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Date: March 27, 2020**Panel:** Non-Small Cell Lung Cancer

On behalf of Eli Lilly and Company, I respectfully request the NCCN Guidelines committee to review the enclosed information for RETEVMO™ (selpercatinib) in reference to NCCN Guidelines V3.2020 for Non-Small Cell Lung Cancer (NSCLC). This submission includes investigator assessment data from a June 2019 data cut from the LIBRETTO-001 trial. Independent review data from a December 2019 data cut will be included in our next submission.

Specific changes recommended:

We respectfully request that the NCCN Clinical Practice Guidelines in Oncology, upon FDA approval, includes selpercatinib as a treatment option for patients with metastatic rearranged during transfection (RET) fusion-positive NSCLC who require systemic therapy.

We also ask that appropriate testing for RET to be included in the NCCN guideline and respectfully suggest the following for NCCN consideration:

NSCL-I (1 of 2), Targeted Therapy for Advanced or Metastatic Disease:

- Add “RET fusion-positive: selpercatinib”

NSCL-18, Molecular Testing:

- Add “RET testing”

NSCL-18, Testing Results:

- Add “RET fusion-positive: selpercatinib”

NSCL-G, Molecular Targets for Analysis:

- RET is a member of the tyrosine kinase family of proteins that activate several downstream signaling pathways, including mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK). Oncogenic gene fusions involving RET kinase domain can be seen in NSCLC.¹
 - Common fusion partners are KIF5B, NCOA4, and CCDC6, however, numerous other fusion partners have been identified.¹
 - Testing Methodologies: Various methodologies can be used to detect RET gene fusions, including break apart FISH,² PCR,² and NGS.³
 - Targeted PCR assays may underestimate RET fusions in NSCLC due to inability to detect novel breakpoint and uncommon fusion partners.²
 - Numerous NGS methodologies can detect RET fusions. Given the many FDA approved therapies in NSCLC, including selpercatinib, and the limited tissue available, up front comprehensive tissue NGS testing is recommended over single analyte testing.³
 - NGS testing is recommended over single analyte testing because it is a more efficient and timely technology for the genomic profiling of cancer. NGS allows for multiplex testing on a small amount of tissue to help identify the most appropriate therapeutic option among the many FDA approved therapies in NSCLC, including selpercatinib.³
 - RNA-based NGS is the preferred methodology to maximize detection of gene fusions.³
 - Current liquid biopsy solutions likely suffer from sensitivity and specificity challenges in the accurate detection of gene fusions.⁴⁻⁵

FDA Clearance:

Selpercatinib is not an FDA-approved treatment for patients with metastatic RET fusion-positive NSCLC who require systemic therapy. Eli Lilly and Company has submitted information to the FDA based on the LIBRETTO-001 study.

Rationale:

LIBRETTO-001 is a multicenter, open-label, phase 1/2 study of selpercatinib administered orally to patients with advanced solid tumors, including RET fusion-positive NSCLC, medullary thyroid cancer (MTC), and other tumors with RET activation.⁶⁻⁷ The phase 1 portion of the study established the recommended phase 2 dose for selpercatinib of 160 mg

by mouth (PO) twice daily (BID).⁷ The phase 2 portion enrolled patients to 1 of 6 cohorts based on tumor type, RET alteration, and prior therapies.⁶⁻⁷ The primary endpoint of phase 2 study was objective response rate (ORR) based on RECIST 1.1. Key secondary endpoints of the phase 2 study were duration of response (DOR), progression-free survival (PFS), and safety.⁷

As of June 17, 2019, a total of 531 patients were enrolled in LIBRETTO-001 including 253 patients with RET fusion-positive NSCLC, 226 patients with RET-mutant MTC, 27 patients with RET fusion-positive thyroid cancer, and 25 patients with other RET altered tumors. Of the 253 patients with RET fusion-positive NSCLC, 184 patients received prior platinum chemotherapy, 16 received prior nonplatinum chemotherapy, and 39 were treatment naïve.⁷

Efficacy – Primary Analysis Set

The primary analysis set, as defined with the FDA, consisted of the first 105 consecutively enrolled RET fusion-positive NSCLC patients who received prior platinum-based chemotherapy.⁷ The patients in the primary analysis set was a heavily pretreated population who received a median of 3 prior systemic therapies.⁵ Fifty-five percent of these patients were previously treated with an anti-programmed death-1 (PD-1)/programmed death-ligand-1 (PD-L1) antibody and 48% were previously treated with at least one multikinase inhibitor (MKI).⁷

Patients with RET-fusion positive lung cancer who had previously received prior platinum doublet therapy (n=105) demonstrated the following with selpercatinib treatment based on investigator-assessments as of June 17, 2019:

- 68% ORR (95% CI 58-76)⁷
- Median DOR of 20.3 months (95% CI: 13.8-24.0) with 8.0 months of median follow-up⁷
- Median PFS of 18.4 months (95% CI 12.9-24.9) with 9.6 months of median follow-up⁷

Central Nervous System (CNS) Activity

The primary analysis set included 11 patients with measurable CNS target lesions at baseline. Intracranial ORR was 91% (95% CI, 59-100) per RECIST 1.1, with 2 confirmed complete responses and 8 confirmed partial responses; 1 patient had stable disease.⁷

Efficacy – Treatment Naïve Patients

34 of the 39 treatment-naïve patients in LIBRETTO-001 were evaluable for overall response.⁵ Patients with RET fusion positive lung cancer who had not been treated previously with chemotherapy (n=34) demonstrated the following with selpercatinib treatment:

- 85% objective response rate (95% CI 69-95)⁷
- Median PFS and DOR were not yet reached⁷

Safety Results

In a safety analysis of all 531 patients enrolled to LIBRETTO-001, nine patients (1.7%) discontinued therapy due to treatment-related adverse events.⁵ The most commonly observed adverse events, regardless of attribution, were dry mouth, diarrhea, hypertension, increased liver enzymes, fatigue, constipation, and headache.⁷

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.

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2. Ferrara R, et al. *J Thorac Oncol*. 2018;13(1):27-45. <https://doi.org/10.1016/j.jtho.2017.10.021>.
3. Drilon A et al. *Clin Cancer Res*. 2015;21(16):3631-3639. <https://doi.org/10.1158/1078-0432.CCR-14-2683>.
4. Hou H, et al. *Sci Rep*. 2017;7(6):14605. <https://doi.org/10.1038/s41598-017-14962-0>.
5. Villalflor V, et al. *Oncotarget*. 2016;7(41):66880-66891. <https://doi.org/10.18632/oncotarget.11801>
6. 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 website. <https://www.clinicaltrials.gov/ct2/show/NCT03157128>. Updated September 13, 2019. Accessed January 14, 2020.
7. Drilon A, et al. Registrational results of LIBRETTO-001: a phase 1/2 trial of selpercatinib (LOXO-292) in patients with RET fusion-positive lung cancers. Talk presented at: 20th Annual World Conference on Lung Cancer; September 7-10, 2019; Barcelona, Spain.

Sincerely,

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