**Name:** Jessie L. Fahrbach, MD
**Title:** Vice President, Global Medical Affairs, Lilly Oncology
**Company:** Eli Lilly and Company
**Address:** Lilly Corporate Center, Indianapolis, IN 46285
**Phone:** 317-276-3974
**Email:** fahrbach_jessie_l@lilly.com
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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 manuscript for RETEVMO™ (selpercatinib) in reference to NCCN Guidelines V8.2020 for Non-Small Cell Lung Cancer (NSCLC)[1]:

**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.**

At FDA approval of selpercatinib in May 2020, limited clinical data was available in the label and in poster disclosures. With the publication of the LIBRETTO-001 trial in the New England Journal of Medicine, I respectfully ask the NCCN panel to (i) update the NCCN Biomarkers Compendium to include *RET* as an actionable biomarker for NSCLC, and (ii) add *RET* to the Principles of Molecular and Biomarker Analysis (NSCL-G) section, based on the level of rigor by which the data in this patient population has now been assessed, reviewed, and published.

**Specific changes recommended:**

1. **Update the NCCN Biomarkers Compendium® to include *RET* as an actionable biomarker for NSCLC.**

2. **Add *RET* to "Principles of Molecular and Biomarker Analysis (NSCL-G)." We respectfully submit the following language for NCCN consideration:**

   The *RET* (REarranged during Transfection) proto-oncogene encodes a transmembrane receptor tyrosine kinase that is involved in normal embryonic development. Fusions between sequences that encode the kinase domain of *RET* and various upstream gene partners result in unregulated signaling and can be seen in NSCLC.[1]

   - Common fusion partners are KIF5B, NCOA4, and CCDC6, however, numerous other fusion partners have been identified.[2]
   - The presence of a *RET* gene fusion is associated with responsiveness to *RET* tyrosine kinase inhibitors (TKIs).[1]
   - Testing Methodologies: Various methodologies can be used to detect *RET* gene fusions, including fluorescence in situ hybridization (FISH),[3] polymerase chain reaction (PCR),[3] and next-generation sequencing (NGS).[4]
     - Immunohistochemistry (IHC) should not be used due to low sensitivity and specificity.[3,5]
     - FISH break apart probe methodology may result in false negative results due to proximity of common fusion partners.[2,5,8]
     - Targeted real time PCR assays may underestimate *RET* fusions in NSCLC due to inability to detect novel breakpoint and uncommon fusion partners.[3]
     - Numerous NGS methodologies can detect *RET* fusions. DNA-based NGS may underrepresent **RET** fusions. Given the many FDA approved therapies in NSCLC and the limited tissue available, up front comprehensive tissue NGS testing is recommended over single analyte testing.[4]

**FDA Clearance:**
Selpercatinib is a kinase inhibitor indicated for the treatment of (i) adult patients with metastatic *RET* fusion-positive non-small cell lung cancer, (ii) 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 (iii) 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 (RAI) refractory (if radioactive iodine is appropriate). 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

**Rationale:**

We are providing the recently published manuscript with efficacy and safety findings from *RET* fusion-positive NSCLC patients enrolled in LIBRETTO-001. 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 and thyroid cancer, *RET*-mutant MTC, and other tumors with *RET* alterations.[1]

Biomarker testing for *RET* alteration is the only way to determine if selpercatinib is an appropriate targeted treatment for a patient's specific type of cancer. In LIBRETTO-001, *RET* alteration status was determined by local molecular testing performed in a certified laboratory with the use of NGS, FISH, or PCR assay.[1]

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. 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
2. Drilon A, et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167. https://www.nature.com/articles/nrclinonc.2017.175
3. Ferrara R, et al. *J Thorac Oncol*. 2018;13(1):27-45. https://doi.org/10.1016/j.jtho.2017.10.021
4. Drilon A et al. *Clin Cancer Res*. 2015;21(16):3631-3639. https://doi.org/10.1158/1078-0432.CCR-14-2683
5. Lindeman NI, et al. *J Thorac Oncol*. 2018;13:323-358. https://doi.org/10.1016/j.jtho.2017.12.001
6. Ferrara R, et al. *J Thorac Oncol*. 2018;13:27-45. https://dx.doi.org/10.1016/j.jtho.2017.10.021
7. Hou H, et al. *Sci Rep*. 2017;7(6):14605. https://doi.org/10.1038/s41598-017-14962-0.
8. Villaflor V, et al. *Oncotarget*. 2016;7(41):66880-66891. https://doi.org/10.18632/oncotarget.11801


Thank you in advance for your review of this data, and please let me know if there is any additional information that you may need.

Sincerely,


Jessie L. Fahrbach, MD
Vice President - Global Medical Affairs
Lilly Oncology