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NCCN Guidelines Panel: Hepatobiliary Cancers

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 cholangiocarcinoma.

Specific Changes: Recommend the addition of ivosidenib to the intrahepatic cholangiocarcinoma guidelines and the extrahepatic cholangiocarcinoma guidelines as a treatment option for patients with unresectable or metastatic disease who received 1–2 prior regimens 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 cholangiocarcinoma.

Rationale Summary: Ivosidenib was associated with low toxicity, objective responses, and durable disease control in a phase 1 study of heavily pretreated patients with advanced mIDH1 cholangiocarcinoma.[2] A phase 3 global, randomized, double-blind clinical trial (ClarIDHy) was conducted to evaluate ivosidenib as a therapeutic option for patients with previously treated IDH1-mutant cholangiocarcinoma, which is currently a patient population with limited treatment options and a high unmet need. In the ClarIDHy trial, patients with advanced IDH1-mutant cholangiocarcinoma (intrahepatic and extrahepatic) were randomized in a 2:1 ratio and treated with either ivosidenib 500 mg orally daily or placebo. Patients had to have documented disease progression following 1–2 prior systemic therapies (at least 1 gemcitabine or 5-FU–containing regimen) and an ECOG performance score of 0–1. Patients randomized to placebo were allowed to crossover to ivosidenib at radiological disease progression.[3,4]

As of the January 31, 2019 data cut for the primary analysis, 185 patients were randomized to ivosidenib (n= 124) or placebo (n=61). The study met the primary endpoint of a significant improvement in progression-free survival (PFS) by Independent Radiology Center (IRC). Ivosidenib demonstrated a 63% reduction in the risk of progression and death compared to placebo (hazard ratio [HR]=0.37 [95% CI 0.25, 0.54]; P<0.001) along with a substantial improvement in progression-free proportion at 6 and 12 months (32% and 22%). The PFS benefit was observed across all subgroups and no placebo-treated patients were progression free for ≥6 months. The median PFS for patients randomized to ivosidenib was 2.7 months (95% CI 1.6–4.2) compared to 1.4 months (95% CI 1.4–1.6) in patients receiving placebo. At the time of the primary PFS analysis, OS data were still maturing. The interim data for overall survival (OS) indicated a trend towards improvement favoring ivosidenib with a median OS of 10.8 months (95% CI 7.7–17·6) for ivosidenib versus 9.7 months (4.8–12.1) for placebo (HR 0.69 [0.44–1.10]; p=0·06) based on 78 OS events and 57% crossover from placebo (35 of 61 patients). The rank-preserving structural failure time (RPSFT) method was applied to reconstruct the survival curve for the placebo subjects as if they never crossed over to ivosidenib, and the adjusted median OS with placebo was 6 months (HR=0.46 [95% CI 0.28, 0.75]; P<0.001).[3,4]

Treatment-emergent adverse events (TEAEs) were evaluated in patients who were treated with ivosidenib (n=121) and placebo (n=59). The most common TEAEs (in ≥10% [all grades] of patients who

started treatment with ivosidenib) included nausea (43 [36%]), diarrhoea (37 [31%]), and fatigue (32 [26%]. Grade ≥3 TEAEs were reported in 55 (45%) ivosidenib patients versus 21 (36%) placebo patients. The most common grade ≥3 adverse event in both treatment groups was ascites (4 [7%] of placebo patients and 9 [7%] of ivosidenib patients.[3,4]

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 Hepatobiliary Cancers Guidelines Panel.

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

2. Lowery MA, Burris HA, Janku F, et al. Safety and activity of ivosidenib in patients with IDH1-mutant advanced cholangiocarcinoma: a phase 1 study. *Lancet Gastroenterol Hepatol.* 2019;4(9):711-720.

3. Abou-Alfa GK, Macarulla T, Javle M, et al. ClarIDHy: A global, phase 3, randomized, double-blind study of ivosidenib vs placebo in patients with advanced cholangiocarcinoma with an isocitrate dehydrogenase 1 (IDH1) mutation. Presented at the European Society for Medical Oncology (ESMO) Annual Meeting 2019, September 27–October 1, Barcelona, Spain. *Ann Oncol*. 2019;30(5):v872-v873 [LBA10_PR].

4. Abou-Alfa GK, Macarulla T, Javle MM, et al. Randomised phase 3 study of ivosidenib in IDH1-mutant chemotherapy-refractory cholangiocarcinoma. *Lancet Oncol*. 2020 (accepted, in press).

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

Sincerely,

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