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Date: December 1, 2020
Panel: Thyroid Carcinoma

On behalf of Blueprint Medicines Corporation, I respectfully request the NCCN Guidelines committee to review the enclosed information for pralsetinib in reference to NCCN Guidelines V2.2020 for Thyroid Carcinoma. This submission includes data from the BLU-667-1101 trial (ARROW), which is the pivotal registrational study for the thyroid carcinoma submission. The purpose of this submission is to provide additional updates:

- Pralsetinib is now FDA-approved (additional details listed under FDA clearance).
- The USPI[1] includes updated independent review data from a February 13, 2020 data cut (safety & efficacy, non-small cell lung cancer (NSCLC); safety, thyroid carcinoma) and a May 22, 2020 data cut (efficacy, thyroid carcinoma) of the BLU-667-1101 study.

Specific Changes Recommended

We respectfully request that the NCCN Clinical Practice Guidelines in Oncology include pralsetinib as a treatment option for:

- 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
- 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 (if radioactive iodine is appropriate).

We respectfully request the following for NCCN consideration:

PAP-10, Treatment of Locally Recurrent, Advanced, and/or Metastatic Disease Not Amenable to RAI Therapy

- Add "Pralsetinib for patients with *RET* fusion-positive tumors"

FOLL-8, Treatment of Locally Recurrent, Advanced, and/or Metastatic Disease Not Amenable to RAI Therapy

- Add "Pralsetinib for patients with *RET* fusion-positive tumors"

HÜRT-8, Treatment of Locally Recurrent, Advanced, and/or Metastatic Disease Not Amenable to RAI Therapy

- Add "Pralsetinib for patients with *RET* fusion-positive tumors"

MEDU-6, Recurrent or Persistent Disease − Locoregional

- Add pralsetinib (*RET* mutant-positive) as a preferred treatment option

MEDU-7, Recurrent or Persistent Disease − Distant Metastases

- Add pralsetinib (*RET* mutant-positive) as a preferred treatment option

ANAP-A (2 of 3), Systemic Therapy Regimens for Metastatic Disease

- Add pralsetinib (*RET* mutant-positive) as a preferred regimen with dosing

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 NSCLC as detected by an FDA approved test. On December 1, 2020 the FDA approved pralsetinib for additional indications, including the treatment of 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 adults and pediatric patients 12 years of age and older with *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is

appropriate). Please refer to the product prescribing information for the full FDA-approved indications and safety information of pralsetinib.[1]

Rationale

BLU-667-1101 is a multicenter, non-randomized, open-label, phase 1/2 study of pralsetinib for patients with advanced solid tumors, including *RET* fusion-positive NSCLC and thyroid cancer, *RET*-mutant MTC, and other tumors with *RET* activation. 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 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 RECIST guidelines (version 1.1) and safety. A key secondary endpoint of the phase 2 study was duration of response (DOR).[1]

***RET*-Mutant Medullary Thyroid Cancer[1]**

The ORR for 55 patients with RET-mutant advanced MTC who were previously treated with cabozantinib and/or vandetanib was 60% (95% confidence interval (CI): 46, 73) with 1.8% achieving complete response (CR) and 58% with partial response (PR). In 33 previously treated patients, 79% had a continued response to treatment at 6 months. The median DOR has not been reached. In 29 cabozaninib and vandetanib-naïve patients with RET-mutant advanced MTC, the overall response rate was 66% (95% CI: 46, 82) with 10% and 55% achieving CR and PR, respectively. In 19 cabozantinib and vandetanib-naïve patients, 84% had a continued response at 6 months. The median DOR has not been reached.

***RET* Fusion-Positive Thyroid Cancer[1]**

The efficacy of pralsetinib was evaluated in 9 patients with advanced *RET* fusion-positive thyroid cancer. All thyroid cancer patients were required to have disease progression following standard therapy with measurable disease by RECIST version 1.1 and have *RET*-fusion as determined by local testing. The ORR was 89% (95% CI: 52, 100) with 89% achieving PR. In 8 patients with RET fusion-positive thyroid cancer, 100% of patients had a continued response to treatment at 6 months. The median DOR has not been reached.

Safety[1]

Among the 438 patients who received pralsetinib in the BLU-667-1101 trial, including 220 NSCLC and 138 RET-altered thyroid cancer, the most common adverse reactions (≥ 25%) were constipation, hypertension, fatigue, musculoskeletal pain, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased platelets, decreased phosphate, decreased sodium, decreased calcium (corrected), increased aspartate aminotransferase, increased alanine aminotransferase, and increased alkaline phosphatase. Of the 138 RET-altered thyroid cancer patients, permanent discontinuation due to an adverse reaction occurred in 9% of patients who received pralsetinib 400 mg once daily.

The following reference is submitted to assist the committee in their review.

1. GAVRETO [package insert]. Cambridge, MA: Blueprint Medicines Corporation; 2020. https://www.blueprintmedicines.com/uspi/GAVRETO.pdf

We appreciate your review and consideration of this submission.

Sincerely,

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