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Date: September 8, 2020
Panel: Non-Small Cell Lung Cancer

On behalf of Blueprint Medicines Corporation, I respectfully request the NCCN Guidelines committee to review the enclosed information for GAVRETO™ (pralsetinib) in reference to NCCN Guidelines V6.2020 for Non-Small Cell Lung Cancer (NSCLC). This submission includes data from the BLU-667-1101 trial[1], (ARROW) which is the pivotal registrational study for the NSCLC submission. The purpose of this submission is to provide additional updates:

1. Pralsetinib is now FDA-approved (additional details listed under FDA clearance).
2. The data in the USPI includes updated independent review data from a February 13, 2020 data cut of the BLU-667-1101 study. As of February 13, 2020, a total of 220 NSCLC patients were enrolled.

Specific Changes Recommended
We respectfully request that the NCCN Clinical Practice Guidelines in Oncology include pralsetinib as a treatment option for adult patients with metastatic rearranged during transfection (*RET*) fusion-positive NSCLC who require systemic therapy. We respectfully request the following for NCCN consideration:

NSCL-1 (1 of 2), Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease
- Add "*RET* Rearrangement Positive: Pralsetinib"

NSCL-29, *RET* Rearrangement Positive
- Add "First-Line Therapy/Subsequent Therapy: Pralsetinib"

FDA Clearance:
On September 4, 2020, the FDA approved pralsetinib as a kinase inhibitor indicated for the treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

Rationale
BLU-667-1101 (ARROW; NCT03037385) is a multicenter, non-randomized, open-label, multi-cohort, phase 1/2 study of pralsetinib for patients with advanced solid tumors, including *RET* fusion-positive NSCLC, medullary thyroid cancer (MTC), and other tumors with *RET* alteration.[1,2] Phase 1 of the study established the recommended phase 2 dose for pralsetinib of 400 mg by mouth (PO) once daily (QD). Phase 2 enrolled patients to 1 of 7[1] cohorts based on tumor type and exposure to prior therapies. The primary endpoints of the phase 2 study were overall response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) and safety. A key secondary endpoint of the phase 2 study was duration of response (DOR).[2]

Efficacy[3]
The efficacy of pralsetinib was evaluated in 114 patients with *RET* fusion-positive metastatic NSCLC with measurable disease in a multicenter, non-randomized, open-label, multi-cohort clinical trial. The study enrolled, in separate cohorts, patients with metastatic *RET* fusion-positive NSCLC who had progressed on platinum-based chemotherapy (n=87) and treatment-naïve patients with metastatic NSCLC (n=27).

[1]RET fusion-positive non-small cell lung cancer (NSCLC), prior platinum; RET fusion-positive NSCLC, platinum naïve; Medullary thyroid cancer (MTC), prior cabozantinib or vandetanib; MTC, no prior cabozantinib or vandetanib; other RET fusion-positive tumors; other RET-mutated tumors; RET-altered, prior selective RET inhibitor

Of the 87 patients previously treated with platinum chemotherapy, patients received a median of 2 prior systemic therapies (range 1-6); 45% has prior anti-PD-1/PD-L1 therapy, and 25% had prior kinase inhibitors. Fifty-two percent of the patients received prior radiation therapy. ECOG performance status was 0-1 at baseline for 94% of patients in this cohort, and 43% had either history of or current central nervous system (CNS) metastasis. The most common RET fusion partners were KIF5B (75%) and CCDC6 (17%).

In the cohort of 27 treatment-naïve patients, ECOG performance status was 0-1 for 96% of patients, and 33% had either history of or current CNS metastasis. The most common *RET* fusion partners were KIF5B (70%) and CCDC6 (11%). Results for both patient cohorts are summarized in **Table 1**.

Table 1: Efficacy Results in Metastatic *RET* Fusion-Positive NSCLC

	Prior platinum (n=87)	**Treatment naïve (n=27)**
Overall Response Rate[a], % (95% CI, %)	**57 (46, 68)**	**70 (50, 86)**
Best overall response, %		
CR	5.7	11
PR	52	59
Duration of Response	**n=50**	**n=19**
Median, months (95% CI)	NE (15.2, NE)	9.0 (6.3, NE)
Patients with DOR ≥6 months[b], %	80	58

[a]Confirmed overall response rate assessed by BICR
[b]Calculated using the proportion of responders with an observed duration of response at least 6 months or greater
CI, confidence interval; CR, complete response; NE, not estimable; PR, partial response

Safety Results[3]

Among 220 NSCLC patients who received pralsetinib 400 mg QD in BLU-667-1101 trial, the most common adverse reactions (≥25%) were fatigue, constipation, musculoskeletal pain, and hypertension. The most common laboratory abnormalities (≥25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased creatine, increased alkaline phosphatase, decreased calcium corrected, decreased sodium, decreased phosphate, decreased hemoglobin, decreased lymphocytes, decreased neutrophils, and decreased platelets. Permanent discontinuation of pralsetinib due to an adverse reaction occurred in 15% of patients. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia.

The following references are submitted to assist the committee in their review:

1. Phase 1/2 Study of the Highly-selective RET Inhibitor, Pralsetinib (BLU-667) in Patients with Thyroid Cancer, Non-Small Cell Lung Cancer, and Other Advanced Solid Tumors (ARROW). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03037385. Updated May 21, 2020. Accessed June 6, 2020.
2. Gainor et al. Registrational Dataset from the Phase 1/2 ARROW Trial of Pralsetinib (BLU-667) in Patients with Advanced RET Fusion+ Non-Small Cell Lung Cancer (NSCLC). Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; virtual format.
3. GAVRETO™ (pralsetinib) Prescribing Information. Blueprint Medicines Corporation; Cambridge, MA September 2020.

We appreciate your review and consideration of this submission.

Sincerely,

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