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Date: May 8, 2020
Panel: Thyroid Carcinoma

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 V2.2019 for Thyroid Carcinoma. The purpose of this submission is to provide two updates:

1. Selpercatinib is now FDA-approved. (Additional details listed under FDA clearance.)
2. The data in the USPI includes updated independent review data from a December 2019 data cut of the LIBRETTO-001 study. As of December 2019, a total of 702 patients were enrolled.

Specific changes recommended:
We respectfully request the NCCN Clinical Practice Guidelines in Oncology to include selpercatinib as a treatment option for 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
- *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (RAI-refractory), if radioactive iodine is appropriate.[1]

We also ask that appropriate testing for *RET* be included in the NCCN guidelines, as detailed in our previous submission.

FDA Clearance:
On May 8, 2020, the FDA approved selpercatinib as 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 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 RAI-refractory (if radioactive iodine is appropriate).[1]

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 and thyroid cancer, *RET*-mutant MTC, and other tumors with RET activation.[1] The primary endpoint of the phase 2 study was objective response rate (ORR) as determined by a blinded independent review committee according to RECIST v1.1. Key secondary endpoints of the phase 2 study were duration of response (DOR) and safety.[1]

***RET*-Mutant Medullary Thyroid Cancer**
Efficacy was evaluated in 55 patients with *RET*-mutant advanced MTC who had been previously treated with cabozantinib or vandetanib and enrolled into a cohort of LIBRETTO-001. Patients received a median of 2 prior systemic therapies. Ninety-eight percent of patients had metastatic disease. *RET* mutation status was detected in 82% of patients using next-generation sequencing (NGS) (78% tumor samples, 4% blood or plasma), 16% using polymerase chain reaction (PCR), and 2% using an unknown test.[1]

The efficacy of selpercatinib was also evaluated in 88 patients with *RET*-mutant MTC who were cabozantinib and vandetanib treatment-naïve. All patients had metastatic disease, and 18% had received 1 or 2 prior systemic therapies. *RET* mutation status was detected in 78% of patients using NGS (76.1% tumor samples, 2.3% blood samples), 18% using PCR, and 3.4% using an unknown test.[1]

Efficacy results for patients with *RET*-mutant MTC are summarized in Table 1.[1]

Table 1: *RET*-Mutant Medullary Thyroid Cancer Efficacy Results in LIBRETTO-001[1]

	Selpercatinib Cabozantinib/Vandetanib Previously Treated n = 55	**Selpercatinib Cabozantinib/Vandetanib Naïve n = 88**
Overall Response Rate[1] **(95% CI)**	69% (55%, 81%)	73% (62%, 82%)
Complete Response	9%	11%
Partial Response	60%	61%
Duration of Response		
Median in months (95% CI)	NE (19.1, NE)	22.0 (NE, NE)
% with > 6 months[2]	76	61

[1] Confirmed overall response rate assessed by blinded independent central review (BICR). [2] Based on observed duration of response
NE = not estimable

***RET*-Fusion Positive Thyroid Cancer**

The efficacy of selpercatinib was evaluated in 27 patients with *RET* fusion-positive thyroid cancer who were RAI-refractory (if RAI was an appropriate treatment option) and were systemic therapy naïve and patients with *RET* fusion-positive thyroid cancer who were RAI-refractory and had received sorafenib, lenvatinib, or both. All patients had metastatic disease with primary tumor histologies including papillary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, and Hurthle cell thyroid cancer. Patients had received a median of 3 prior therapies. *RET* fusion-positive status was detected in 93% of patients using NGS tumor samples and in 7% using blood samples. Efficacy results for *RET* fusion-positive thyroid cancer are summarized in Table 2.[1]

Table 2. *RET* Fusion-Positive Thyroid Cancer Efficacy Results in LIBRETTO-001[1]

	Selpercatinib Previously Treated (n = 19)	**Selpercatinib Systemic Therapy Naïve (n = 8)**
Overall Response Rate[1] (95% CI)	79% (54%, 94%)	100% (63%, 100%)
Complete response	5.3%	12.5%
Partial response	74%	88%
Duration of Response		
Median in months (95% CI)	18.4 (7.6, NE)	NE (NE, NE)
% with ≥ 6 months[2]	87	75

[1] Confirmed overall response rate assessed by blinded independent central review (BICR). [2] Based on observed duration of response
NE = not estimable

Safety

In a safety analysis of all 702 patients enrolled to LIBRETTO-001, permanent discontinuation due to an adverse reaction occurred in 5% of patients who received selpercatinib. Two percent of discontinuations were considered treatment-related, as assessed by the trial investigator (Data on file). Adverse reactions resulting in permanent discontinuation included increased alanine aminotransferase (ALT) (0.4%), sepsis (0.4%), increased aspartate aminotransferase (AST) (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%). The most common adverse reactions, including laboratory abnormalities, (≥ 25%) were increased AST, increased ALT, increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation. The most frequent serious adverse reaction (in ≥ 2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).[1]

The following reference is submitted to assist the committee in their review:

1. Retevmo [package insert]. Indianapolis, IN: Eli Lilly and Company; 2020.

We appreciate your review and consideration of this recommendation.

Sincerely,

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