January 07, 2020

Submitted by:
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Attention:
Kristina M. Gregory, RN, MSN, OCN
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Specific Changes Requested to the NCCN Guidelines: 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, in section SARC-F of the STS Guidelines, avapritinib as a preferred treatment option for adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) Exon 18 D842V mutation.

Relevant FDA Approvals and Activity:
Avapritinib is under priority review by the FDA (PDUFA Date Feb 14, 2020), which is reserved for medicines that could provide significant improvements in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious disease. The indication under review is for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA Exon 18 mutation, including PDGFRA D842V mutations (see attached draft label).[1] The FDA had also granted Breakthrough Therapy Designation to avapritinib for the treatment of patients with metastatic GIST harboring a PDGFRA D842V mutation. FDA administratively split the initial NDA for avapritinib, and therefore the indication for 4th-line GIST will be considered in the second quarter of 2020 when top-line data from the Phase 3 VOYAGER clinical trial in 3rd-line GIST are anticipated to be available. An NDA for 3rd-line GIST is planned for submission in the second half of 2020.

Clinical Data to Support Inclusion of Avapritinib in the Guidelines:
Patients with advanced PDGFRA D842V-mutant GIST have a poor prognosis. Studies have repeatedly shown that this mutation confers primary resistance to imatinib.[2,3] PDGFRA D842V mutations have also demonstrated resistance to the approved 2nd- and 3rd-line tyrosine kinase inhibitors (TKIs) sunitinib and regorafenib, as well as other TKIs such as sorafenib.[3-7] The largest available retrospective study in patients with PDGFRA D842V-mutant GIST who were treated with available agents demonstrated a median progression-free survival (PFS) of only 2.8 months, and an overall survival (OS) of only 15 months, which is similar to the OS of patients with GIST prior to the availability of imatinib.[2]

The NCCN guidelines recommend mutational testing prior to initiating therapy, noting that imatinib and other approved therapies are not active in PDGFRA D842V-mutant GIST.[8] Unfortunately, the rate of mutational testing in GIST in both academic and community settings remains low, despite current NCCN guidelines and literature that emphasizes its therapeutic importance.[9] Indeed, even in patients who have testing performed, imatinib use in PDGFRA D842V-mutant GIST is common and may expose patients to unnecessary clinical toxicity and use of healthcare resources without clinical benefit.

Avapritinib was designed to potently and selectively target the active conformation of KIT and PDGFRA mutant kinases via a type 1 inhibition mechanism. In preclinical studies, avapritinib demonstrated marked selectivity within the kinome for KIT and PDGFRA, potent biochemical activity against KIT and PDGFRA, including PDGFRA D842V (IC_{50}=0.2 nM), and *in vivo* efficacy against GIST xenografts resistant to imatinib.[10]

The open-label NAVIGATOR trial[11] evaluated safety, pharmacokinetics, and efficacy of avapritinib in 38 patients with tumors harboring PDGFRA D842V mutations. This is one of the largest prospective clinical trials conducted in patients with PDGFRA D842V-mutant GIST. Among these patients[1, 12]:

- 97% of treated patients exhibited a reduction in tumor burden
- The overall response rate for patients with PDGFRA D842V mutant GIST was 89%
    - 8% complete response (CR) and 82% partial response (PR)
- Median duration of response was not reached
- Median PFS was not reached

Additionally, five other patients on trial harbored PDGFRA non-D842V Exon 18 mutations (deletion of D842_H845 (n=3); D842Y (n=1); and deletion 383 of D842_H845 with insertion of V (n=1). In the broader PDGFRA Exon 18 patient population (i.e., including patients with a D842V mutation, n = 43) the ORR was 84% (7% CR, 77% PR).[1]

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. The discontinuation rate due to AEs was 16%[1], and for treatment-related AEs was 8%.[12]

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.[13] 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.[13]

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[10,13-16] 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 tumors harboring 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 references and 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. 14 and 15, Figs. 1 and 2), and there is no statistically significant difference in PFS for PDGFRA Exon 18 patients (including D842V) by exposure level (Ref. 16, Fig. 9). As there is high inter-patient dose variability with avapritinib (Ref. 16, 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 16. 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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