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NCCN Guidelines Panel: Bone Cancer

On behalf of Agios Pharmaceuticals, I respectfully request the Panel to review the enclosed data for inclusion of ivosidenib as a treatment option for patients with advanced previously treated isocitrate dehydrogenase-1 (IDH1)–mutant chondrosarcoma.

Specific Changes: Recommend the addition of ivosidenib to the chondrosarcoma guidelines as a treatment option for patients with chondrosarcoma (any tumor grade) who received prior surgery, systemic therapy, or radiotherapy and have an IDH1 mutation.

FDA Status: TIBSOVO® (ivosidenib) is indicated for the treatment of newly-diagnosed acute myeloid leukemia (AML) with a susceptible IDH1 mutation, as detected by an FDA-approved test in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy and adult patients with relapsed or refractory AML.[1] TIBSOVO is not approved in any country for the treatment of patients with advanced chondrosarcoma.

Rationale Summary: Surgery is the primary therapy for localized chondrosarcoma, and no known effective systemic therapy exists for locally advanced and/or metastatic disease. A phase 1 multicenter open label dose-escalation and expansion study of ivosidenib monotherapy was conducted in patients (N=168) with mutant IDH1 advanced solid tumors, including chondrosarcoma. The primary objectives of this study were to assess safety and tolerability and to determine the maximum tolerated dose and recommend phase 2 dose of ivosidenib. The escalation phase cohort included patients with mutant IDH1 advanced chondrosarcoma that had recurred or progressed during or not responded to standard therapy and had measurable disease by RECIST (version 1.1). The expansion phase cohort included patients with mutant IDH1 chondrosarcoma that was either locally advanced or metastatic and not amenable to complete surgical resection and had an ECOG score of 0 to 1. Ivosidenib was administered orally (100 mg twice daily to 1200 mg once daily) in continuous 28-day cycles. Ivosidenib showed minimal toxicity, substantial 2-HG reduction, and durable disease control.[2]

As of the January 16, 2019 data cut, 21 patients with advanced chondrosarcoma received study treatment (dose escalation, n=12; expansion, n=9). Enrollment is complete and the study is ongoing. As of the data cut, four patients (19%) were still receiving treatment extending beyond 2.5 years.
Median age was 55 (range 30-88) years, most patients (67%; n=14) had tumor grade 2 or 3 at screening, and 11 patients (52%) received prior systemic therapy. Plasma 2-HG was inhibited in all patients (14% to 94%) compared with levels seen in healthy volunteers. [2]

The maximum tolerated dose was not established in this study for the entire patient population (including all solid tumors) because there were no dose-limiting toxicities. The most common treatment-emergent adverse events regardless of attribution in the chondrosarcoma cohort were grade 1 or 2 and included diarrhea (43%), nausea (33%) and fatigue (29%). Grade ≥3 adverse events were reported in 12 (57%) patients and only one event (hypophosphatemia) was assessed to be treatment related by the investigator.[2] The recommended phase 2 dose was determined to be 500 mg once daily. The efficacy evaluation included all 21 patients. As of the data cut, the median progression-free survival (PFS) was 5.6 months (95% CI, 1.9 to 7.4), with 3- and 6-month PFS rates of 62% and 39.5%, respectively. Eleven (52%) patients experienced

stable disease as the best overall response by RECIST, and four patients (19%) with a best response of stable disease have continued therapy for ≥ 2.5 years.[2]

The following articles and presentations are submitted in support of this proposed change. We appreciate the opportunity to provide this information for consideration by the NCCN Bone Cancer Guidelines Panel.

1. TIBSOVO® (ivosidenib) [package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc; 2019.

2. Tap WD, Villalobos VM, Cote GM et al. Phase I study of the mutant IDH1 inhibitor ivosidenib: safety and clinical activity in patients with advanced chondrosarcoma. *J Clin Oncol*. 2020 Mar 24:JCO1902492. doi: 10.1200/JCO.19.02492. [Epub ahead of print].

If you have any questions or require additional information, please do not hesitate to contact me. Thank you for your time and consideration.

Sincerely,

Eva Gallagher

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