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Submitted by:
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Attention:
Kristina M. Gregory, RN, MSN, OCN
Vice President of Clinical Information Operations

Specific Changes Requested to the NCCN Guidelines for Soft Tissue Sarcoma:

On behalf of Blueprint Medicines, I am writing today to respectfully request that the NCCN Soft Tissue Sarcoma Panel kindly consider listing avapritinib in section SARC-F of the STS guidelines as a treatment option for patients with a metastatic or unresectable gastrointestinal stromal tumor (GIST) who have been treated with at least 3 prior lines of therapy (4th-line; 4L). Supportive clinical data are provided below.

Relevant FDA Approvals and Activity:

Avapritinib was approved on January 09, 2020, for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) Exon 18 mutation, including PDGFRA D842V mutations.[1] The NDA application to the FDA included indications for the PDGFRA Exon 18 indication and the 4L indication simultaneously. However, based on discussions with FDA, the NDA was administratively split : one for PDGFRA Exon 18 mutant GIST and one for 4L GIST. For the indication for 4L GIST, the FDA requested topline results of the ongoing, confirmatory Phase 3 VOYAGER[2] trial in 3rd-line (3L)/4L GIST. The VOYAGER data are expected in the second quarter (2Q) of 2020, and we anticipate an extension of the current PDUFA date for 4L GIST to 2Q 2020. An NDA application for 3L GIST is anticipated for submission in the second half of 2020.

Clinical Data to Support Inclusion of Avapritinib in the Guidelines:

Currently, there are no therapies that are FDA-approved for GIST patients following treatment with imatinib, sunitinib, and regorafenib. Based on limited data, the NCCN guidelines recommend options for 4L therapy that include additional tyrosine kinase inhibitors (TKIs; sorafenib, dasatinib, nilotinib, and pazopanib), and the mTOR inhibitor everolimus together with a TKI for patients who are no longer benefiting from any of the three TKIs used in 1st line through 3L therapy.[3]

Avapritinib was designed to potently and selectively target the active conformations of KIT and PDGFRA via a type I inhibition mechanism, in contrast to the approved type II inhibitors. In pre-clinical studies, avapritinib inhibited demonstrated activity across activation loop mutations in GIST that are resistant to imatinib.[4]

The open-label phase 1 NAVIGATOR trial[5] evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, and antineoplastic activity of avapritinib in adult patients with unresectable GIST. The efficacy results from this trial served as the basis for the recent approval in patients with a tumor harboring a PDGFRA Exon 18 mutation, and the results from NAVIGATOR will also support the NDA application in 4L patients. As recently presented at the annual Connective Tissue Oncology Society meeting[6], avapritinib demonstrated significant clinical activity, with a centrally confirmed ORR of 17% in the 4L+ setting (excluding patients with a PDGFRA D842V mutation; starting dose 300/400 mg once daily) and with a median duration of response (mDOR) of 10.2 months. (95% CI: 7.2-NE). The ORR and mDOR of avapritinib in 4L+ patients exceeded that of approved 2nd and 3rd line therapies[7,8]

Avapritinib was well-tolerated; most adverse events (AEs) were Grade 1 or 2 by investigator assessment. In 204 patients with unresectable or metastatic GIST, the most common adverse reactions (≥20%) of any grade were edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash and dizziness.[1] Grade 3 or 4 treatment-related AEs which occurred in ≥2% of patients included: anemia, fatigue, hypophosphatemia, increased bilirubin, decreased white blood count/neutropenia, and diarrhea. There were no treatment-related grade 5 AEs.[6] The discontinuation rate due to AEs was 16%[1], and for treatment-related AEs was 8%.[6]

Intracranial hemorrhage is noted as an important risk and occurred in 1% of 267 patients with GIST.[1] Cognitive effects were observed in 35% of patients treated with the 300 mg once daily dose.[9] A combination of dose interruption and/or reduction was used to effectively manage cognitive effects in patients during the study. When dose modification was employed (dose interruption, reduction, or both) cognitive effects improved in a median of 12 days. A post-hoc analysis on the impact of dose modifications on PFS in the NAVIGATOR trial demonstrated no apparent reduction in PFS in patients who had a dose modification in either the PDGFRA D842V and KIT patient populations.[9]

The starting dose of avapritinib for patients in the proposed FDA label is 300 mg once daily. Based on pre-clinical potency studies, clinical analyses of safety, efficacy, and risk factors for cognitive effects; as well as exposure response analyses[4,9-12] starting patients at 200 mg once daily and escalating to 300 mg based on tolerability could be an additional alternative approach for select patients, in particular:

- Patients with the PDGFRA D842V mutation
- Patients with compromised performance status or who for other reasons are considered at risk of poor tolerability

The data that form the basis for this recommendation can be seen in the included Data on File reports in which, for patients with a tumor harboring a PDGFRA D842V mutation, no trends in tumor growth were

seen at doses starting at less than 300 mg, nor during reductions to 200 mg or 100 mg (Refs. 10 and 11, Figs. 1 and 2), and there is no statistically significant difference in PFS for PDGFRA Exon 18 patients (including D842V) by exposure level (Ref. 12, Fig. 9). As there is high inter-patient dose variability with avapritinib (Ref. 12, Fig. 8) and given that the time to onset of Grade 3 and 4 AEs and cognitive AEs were higher in higher exposure quartiles among all patients (Ref 12, Figs. 13 and 17), we believe there is a clinical rationale to allow dose escalation from 200 mg daily to 300 mg daily based on tolerability for the subset of patients described above.

To allow for practice flexibility, we ask the panel to please consider the data enclosed to determine if this additional approach to dosing described above for select patients would be acceptable for patient care and appropriate to note in practice guidelines to inform the broader oncology community.

Thank you for considering this request. Below is my contact information if you require additional information.

Sincerely,

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References:

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