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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

Dear NCCN Non-Small Cell Lung Cancer Panel Members,

On behalf of the Pfizer , I respectfully request the NCCN Guideline Panel for Non-Small Cell Lung Cancer to review the enclosed information for inclusion of lorlatinib as a first-line therapy for patients with previously untreated advanced anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose tumors are positive as detected by an FDA approved test.

Specific Changes Requested: Recommend inclusion of lorlatinib as a first-line therapy for patients with previously untreated advanced anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose tumors are positive as detected by an FDA approved test.

FDA Clearance (Non-Small Cell Lung Cancer):

Lorlatinib is FDA-approved 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.

The data from the first-line CROWN trial (NCT03052608) will be reviewed under the FDA's Real Time Oncology Review (RTOR) pilot program (https://www.pfizer.com/news/press-release/press-release-detail/results-phase-3-crown-trial-pfizers-lorbrenar-lorlatinib).

Rationale: At a planned interim analysis for the CROWN trial (NCT03052608), lorlatinib demonstrated statistically significant improvement in progression-free survival (PFS) according to blinded independent central review (BICR) and a higher frequency of intracranial response than those who received crizotinib.

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

1. Shaw, A.T. et al. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. N Engl J Med 2020; 383; 2018-2029
2. Shaw, A.T. et al. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. N Engl J Med 2020; 383; 2018-2029 (Supplementary Appendix)

The basis for this request are the results from an international, multicenter, randomized, open-label, phase 3 trial (CROWN Trial), which evaluated the efficacy and safety of lorlatinib versus crizotinib as first-line therapy in patients with advanced ALK-positive NSCLC who had rceived no previous systemic treatment for metastatic disease.

The primary endpoint was progression-free survival by blinded independent central review (BICR). Secondary endpoints included independently assessed objective response rate and intracranial response, overall survival and safety. A total of 296 patients were randomized to lorlatinib (n=149) or crizotinib (n=147).

At a planned interim analysis, progression-free survival at 12-months was 78% (95% CI, 70 to 84) with lorlatinib vs. 39% (95% CI, 30 to 48) with crizotinib (HR, 0.28; 95% CI, 0.19 to 0.41; P<0.001). The hazard ratio for progression-free survival as assessed by BICR favored lorlatinib over crizotinib across all prespecified patient subgroups. The objective response rate was 76% (95% CI, 68 to 83) with lorlatinib and 58% (95% CI, 49 to 66) with crizotinib. Intracranial response rates in patients with measurable brain metastases were 82% (95% CI, 57 to 96) and 23% (95% CI, 5 to 54), respectively, with intracranial complete responses in 71% of lorlatinib-treated patients and 8% in crizotinib-treated patients. The time to CNS progression was significantly longer with lorlatinib than with crizotinib The percentage of patients who were alive without CNS progression at 12 months was 96% (95% CI, 91 to 98) with lorlatinib and 60% (95% CI, 49 to 69) with crizotinib (hazard ratio, 0.07; 95% CI, 0.03 to 0.17).

The most common adverse events with lorlatinib included hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects. Lorlatinib was associated with more Grade 3 or 4 adverse events (72% vs. 56% with crizotinib), mainly altered lipids. Treatment discontinuation from adverse events occurred in 7% and 9% of patients, respectively. Adverse events leading to dose interruption or dose reduction, respectively, were reported in 49% and 21% of the patients in the lorlatinib group and in 47% and 15% of those in the crizotinib group.

We greatly appreciate the Panel's thorough consideration of the data for lorlatinib as a first-line therapy for patients with previously untreated advanced ALK-positive metastatic NSCLC whose tumors are positive as detected by an FDA approved test.

Best regards,

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