Date: June 17, 2021
Panel: Systemic Mastocytosis

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Dear Kris,

On behalf of Blueprint Medicines Corporation, I respectfully request the NCCN Guidelines Committee review the enclosed information for AYVAKIT™ (avapritinib) in reference to NCCN Guidelines V2.2021 for Systemic Mastocytosis (SM). This submission includes data from the Phase 1 BLU-285-2101 (EXPLORER)[1] and Phase 2 BLU-285-2202 (PATHFINDER)[2] studies, as well as evidence documenting the safety and efficacy of avapritinib in Advanced SM (AdvSM).[3]

Specific Changes Recommended

We respectfully request that the NCCN SM Guidelines Panel include avapritinib for use in patients with AdvSM, along with recommendations for dose interruption, dose reduction, platelet monitoring, and platelet support to evaluate and manage potential severe thrombocytopenia.

- **SM-5: "Treatment for Aggressive Systemic Mastocytosis (ASM)"**
  - Add: avapritinib for patients with platelet counts ≥50,000/μL
- **SM-7: "Treatment for Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN)"**
  - Add: avapritinib for patients with platelet counts ≥50,000/μL
- **SM-8: "Treatment for Mast Cell Leukemia (MCL)"**
  - Add: avapritinib for patients with platelet counts ≥50,000/μL
- **MS-12:**

  Add: Avapritinib. Avapritinib may be used as a treatment option because of demonstrated clinical benefit. In the phase 1 EXPLORER (n=53) and phase 2 PATHFINDER (n=32) trials, avapritinib resulted in a 76% and 75% confirmed overall response rate (ORR), defined as complete remission with full or partial recovery of peripheral blood counts (CR + CRh), partial remission (PR), or clinical improvement (CI), among patients with AdvSM, respectively.[1,2] Among 53 evaluable patients dosed up to 200 mg across both studies, patients with ASM, SM-AHN, and MCL had ORRs of 100%, 78%, and 45%, respectively.[3] In this evaluable population, 57% of patients achieved a CR, CRh, or PR; and 72% achieved a CR, CRh, PR, or CI.[3] Both studies utilized the modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) criteria, which includes a new response category of complete response with partial hematologic recovery to allow for residual cytopenias considered unrelated to AdvSM.[4] The modified IWG-MRT-ECNM criteria requires greater than or equal to 12 week response duration, resolution of greater than or equal to one c-finding, and >50% reduction of mast cell aggregates and serum tryptase for an overall response. Avapritinib was generally well-tolerated, with most adverse events (AEs) reported as Grade 1 or 2.[3,4,5] Of note, a case report of a patient with SM-AHN complicated by severe, recurrent anaphylaxis refractory to multiple medications noted complete resolution of anaphylaxis upon initiation of avapritinib and no further episodes after one year of continued treatment.[6] Although the recommended dosage of avapritinib for patients with gastrointestinal stromal tumors (GIST) is 300 mg orally QD,[4] the recommended dose for AdvSM patients based on the EXPLORER and PATHFINDER clinical trials is 200 mg orally QD.[3,7] Strict dose interruption/reduction and platelet support are recommended to manage severe thrombocytopenia among AdvSM patients receiving avapritinib.[3]

FDA Clearance

On June 16th, 2021 the FDA approved avapritinib for the treatment of adult patients with AdvSM. AdvSM includes patients with ASM, SM-AHN, and MCL. Avapritinib is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L.[3]

The FDA previously approved avapritinib for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA Exon 18 mutation, including PDGFRA D842V mutations, on January 9, 2020.[3]

Rationale

EXPLORER is a phase 1, open-label study designed to determine the recommended phase 2 dose (RP2D) and evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antineoplastic activity of avapritinib in adult patients with AdvSM and relapsed or refractory myeloid malignancies. A total of 86 patients were enrolled in this study and received avapritinib at doses ranging from 30 mg to 400 mg once daily. Response to treatment was evaluated per modified IWG-MRT-ECNM criteria. Of those enrolled, 53 patients were response-evaluable with a median follow-up of 27.3 months (data cut-off: May 27, 2020). Seventy-six percent of patients achieved a CR, CRh, PR, or CI, and 36% of patients had a CR/CRh.[3,4,8]

PATHFINDER is an ongoing phase 2, open-label, single arm study evaluating the efficacy and safety of avapritinib in patients with AdvSM, including patients with ASM, SM-AHN, and MCL. A total of 62 patients were enrolled in this study and received avapritinib at the recommended starting dose of 200 mg once daily. Response to treatment was evaluated per modified IWG-MRT-ECNM criteria. Of those enrolled, a total of 32 were response-evaluable for a pre-specified interim analysis with a median follow-up of 10.4 months (data cut-off: June 23, 2020). Seventy-five percent of patients had a CR, CRh, PR, or CI, and 19% of patients had a CR/CRh.[5,6]

Table 1 reports key outcomes in an efficacy population of 53 patients across both pivotal studies who received avapritinib up to a dose of 200 mg once daily. In this evaluable population, 57% of patients achieved a CR, CRh, or PR; and 72% achieved a CR, CRh, PR, or CI.[3]

Table 1: Efficacy of Avapritinib at Up to 200 mg Daily Among Patients with AdvSM in EXPLORER and PATHFINDER[3]

	All evaluable patients (N=53)	ASM (N=2)	SM-AHN (N=40)	MCL (N=11)
ORR*, % per modified IWG-MRT-ECNM criteria (95% CI, %)**	**57 (42, 70)**	**100 (16, 100)**	**58 (41, 73)**	**45 (17, 77)**
CR + CRh, %	28	50	33	9
Partial Remission, %	28	50	25	36
Clinical Improvement, %	**15**	**0**	**20**	**0**
Stable Disease, %	19	0	13	45

Abbreviations: CI=confidence interval; CR=complete response; CRh=complete remission with partial recovery of peripheral blood counts.
*Overall Response Rate (ORR) per modified IWG-MRT-ECNM is defined as patients who achieved a CR, CRh, or PR (CR + CRh + PR)
**This is the first FDA-approved targeted therapy for AdvSM whose efficacy has been prospectively evaluated using modified IWG-MRT-ECNM criteria.

Two patients with smoldering systemic mastocytosis (SSM) were treated with avapritinib in the EXPLORER study. While on avapritinib therapy, both patients had a ≥50% decrease in mast cell bone marrow infiltration and serum tryptase levels.[7,9]

Safety

Safety data were consistent with previously reported results.[8,10] No new signals were observed. Avapritinib was generally well-tolerated, with most AEs reported as Grade 1 or 2. Across both trials, 10% of patients treated at the recommended starting dose of 200 mg once daily discontinued avapritinib due to AEs. The most common AEs of any grade (≥20%) observed in patients who received 200 mg avapritinib once daily (n=80) were edema, diarrhea, nausea, and fatigue/asthenia.[3] The most common laboratory abnormalities with any grade of worsening from baseline (≥30%) in the safety population in patients who received 200 mg avapritinib once daily (n=80) included decreased platelets, decreased hemoglobin, decreased neutrophils, decreased lymphocytes, decreased calcium, increased bilirubin, and increased aspartate aminotransferase.[3]

In patients with AdvSM who received avapritinib at 200 mg daily, intracranial hemorrhage occurred in 2 of 75 patients (2.7%) who had platelet counts ≥ 50 x 10^9/L prior to initiation of therapy and in 3 of 80 patients (3.8%) regardless of platelet counts. Dose-interruptions and dose-reductions for thrombocytopenia occurred in 20% and 22% of avapritinib-treated patients, respectively. Thrombocytopenia was generally reversible by reducing or interrupting avapritinib.[3]

In patients with AdvSM, a platelet count must be performed prior to initiating therapy; avapritinib is not recommended in AdvSM patients with platelet counts < 50 X 10^9/L.[3] Following treatment initiation, platelet counts must be monitored, and platelet counts of < 50 X 10^9/L should be managed according to the treatment plan provided in Table 2.[3]

Table 2: Avapritinib Platelet Monitoring[3]

Time on Therapy	Monitoring Plan	Treatment Plan
Prior to initiation	Perform platelet count	Avapritinib is not recommended in AdvSM patients with platelet counts <50 x 10^9/L.
First 8 weeks	Perform platelet count every 2 weeks regardless of baseline platelet count	If platelet count <50 X 10^9/L occurs, interrupt avapritinib until platelet count is ≥ 50 X 10^9/L, then resume at reduced dose. If platelet counts do not recover above 50 x 10^9/L, consider platelet support.
After 8 weeks	Monitor platelet counts: • Every 2 weeks if values are <75 x 10^9/L (or more frequently as clinically indicated) • Every 4 weeks if values are 75-100 x 10^9/L • As clinically indicated if values are >100 x 10^9/L	

We appreciate your review and consideration of this submission.

Sincerely,

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References

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