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National Comprehensive Cancer Network (NCCN) 275 Commerce Drive, Suite 300 Fort Washington, PA 19043

15 October, 2018

RE: Request for addition of Larotrectinib[®](Vitrakvi) in the NCCN Clinical Practice Guidelines for Head and Neck Cancers[™]

On behalf of Bayer HealthCare Pharmaceuticals, I respectfully request the NCCN Panel to review the enclosed data for potential tumor agnostic inclusion of Larotrectinib[®](Vitrakvi) pending FDA approval. (1,2,5)

<u>Specific Changes:</u> We respectfully suggest the following for NCCN consideration:

- **CHEM-A 1 of 5, Principles of Systemic Therapy**: Add bullet "Larotrectinib is recommended for tumors harboring an NTRK gene fusion."
- CHEM-A 2 of 5, First-line Single-agent or Second-line/Subsequent Therapy: Add "larotrectinib if NTRK+"
- SALI-4, Salivary Gland Tumors, Unresectable Disease or Distant Metastases: Add "larotrectinib if NTRK+"

<u>FDA Clearance:</u> Pending approval (PDUFA November 26, 2018)– FDA Priority Review for larotrectinib for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring an NTRK gene fusion.

<u>Rationale:</u> A total of 90 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.

Head and Neck-specific evidence: (1,3)

- Of the 55 patients enrolled at the primary data-cutoff, 12 had salivary gland cancer.
- Eighty-three (83%) of salivary gland patients demonstrated an objective response with duration of responses ranging from 7.7 to 27.9+ months. All (100%) of patients demonstrated duration of response for more than 6 months.

Overall evidence:



- Of the 55 patients (primary analysis set) enrolled at primary data cutoff (July 17, 2017), 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)
 - Of the 55 patients enrolled at the primary data-cutoff, 12 had salivary gland cancer. (3, 4)
 - Eighty-three (83%) of salivary gland patients demonstrated an objective response with duration of responses ranging from 7.7 to 27.9+ months. All (100%) of patients demonstrated duration of response for more than 6 months. (3, 4)
- In an update of an additional 35 evaluable patients (Feb 19, 2018), the ORR by investigator assessment was 74% (5 CR, 21 PR, 6 SD, 2 PD, 1 not determined). In these patients, with median follow-up of 5.5 months, median duration of response had not yet been reached, and 88% of responses were ongoing at 6 months, consistent with the primary analysis set. (5)
- 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.

We appreciate your review and consideration of this recommendation.

Sincerely,

Germino

Joseph Germino, MD, PhD Vice President U.S. 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. Wirth L, Drilon A, Albert CM, et al. Larotrectinib is Highly Active in Patients with Advanced Recurrent TRK Fusion Thyroid (TC) and Salivary Gland Cancers (SGC). Presented at: Multidisciplinary Head and Neck Cancers Symposium; Scottsdale, Arizona. Feb 15, 2018. Abstract 20570.
- 4. Brose, M.S. Albert C.M, Waguespack S.G., et al ; ACTIVITY OF LAROTRECTINIB IN PATIENTS WITH ADVANCED TRK FUSION THYROID CANCER; Clincal Oral Presentation 10 at ATA 2018
- 5. 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.
- 6. Vitrakvi (larotrectinib) [package insert]. Bayer Healthcare. 2018.