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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). 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 patients with metastatic *RET* fusion-positive NSCLC.

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 NSCLC, (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-refractory (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]

Metastatic *RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy
Efficacy was evaluated in 105 patients with *RET* fusion-positive NSCLC who received prior platinum-based chemotherapy enrolled into a cohort of LIBRETTO-001. These patients received a median of 3 prior systemic therapies. *RET* fusions were detected in 90% of patients using next generation sequencing (NGS) (82% tumor samples, 8% blood or plasma samples), 9% using fluorescence in situ hybridization (FISH), and 2% using polymerase chain reaction (PCR).[1]

Among these 105 patients with *RET* fusion-positive NSCLC,

- 58 patients were previously treated with an anti-programmed death-1 (PD-1) or anti-programmed death-ligand-1 (PD-L1) antibody, either sequentially or concurrently with platinum-based chemotherapy, and
- 11 patients had measurable central nervous system (CNS) metastases at baseline and had not received radiation therapy to the brain within 2 months prior to study entry.[1]

Efficacy results for all 105 patients with *RET* fusion-positive NSCLC are summarized in Table 1. For the patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 66% (95% CI: 52%, 78%) and the median DOR was 12.5 months (95% CI: 8.3, NE). Responses in intracranial lesions were observed in 10 of 11 patients with measurable CNS metastases at baseline; all responders had a DOR of $\geq$ 6 months.[1]

Table 1: Efficacy Results in Metastatic *RET* Fusion-Positive NSCLC previously treated with platinum chemotherapy.[1]

	Selpercatinib n=105
Overall Response Rate (95% CI)[1]	64% (54%, 73%)
Complete Response	1.9%
Partial Response	62%
Duration of Response	
Median in months (95% CI)	17.5 (12, NE)
% with > 6 months[2]	81

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

Treatment-naïve *RET* Fusion-Positive NSCLC

Efficacy was evaluated in 39 patients with treatment-naïve *RET* fusion-positive NSCLC enrolled into a cohort of LIBRETTO-001. All patients (100%) had metastatic disease. *RET* fusions were detected in 92% of patients using NGS (69% tumor samples; 23% in blood) and 8% using FISH. Efficacy results for treatment naïve *RET* fusion-positive NSCLC are summarized in Table 2.[1]

Table 2. Efficacy Results in Treatment-Naïve Metastatic *RET* Fusion-Positive NSCLC[1]

	Selpercatinib (n =39)
Overall Response Rate (95% CI)[1]	85% (70%, 94%)
Complete response	0
Partial response	85%
Duration of Response	
Median in months (95% CI)	NE (12, NE)
% with ≥ 6 months[2]	58

[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 submission.

Sincerely,

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