28 May 2019

RE: Request for addition of Larotrectinib®(Vitrakvi) in the NCCN Clinical Practice Guidelines for Hepatobiliary Cancers

On behalf of Bayer Healthcare Pharmaceuticals, I respectfully request the NCCN Panel to review the enclosed data (1-4) for potential tumor agnostic inclusion of Larotrectinib®(Vitrakvi) which was approved November 26, 2018. (5)

We respectfully suggest the following for NCCN consideration:

- **Hepatocellular Carcinoma (HCC)**
  - **Principles of Systemic Therapy (HCC-F):** to include the addition of “NTRK gene fusion” testing and “larotrectinib for patients with NTRK gene fusion”

- **Gallbladder Cancer**
  - **Metastatic Disease (GALL-4):** to include the addition of “NTRK gene fusion” testing and “larotrectinib for patients with NTRK gene fusion”

- **Intrahepatic Cholangiocarcinoma**
  - **Presentation, Workup, Primary Treatment (INTRA-1and INTRA-2):** to include the addition of “NTRK gene fusion” testing and “larotrectinib for patients with NTRK gene fusion”

- **Extrahepatic Cholangiocarcinoma**
  - **Presentation, Workup, Primary Treatment (EXTRA-1 and EXTRA-2):** to include the addition of “NTRK gene fusion” testing and “larotrectinib for patients with NTRK gene fusion”

**FDA Clearance:** (approval November 26, 2018) – FDA approved Larotrectinib (Vitrakvi®) for the treatment of adult and pediatric patients with solid tumors harboring a neurotropic receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, have metastatic disease or where surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments of that have progressed following treatment. (5)

**Rationale:** A total of 55 patients with TRK fusion-positive cancers were enrolled in one of three protocols (phase I adults, phase I/II adults and children and phase II study involving adolescents and adults). (1-5) These patients represented 17 unique TRK fusion-positive tumor types. TRK fusions were identified by next generation sequencing or fluorescence in situ hybridization. All testing was performed in Clinical Laboratory Improvement Amendments certified or equivalent independent laboratories.

**Overall evidence:**
- Of the 55 patients (primary analysis set) enrolled at primary data cutoff (July 17, 2017; median follow up 8.3 months), the ORR was 75% according to independent review. At one year, 71% of the responses were ongoing and 55% of patients remained progression-free. (1, 2)
Follow up analysis of the primary set (July 30, 2018 data cut off; median follow up 17.6 months)) demonstrated an objective response rate per investigator assessment of 80% with CR 18% and 62% PR. Independent Radiologic review pending. (4) Adverse events (AEs) were predominantly grade 1, with dizziness, increased AST/ALT, fatigue, nausea and constipation the most common AEs reported in ≥10% of patients. No AE of grade 3 or 4 related to larotrectinib occurred in more than 5% of patients. (1-5)

We appreciate your review and consideration of this recommendation.

Sincerely,

Joseph Germino, MD, PhD
Vice President
US Medical Affairs, Oncology
Bayer Healthcare Pharmaceuticals
100 Bayer Boulevard, P.O. Box 915
Whippany, N.J. 07981
(862) 404-5184

Reference List