon discontinuation, resume larotrectinib at the original dose after 3-5 elimination half-lives
    - Half-life is 2.9 hours following oral administration in a conventional situation
- Monitoring
  - Ensure that LFTs are being monitored 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 mg 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
- The most common adverse reactions (≥20%) were: any neurological event (53%), Increased ALT (45%), Increased AST (45%), anemia (42%), fatigue (37%), nausea (29%), dizziness (28%), cough (26%), vomiting (26%), constipation (23%), and diarrhea (22%)

Patient Centered Activities:

- Provide Oncology Chemotherapy Education (OCE) Sheet
- Counsel patients on:
  - 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. Discard after 90 days of first opening the bottle
  - Pregnancy concerns: females of reproductive potential should use effective contraception during therapy and for at least 1 week after the final larotrectinib dose. Males with female partners of reproductive potential should also use effective contraction during therapy
- Ensure patients are aware of side effects to monitor for at home
  - Nervous system problems: patients should reach out to their provider if they develop symptoms such as confusion, difficulty speaking, dizziness, coordination problems, tingling, numbness, or burning sensation in hands and feet

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  - Liver problems: patients should reach out to their provider if they develop symptoms such as loss of appetite, nausea or vomiting, pain in the upper right side of the stomach area
- Oral solution counseling points:
  - Drawing up the dose
    - Always use the bottle adaptor and oral syringes provided with larotrectinib to ensure the dose is measured correctly
    - Both 1mL and 5mL syringes are provided for accurate measurement
    - Each syringe may be used over a 7-day period
    - Do not use a household teaspoon to measure the dose
  - Administering the dose
    - Place the tip of the oral syringe into the child's mouth against the side of the check and slowly squirt as they swallow
    - Child should be in the upright position for a few minutes following dose administration
    - If the child spits up the dose, do not give another. Wait until the next scheduled dose
  - After a dose is administered, always place the child-resistant cap back on the bottle. Do NOT remove the bottle adaptor.
  - Clean the oral syringes by moving the plunger from the barrel of the oral syringe and rinsing with warm water

Patient Financial Assistance:

- TRAK Assist is a program that Bayer has created to help patient access treatment
  - Learn more at VITRAKVI.com or call 1-844-634-8725
- TRAK Assist $0 co-pay program for eligible patients with commercial or private insurance
- Vitrakvi Bridge Program is available for commercially insured patients whose coverage is delayed or who experience a temporary lapse in coverage
- TRAK Assist can help with referral to independent assistance foundations for publicly insured patients who need help with out-of-pocket cost related to treatment
- Bayer US Patient Assistance Foundation is available for qualified uninsured or underinsured patients
- Vitrakvi Commitment Program™ will refund the cost of up to 60 days' supply in certain situations

References:

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8. McDermott R, van Tillburg CM, Farago AF, 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
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