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 our most recent data regarding Larotrectinib®(Vitrakvi)

We respectfully suggest the following for NCCN consideration:

- To maintain the recommendation of "any" breast cancer subtype for *NTRK* gene fusion testing and larotrectinib
- To provide further recommendations and NTRK testing for TNBC based on the enclosed data (i.e., provide a patient population enriched for *NTRK* gene fusions)

FDA Clearance: (approval November 26, 2018; updated Package insert March 2021) – 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. (1)

Rationale: For the FDA approval, 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) 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. Updated data has recently been presented at ASCO 2021 for 218 patients identified with NTRK gene fusions (2). Additionally, a subset analysis of patients with breast cancer (n=6) was presented at San Antonio Breast Conference (3)

Breast Cancer evidence (3):

- For the breast subset analysis presented at SABC, 6 patients with TRK Breast Cancer were identified. ORR overall (for n=6) was 83%.
    - Median DOR was no reached at a median follow-up time of 7.4 mo. DOR was 100% at 6 months
    - Median PFS was 9.1 months at a median follow-up time of 7.4 mo; PFS at 6 months was 83%
    - Median OS was not reached at a median follow-up of 7.4 months
    - Median time to response was 1.7 months (range 0.9 to 1.9 months)
- Of the 6 patients:
    - Three patients were diagnosed with secretory carcinoma, in which there was 100% ORR (3 PRs)
    - Three patients were diagnosed with "non-secretory carcinoma (1 ER+,HER2-; 2 TNBC)
        - ORR for this group (n=3) was 67% (2 PRs), in which both PRs were in the patients identified with TNBC

- Relative to the larger datasets (1,2) , there were no unexpected safety concerns

Overall evidence (3):

- From the integrated data set (original n=55 cohort + supplemental patients enrolled), a total of 21 tumor types were identified across 218 patients, in which 206 were evaluable at the time of data cutoff (July 2019), with a 75% ORR (22% CR, 53% PR) by investigator assessment
- In terms of efficacy:
    - Median time to response was 1.84 months (range 0.89 to 9.07 months)
    - Median DoR was 49.3 months with a median follow up time of 22.3 months; 12 mo., 24 mo. and 36 mo. rates were 80%, 64% and 54% respectively.
    - Median PFS was 35.4 months with a median follow-up time of 20.3 months; 12- 24- and 36 – month rates were 9%, 57% an 48%, respectively
    - Median OS was not reached with a medial follow-up time of 22.3 months; 12- 24- and 36- mon rates were 89%, 81% and 77% respectively.
- In terms of safety
    - There were no new or unexpected safety signals, with a longer follow-up to the previous report and with 53 patients (24%) on larotrectinib treatment for ≥24 months
    - TRAEs were predominantly grade 1–2; There were no grade 5 TRAEs reported
    - Grade 3 and 4 TRAEs were reported in 18% of patients
        - The most common were decreased neutrophil count (7%), increased ALT (3%), and increased AST (2%)

Intra-Patient Comparison (4)

- Patients with TRK fusion cancer enrolled in three clinical trials (NCT02122913, NCT02637687, NCT02576431) who were treated with larotrectinib and had ≥1 prior line of systemic therapy were eligible for retrospective GMI analysis
- GMI is an innovative measure that uses patients as their own control by comparing PFS on their current therapy vs TTP on their most recent prior therapy, i.e., PFS/TTP
    - PFS was defined as the time from the start of larotrectinib treatment to radiological progression (as determined by IRC per RECIST v1.1), clinical progression or death by any cause
    - TTP was defined as the time from the start of the last prior treatment to progression (INV), clinical progression, or treatment end date
- A GMI of ≥1.33 indicates a ≥33% improvement in PFS over the previous line of therapy and has been proposed as a threshold of meaningful clinical activity[1]
- In the initial GMI initial group (n=122)
    - the Kaplan–Meier-estimated median GMI was 7.6 (95% CI 5.7, 88.0); 84 patients (69%) had a GMI ≥1.33
- In the initial MGI cohort with a longer follow-up (n=122)
    - the Kaplan–Meier-estimated median GMI increased to 9.5 (95% CI 5.7, 17.4); The proportion of patients who met the GMI threshold of ≥1.33 increased to 74%
- an expanded dataset (N=140)
    - The proportion of patients who met the GMI threshold of ≥1.33 was 74%
- In comparison of PFS and TTP (n=140; n=91 in adults and n=49 in pediatrics)
    - PFS on larotrectinib was 33.0 months overall (29.4 mo. In adults; 34.9 mo. In pediatrics)
    - Median TTP on prior therapy 3.0 mo. Overall (3.1. in adults; 2.0 mo. In pediatrics)
    - Hazard ratio in the overall cohort was 0.22 (0.29 mo. In adults; 0.10 mo. In pediatrics)

CNS Metastatic Data (5)

- As of July 15, 2019, 14 patients with TRK fusion cancer and CNS metastases had been treated with larotrectinib

  - Seven (50%) patients had non-small cell lung cancer, 4 (29%) had papillary thyroid cancer, 2 (14%) had melanoma, and 1 (7%) had triple-negative breast cancer
  - A total of 13 (93%) patients had received prior systemic therapy; 10 (71%) had received ≥2 prior systemic therapies
  - Patients had received a median of 3 (range 1–5) prior systemic therapies
  - Six (43%) patients had previously received radiotherapy to the brain; this was ≥6 months prior to starting larotrectinib in 4 (29%) patients
- Including all sites of disease, overall ORR was 71% (95% CI 42, 92)
  - Ten (71%) patients had a PR, 2 (14%) patients had SD, and 2 (14%) patients (lung cancer and melanoma) had PD as best response
    - The patient diagnosed with TNBC, achieved a high partial response rate (90%+)
  - Three patients had measurable intracranial disease, with intracranial tumor reductions of 14%, 46%, and 100%
  - 2 of these patients had received radiotherapy to the brain ~14–15 months prior to starting larotrectinib
- Among all patients, median time to response was 1.8 months (range 0.9–3.5)
  - Duration of treatment ranged from 1.4 to 25.0 months, with treatment ongoing in 6 patients at data cut-off
  - Six patients continued treatment beyond progression, lasting between 0.1+ and 8.5 months
- In terms of efficacy:
  - Median DOR was 14.8 mo. with a median follow-up time of 9.5 months; 12 mo. DoR rate was 61%
  - Median PFS was 9.9 months with a median follow-up time of 13.6 mo.
  - Median OS was 27.8 mo. with a median follow-up time of 10.7 mo.; 12 mo. OS rate was 79%

We appreciate your review and consideration of this recommendation.

Sincerely,

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Reference List

1. Updated Package Insert - http://labeling.bayerhealthcare.com/html/products/pi/vitrakvi_PI.pdf
2. Hong, DS. Et al. Long-term efficacy and safety of larotrectinib in an integrated dataset of patients with TRK fusion cancer. ASCO 2021 Presentation. https://meetinglibrary.asco.org/record/195782/abstract
3. Rosen, E. et al. Efficacy and Safety of Larotrectinib in Patients with TRK Fusion Breast Cancer. Poster PS11-06
4. Italiano, A. et al. Intra-patient comparison from larotrectinib clinical trials in TRK fusion cancer – an expanded dataset. ASCO 2021 Presentation. https://meetinglibrary.asco.org/record/197499
5. Patel, JD. Et al. Activity of larotrectinib in TRK fusion cancer patients with CNS metastases. SNO 2020 Presentation.