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RE: Request for addition of Larotrectinib®(Vitrakvi) in the NCCN Clinical Practice Guidelines for Colon Cancer™

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)

Specific Changes: We respectfully suggest the following for NCCN consideration:

- **COL-B 4 of 5, Principles of Pathologic Review:** Add “NTRK testing”**COL-4, Workup:** Add “Determine NTRK fusion gene status (if not previously done)”
- **COL-9, Recurrence, Footnote ee:** Add “Determine NTRK fusion gene status (if not previously done)”
- **COL-11, Unresectable metachronous metastatic:** Add “Determine NTRK fusion gene status (if not previously done)”
- **COL-D, Advanced or Metastatic:** Add “larotrectinib if NTRK+”
- **MS-23, Principles to the Management of Metastatic Disease:** Add bullet “Larotrectinib is recommended for tumors harboring an 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 neurotrophic receptor tyrosine receptor (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.

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

- Of the 55 patients enrolled at the primary data-cutoff, 4 had colon cancer.
 - All 4 patients demonstrated some tumor shrinkage with 1 patients demonstrating a partial response per investigator assessment. Objective response rate was 25% and ongoing with duration of therapy at 5.6 months.
 - Toxicity profile was similar to that observed in the larger (n=55) cohort



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)
- In an update of an additional 54 evaluable patients (July 30, 2018), the ORR by investigator assessment was 81% (95 CI 69-91%; 17% CR, 65% PR). In these patients, with median follow-up of 7.4 months, 13 patients continue on study and await response assessment. (4)
- Adverse events (AEs) were predominantly grade 1, with dizziness, increased AST/ALT, fatigue, nausea and constipation the most common AEs reported in $\geq 10\%$ 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,

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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 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. Demetri et al. Activity of Larotrectinib in patients with TRK fusion GI malignancies, WCGI 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.