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Panel: Non-Small Cell Lung Cancer

On behalf of Eli Lilly and Company, I respectfully request the National Comprehensive Cancer Network (NCCN) to review the enclosed information for RETEVMO® (selpercatinib) in reference to NCCN Guidelines V5.2021 for Non-Small Cell Lung Cancer (NSCLC).

Specific changes recommended

We request that the NSCLC panel review the attached clinical data and consider recommending selpercatinib treatment in patients with rearranged during transfection (*RET)* fusion-positive NSCLC with intracranial metastases in section ***RET*-Rearrangement Positive NSCLC** of the Guidelines. **(NSCL-32).** In addition, please consider updating the **Discussion** section to include data on selpercatinib as a treatment option for patients with *RET* fusion-positive NSCLC and brain metastases.

FDA clearance

Selpercatinib is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic (*RET)* fusion-positive NSCLC
- Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy, and
- Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).[1]

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Please refer to the product prescribing information for the full FDA-approved indications and safety information. Full prescribing information is available at: http://pi.lilly.com/us/retevmo-uspi.pdf.[1]

Rationale:

Selpercatinib was evaluated in patients with advanced *RET* fusion-positive NSCLC, *RET*-mutant MTC, *RET* fusion-positive thyroid cancer, and other tumors with *RET* activation enrolled in the LIBRETTO-001 phase 1/2, multicenter, open-label, single-arm clinical study (NCT03157128).[2-3] Patients with known brain metastases were eligible to participate in the study if neurological symptoms and CNS imaging were stable, their steroid dose was stable for 14 days prior to the first dose of selpercatinib, and no CNS surgery or radiation had been performed for 28 days (14 days if stereotactic radiosurgery) prior to dosing. For patients who had received CNS radiation prior to the trial, intracranial lesions needed to show post-radiation progression to be selected as a target lesion at baseline.[4] Patients with baseline intracranial metastases had radiologic assessments every 8-weeks for 1 year, and every 12 weeks thereafter.[4]

A preplanned subgroup analysis was performed to evaluate the efficacy and safety of selpercatinib in patients with *RET* fusion-positive NSCLC who had brain metastases at baseline, with or without prior radiation therapy. The primary endpoint was intracranial objective response rate (ORR) by RECIST 1.1 determined by an independent review committee. Secondary endpoints included intracranial disease control rate, intracranial duration of response, and intracranial progression-free survival (PFS)

independently reviewed. Safety was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).[4]

As of June 17, 2019, a total of 531 patients were enrolled in LIBRETTO-001 including 253 patients with *RET* fusion-positive NSCLC. Among the 253 patients with *RET* fusion-positive NSCLC, 80 patients had brain metastases at baseline. Of those 80 patients, 22 had measurable CNS metastases as assessed by an independent review committee, including 8 patients who have received prior cranial radiotherapy.[4]

CNS Efficacy Results

- Among the 22 patients with measurable intracranial disease at baseline, the intracranial ORR was 82% (95% CI: 60–95), including 23% with complete response. Of these, the intracranial ORR for the subset of 8 patients with measurable disease and prior cranial radiotherapy was 75% (95% CI: 35-97), and the intracranial ORR for subset of 14 patients with measurable disease without prior cranial radiotherapy was 86% (95% CI: 57-98). Because all the patients achieved a tumor response or disease stabilization, the intracranial disease control rate was 100%.[4]

- Among the 58 patients with exclusively non-measurable intracranial disease at baseline, 20 patients (34%) achieved a complete intracranial response based on complete resolution of all non-measurable lesions and 29 patients (50%) had non-complete response/non-progressive disease. Five patients (9%) had progressive disease as best intracranial response.[4]

- In all 80 patients with brain metastases at baseline, the median intracranial PFS was 13.7 months (95% CI: 10.9-NE) at a median duration of follow-up of 11.0 months (interquartile range, IQR: 7.4-16.5). Thirty-eight patients (48%) from this the population had an intracranial response to selpercatinib. Among this group of responders, the median intracranial duration of response was not reached (95% CI: 9.3-NE) at a median duration of follow-up of 9.5 months (IQR 5.7,12.0). At 12 months, 55% of intracranial responses were ongoing.[4]

CNS Safety Results

Among the 80 patients with NSCLC and baseline brain metastases, treatment-emergent adverse events (TEAEs) grade ≥3 reported in >10% of patients were alanine aminotransferase (ALT) increase (18%), aspartate aminotransferase (AST) increase (11%), hypertension (21%, all grade 3), and hyponatremia (11%). Treatment-related adverse events (TRAEs) grade ≥3 reported in >10% of patients were ALT increase (14%), and hypertension (16%). No Grade 5 TRAEs were reported.[4]

No new safety signals were identified in patients with brain metastases compared to the full NSCLC trial population. TEAEs and TRAEs were reported at similar levels in patients with baseline intracranial disease compared with all patients with *RET* fusion-positive NSCLC in LIBRETTO-001 (n=253).[4]

References

The following references are submitted to assist the committee in their review. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or contributors of some of these data disclosures.

1. Retevmo [package insert]. Indianapolis, IN: Eli Lilly and Company; 2021.

2. Phase 1/2 study of LOXO-292 in patients with advanced solid tumors, RET fusion-positive solid tumors, and medullary thyroid cancer (LIBRETTO-001). ClinicalTrials.gov identifier: NCT03157128. Updated May 6, 2021. Accessed June 7, 2021. https://www.clinicaltrials.gov/ct2/show/NCT03157128.

3. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med. 2020;383(9):813-824. https://dx.doi.org/10.1056/NEJMoa2005653.

4. Subbiah V, Gainor JF, Oxnard GR et al. Intracranial efficacy of selpercatinib in RET fusion-positive non-small cell lung cancers on the LIBRETTO-001 trial. Clin Cancer Res 2021; ePub ahead of print. http://dx.doi.org/10.1158/1078-0432.CCR-21-0800.

We appreciate the Panel's thorough consideration of this request. Please do not hesitate to contact me with any questions.

Sincerely,

Jessie L. Fahrbach, MD
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