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NCCN Guidelines Panel: Non-Small Cell Lung Cancer (NSCLC)

Dear NCCN NSCLC Panel Members,

On behalf of Pfizer Oncology, I respectfully request the NCCN Guideline Panel for Non-Small Cell Lung Cancer to review the enclosed information for inclusion of LORBRENA(lorlatinib) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease.

Specific Changes Requested: Recommend the inclusion of LORBRENA(lorlatinib) as a treatment option on the following pages in the current NSCLC guidelines: NSCL-22, NSCLC-23 and relevant discussion sections

FDA Approval: On Nov 2, 2018, the FDA approved LORBRENA(lorlatinib) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on

- crizotinib and at least one other ALK inhibitor for metastatic disease; or
- alectinib as the first ALK inhibitor therapy for metastatic disease; or
- ceritinib as the first ALK inhibitor therapy for metastatic disease.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication maybe contingent upon verification and description of clinical benefit in a confirmatory trial.

Rationale: Based on the FDA-approved indication and data from Study B7461001 (NCT01970865), LORBRENA(lorlatinib) demonstrated clinically meaningful responses in patients with ALK-positive metastatic NSCLC whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease.

The following resources are submitted in support of this requested change:

- LORBRENA (lorlatinib), prescribing information. Pfizer Inc
- Shaw AT, Felip E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol. 2017;18(12):1590–1599.
- Besse B, Solomon B, Felip E, et al. Lorlatinib in Patients With Previously Treated ALK+ Advanced Non-Small Cell Lung Cancer (NSCLC): Updated Efficacy and Safety. Presented at ASCO 2018. Abstract #9032
- Solomon B, Shaw A, Ou S, et al. OA 05.06 Phase 2 study of lorlatinib in patients with advanced ALK +/ROS1 + non-small-cell lung cancer. J Thorac Oncol. 2017;12(11):S1756.
- Felip E, Shaw A, Solomon B, et al. Efficacy and Safety of Lorlatinib in Patients With ALK+ Non-Small Cell Lung Cancer (NSCLC) Previously Treated With Second-Generation ALK TKIs. Presented at ESMO 2017. Abstract #1343P

The efficacy of LORBRENA was demonstrated in a subgroup of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) previously treated with one or more ALK kinase inhibitors who were enrolled in a non randomized, multi cohort, study (Study B7461001; NCT01970865). Patients included in this subgroup were required to have metastatic disease with at least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1), ECOG performance status of 0 to 2, and documented ALK rearrangement in tumor tissue as determined by fluorescence in situ hybridization (FISH) assay or by Immunohistochemistry (IHC), and received LORBRENA 100 mg orally once daily. Patients with asymptomatic CNS metastases,



including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were eligible. The extent and type of prior treatment was specified for each individual cohort. The major efficacy outcome measures were overall response rate (ORR) and intracranial ORR, according to RECIST v1.1, as assessed by Independent Central Review (ICR) committee. Data were pooled across all subgroups listed in Table 4 of the US Prescribing Information (copied below). Additional efficacy outcome measures included duration of response (DOR), and intracranial DOR.

A total of 215 patients were enrolled across the subgroups in Table 4 of the US Prescribing Information (copied below). The distribution of patients by type and extent of prior therapy is provided below:

Extent of Prior Therapy in the Subgroup of Patients with Previously Treated ALK-Positive Metastatic NSCLC in Study B7461001

Extent of prior therapy	Number of patients
Prior crizotinib and no prior chemotherapy ^a	29
Prior crizotinib and 1-2 lines of prior chemotherapy ^a	35
Prior ALK inhibitor (not crizotinib) with or without prior chemotherapy ^a	28
Two prior ALK inhibitors with or without prior chemotherapy ^a	75
Three prior ALK inhibitors with or without prior chemotherapy ^a	48
Total	215

Abbreviations: ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer.

^a Chemotherapy administered in the metastatic setting.

The ORR was 48%, (95% CI 42, 55) including 4% complete response (CR) and 44% partial response (PR). The median duration of response was 12.5 months (95% CI 8.4, 23.7). An assessment of intracranial ORR and the duration of response for CNS metastases was conducted in the subgroup of 89 patients in Study B7461001 with baseline measurable lesions in the CNS according to RECIST v1.1. Of these, 56 (63%) patients received prior brain radiation, including 42 patients (47%) who completed brain radiation treatment at least 6 months before starting treatment with LORBRENA. The intracranial ORR was 60%, (95% CI 49, 70) including 21% intracranial-CR and 38% intracranial-PR. The median duration of intracranial response was 19.5 months (95% CI 12.4, NR). In exploratory analyses conducted in subgroups defined by prior therapy, the response rates to LORBRENA were:

- ORR = 39% (95% CI: 30, 48) in 119 patients who received crizotinib and at least one other ALK inhibitor, with or without prior chemotherapy
- ORR = 31% (95% CI: 9, 61) in 13 patients who received alectinib as their only ALK inhibitor, with or without prior chemotherapy
- ORR = 46% (95% CI: 19, 75) in 13 patients who received ceritinib as their only ALK inhibitor, with or without prior chemotherapy

The data described below reflect exposure to LORBRENA (lorlatinib) in 295 patients with ALK-positive or ROS1-positive metastatic NSCLC who received LORBRENA (lorlatinib) 100 mg orally once daily in Study B7461001. The most common ($\geq 20\%$) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea; the most common ($\geq 20\%$) laboratory abnormalities were hypercholesterolemia, hypertriglyceridemia, anemia, hyperglycemia, increased AST, hypoalbuminemia, increased ALT, increased lipase, and increased alkaline phosphatase. Serious adverse reactions occurred in 32% of the 295 patients; the most frequently reported serious adverse reactions were pneumonia (3.4%), dyspnea (2.7%), pyrexia (2%), mental status changes (1.4%), and respiratory failure (1.4%).

We greatly appreciate the Panel's thorough consideration of the data for LORBRENA (lorlatinib).

Sincere regards,

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