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Date: October 2, 2020
Panel: Hepatobiliary Cancers

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 V5.2020 for Hepatobiliary Cancers. This submission includes investigator assessment data from a February 13, 2020 data cut of the BLU-667-1101 trial.

Specific Changes Requested:

Please consider inclusion of pralsetinib into the guideline as a treatment option for patients with cholangiocarcinoma in both the first-line and second-line/subsequent therapy settings based on the results from the recent Phase 1/2 BLU-667-1101 trial.[1] The results for the *RET* fusion-positive advanced and metastatic solid tumors were presented at the 2020 American Society for Clinical Oncology (ASCO) meeting.[2]

We respectfully request the following for NCCN consideration:

- **INTRA-1:** Under "Workup", add "Consider *RET* fusion-positive genomic testing"
- **INTRA-1:** Under "Primary treatment" for "Unresectable" and "Metastatic disease", add praseltinib
- **EXTRA-1:** Under "Presentation and workup", add "Consider *RET* fusion-positive genomic testing"
- **EXTRA-1:** Under "Primary treatment for "Unresectable" and "Metastatic disease", add praseltinib
- **BIL-C 1 of 3:** Under "adjuvant Therapy", add pralsetinib as "Useful in certain circumstances"
- **BIL-C 2 of 3:** Under "Primary treatment for unresectable and metastatic disease", add pralsetinib as "Useful in certain circumstances"
- **BIL-C 3 of 3:** Under "Subsequent-line therapy for biliary tract cancers if disease progression" add pralsetinib as "Other recommended regimens"

Rationale

BLU-667-1101 was a multicenter, open-label, phase 1/2 study of pralsetinib administered orally to patients with advanced solid tumors. The trial evaluated the use of pralsetinib in patients with *RET*-mutant and *RET* fusion-positive advanced and metastatic solid tumors, including cholangiocarcinoma, papillary thyroid carcinoma, and poorly differentiated thyroid, mixed histology lung, pancreatic, thymus, colon, ovarian, and neuroendocrine (unknown primary) cancers. Phase 1 of the study established the recommended phase 2 dose for pralsetinib of 400 mg by mouth daily. The primary endpoints of the phase 2 study was overall response rate (ORR) based on RECIST guidelines (version 1.1) and safety.

Efficacy of Pralsetinib[2]

Efficacy was evaluated in 27 patients with *RET* fusion-positive advanced solid tumors enrolled in BLU-667-1101. This cohort included 2 patients with cholangiocarcinoma, both of whom (2/2, 100%) exhibited a partial response. All patients had been previously treated with chemotherapy, or other anticancer therapies. Efficacy data for patients with *RET* fusion-positive solid tumors is summarized in Figure 1 and Table 1 below.

Figure 1: Waterfall Plot, Activity of Pralsetinib in Various *RET* Fusion-positive Solid Tumors[2]

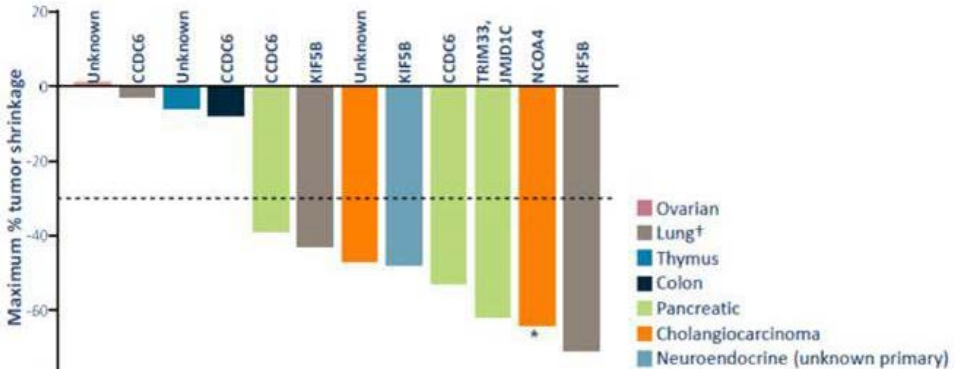

Table 1: Activity of Pralsetinib in Various *RET* Fusion-positive Solid Tumors[2]

	Thyroid cancer N = 11[+]	**Other *RET* fusion-positive solid tumors** N = 12[†]
Overall Response Rate, % (95% CI)	91 (59, 100)	50 (21, 79)
Partial Response, %	91	50[‡]
Stable Disease, %	9	42
Progressive Disease, %	0	8
Disease Control Rate, % (95% CI)	100 (72, 100)	92 (62, 100)

[+]Response-evaluable population excludes 2 patients with papillary thyroid carcinoma without measurable disease at baseline per blinded central review. These patients were assessed with complete response and stable disease, and continue treatment at 12.9 and 23.3 months, respectively.
[†]Response-evaluable population excludes 2 patients with colon cancer that had alternate driver mutations. These patients were assessed with stable disease, and continue treatment at 9.7 and 3.7 months, respectively.
[‡]One PR pending confirmation

Safety of Pralsetinib[2]

A safety analysis of 27 patients with *RET* fusion-positive advanced solid tumors enrolled in BLU-667-1101 was consistent with a broader safety analysis of the overall population (n=354). The most common treatment related adverse events (≥ 15%), including laboratory abnormalities, were anemia (33%), increased aspartate aminotransferase (AST) (33%), decreased white blood cell (WBC) count (33%), hypertension (30%), increased alanine aminotransferase (ALT) (26%), hyperphosphatemia (19%), and neutropenia (19%). No patients discontinued treatment with pralsetinib due to treatment-related adverse events. Treatment duration was 23.5 months with a median relative dose intensity of 96%.

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. However, pralsetinib is not an FDA-approved treatment for patients with *RET* fusion-positive cholangiocarcinoma. Please refer to the product prescribing information for the full FDA-approved indications and safety information of pralsetinib, available at:

- https://www.blueprintmedicines.com/uspi/GAVRETO.pdf

The following reference is 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 23, 2020.
2. Subbiah V. Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with RET fusion+ solid tumors. Oral presentation at: American Society of Clinical Oncology Meeting; 2020; Virtual format.

We appreciate your review and consideration of this submission.

Sincerely,

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