Bayer HealthCare

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

We respectfully suggest the following for NCCN consideration:

- **The addition of molecular testing for Secretory Breast Cancer, specifically:**
  - To include "NTRK gene fusions (i.e., not NTRK mutations nor amplifications)" as part of the genomic analysis
  - To include larotrectinib as a treatment option for patients identified with a *NTRK* gene fusion
- **The additional of molecular testing for Invasive Carcinomas of the Breast**
  - To include "NTRK gene fusions (i.e., not NTRK mutations nor amplifications)" as part of the genomic analysis
  - To include larotrectinib as a treatment option for patients identified with a *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.

Breast Cancer evidence (1, 3, 5, 6):

- A total of 5 patients with secretory breast cancer have been treated with larotrectinib (3)
  - One patient was treated on trial and 4 patients were treated via single patient protocol
  - ORR was 80% (4 PRs and 1PD)
- Case report of a 37 year-old female with advanced triple-negative secretory breast cancer with a documented *ETV6-NTRK3* fusion, who experienced rapid clinical and radiographic response to first-line larotrectinib therapy (6)
  - Patient originally presented with T2N0M0 stage 2a that was treated with mastectomy that yielded tumor-free margins. A few years later, patient complained of backaches was discovered to have

metastases to bone and bilateral lung nodules. Molecular testing via FoundationOne identified a *EVT6-NTRK3* gene fusion
    - Patient was admitted to the oncology ward for increasing dyspnea (eventually becoming dependent on oxygen support) vigorous pain control and performance status of 3 and CA-125 level was determined to be 2521 U/mL
    - Patient received radiation but refused chemotherapy and the patient requested larotrectinib, which she received under compassionate use since she did not qualify for the Phase II clinical trial
    - Within days patient reported improved dyspnea, required less oxygen, rapid reduction in the size of cervical lymph node on physical exam. Patient's performance status improved to 1 and was discharged after 2 weeks on larotrectinib.
    - At 6 weeks of treatment, patient required no oxygen, needed fewer analgesics, cervical and axillary lymph nodes were impalpable, abdominal swelling resolved and a >80% reduction via RECIST. At 8 weeks, patient continued to show clinical improvement and 19 U/mL CA-125 level
- Case report of 14 year-old female from Bangladesh, who presented with recurrent breast mass that was unamenable to lumpectomy and showed rapid clinical and radiographic improvement on larotrectinib (7)
    - Upon the second lumpectomy the diagnosis was changed to secretory breast cancer (from fibroadenoma), underwent two cycles of chemotherapy
    - Patient experienced recurrent about 1 year later, she underwent mastectomy and two cycles of chemotherapy. In less than 1 year, disease recurred with no benefit received from chemotherapy
    - Patient was tested for ETV6-NTRK3 fusion at Memorial Sloan Kettering Cancer Center (MSKCC). Patient started a single patient protocol to be treated with larotrectinib.
    - At patient's baseline examination at MSKCC, patient was determined to have numerous pulmonary metastases, bone metastases and a fungating chest pass 10.4 x 8.5 cm.
    - Within 3 days, patient noted remarkable improvement of tumor-related pain; Within 1 week a significant reduction in size of the chest wall mass with near complete response at 2 months. CT imaging revealed near complete resolution of the pulmonary metastases. Response was ongoing at 4 months. Patient experienced two episodes of dizziness (Grade 1 and 2)
- 43 year old female who originally presented with a palpable mass (8)
    - Patient underwent a right-sided therapeutic mastectomy and axillary lymph node dissection.
    - Pathology showed a stage IIIC (T1cN3M0) multifocal invasive ductal carcinoma; the largest lesion measured 1.8 cm that demonstrated ER+ PR+ HER2- on IHC
    - All 13 lymph nodes examined were positive for disease. She was treated initially with adjuvant dose-dense doxorubicin, cyclophosphamide, plus paclitaxel and radiotherapy, after which she received anastrozole followed by bilateral salpingo-oophorectomy.
    - The patient developed recurrent, metastatic disease approximately 17 months after completing adjuvant radiotherapy. An abdominal lymph node biopsy confirmed recurrent, metastatic, triple-negative breast cancer that was also positive for androgen receptor expression. She received palbociclib and bicalutamide for 9 months, after which she briefly received capecitabine. Sequencing of an abdominal lymph node and a subsequently biopsied liver metastasis using MSK-IMPACT revealed the previously reported fusion between LMNA and NTRK1
    - Patient enrolled to receive larotrectinib at her disease was widely metastatic to liver, adrenal gland, lymph nodes, and bone. Brain imaging obtained in the absence of symptoms showed at least three subcentimeter brain metastases
        - A brisk and confirmed partial response by RECIST version 1.1 (−32%, −47%, and −56% at 4, 8, and 16 weeks, respectively) was achieved
        - Disease regression in the liver and adrenal gland and decreased uptake of hypermetabolic bony metastases were noted on serial imaging

- CNS metastases likewise regressed at the first follow-up assessment at 4 weeks, with a complete response in the CNS at 8 weeks (Fig 4).
- The patient remains on larotrectinib with good tolerability and disease control after 4 months of treatment.

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,

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