Bayer HealthCare

Joseph F. 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

10 December 2018

RE: Request for addition of Larotrectinib®(Vitrakvi) in the NCCN Clinical Practice Guidelines for Non-Small Cell Lung 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)

In line with the NCCN NSCLC Guidelines panel of "strongly advising molecular profiling with the goal of identifying rate driver mutations for which effective drugs…[are] available" (page NSCL-17),
We respectfully suggest the following for NCCN consideration:

- **NSCL-I 1 of 2, Targeted Therapy for Advanced or Metastatic Disease**: Add "NTRK fusion positive: Larotrectinib"
- **NSCL-17, Molecular Testing**: Add "NTRK testing should be conducted as part of broad molecular testing"
- **NSCL-17, Testing Results**: Add "NTRK positive: larotrectinib"
- **NSCL-G, Principles of Molecular and Biomarker Analysis: Molecular tests for Analysis**
    - NTRK (Neurotrophin Receptor Kinase) Gene Fusions results in the dysregulation and inappropriate signaling through the MAP, PI3K and PLC-gamma pathways promoting oncogenesis
    - NTRK fusions can have various fusion partners (with at least 15 identified to date and more still being identified)
    - To date, no clinicopathological features have been identified in patients with NTRK fusion lung cancer
    - Various methodologies can be utilized to detect NTRK fusions – FISH, IHC, NGS and PCR assays. In the original clinical trial (NEJM n=55 patients), 50 NTRK fusions were identified with NGS and 5 with FISH

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.

Lung-specific evidence (1, 3, 5):

- Of the 55 patients enrolled at the primary data-cutoff, 4 had lung cancer.
    - Three (75%) lung cancer patients demonstrated an objective response with duration of responses ongoing at the time of the data analysis, ranging from 8.2 to 20.3+ months. One patient had stable disease with a possible brain metastasis and demonstrated regression of mass on MRI. This patient progressed outside of the CNS after 300 days of treatment and continued on larotrectinib for clinical benefit per the treating physician
    - Larotrectinib was well tolerated, with 3 of 4 patients having grade 1 events only.

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

1. Drilon A, Laetsch TW, Kummar W et al. Efficacy of Larotrectinib in TRK fusion-positive cancers in adults and Children. N Engl J Med. 2018;378(8):731-739.
2. Laetsch TW, Dubois SG, Mascarenhas L et a al. Larotrectinib for paediatric solid tumors harbouring NTRK gene fusions: phase I results from a multicenter, open-label, phase 1/2 study. Lancet Oncol. 2018;19(5):705-714.
3. Farago A et al. Rapid, Robust and Durable Responses to Larotrectinib in patients with TRK fusion Non-small cell lung cancer. IASCL 2018

4. Lassen UN. Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach. Presented at: ESMO Annual Meeting; Munich, Germany. October 21, 2018. Abstract 409O.
5. Vitrakvi (larotrectinib) [package insert]. Bayer Healthcare. 2018.