RE: Request for addition of Stivarga® (regorafenib) the single arm phase II of regorafenib in advanced metastatic biliary tract cancer in the NCCN Clinical Practice Guidelines in Oncology™ – Hepatobiliary Cancers

On behalf of Bayer HealthCare Pharmaceuticals, I respectfully request the NCCN Hepatobiliary Cancers panel to review the enclosed data to support the addition of Stivarga® (regorafenib) listing as a single agent to category 2a for patients with advanced metastatic biliary tract cancer based on recently published results of phase II single arm study.

FDA Clearance: Stivarga® (regoratinib) is a kinase inhibitor indicated for the treatment of metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy; locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate; hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.1

Rationale: In a single arm-study, patients with advanced/unresectable or metastatic biliary tract cancer who failed at least 1 line of systemic chemotherapy received regorafenib once daily on a schedule of 21-days on/7-days off in a 28-day cycle. Patients initially received a standard 160 mg dose. After toxicity assessments in the first 3 patients, the dose was reduced to 120 mg for subsequent patients, as preplanned. Forty-three patients received at least 1 dose of regorafenib, and 34 patients who received at least 1 cycle of treatment were evaluable for tumor response. Study results from this trial were published in Cancer 2018;0:1-8.

This single arm phase II study was conducted in the United States. In the primary analysis, the null hypothesis that the median PFS was <2 months was to be tested by fitting a 2-sided 80% CI around the median PFS; if the interval did not include 2 months, then the null hypothesis was to be rejected (α = .10). The study as designed (n = 37) had 83% power to reject the null hypothesis if the true median PFS was ≥3.5 months then regorafenib could be considered as an active treatment in this disease.

This study results3 are summarized below:
- The median PFS was 15.6 weeks (90% confidence interval, 12.9-24.7 weeks)
- The median OS was 31.8 weeks (90% confidence interval, 13.3-74.3 weeks), with survival rates 40% at 12 months and 32% at 18 months.
- A partial response was achieved in 5 patients (11%), and 19 had stable disease (44%), for a disease control rate of 56%.
- The toxicity profile was as expected, with grade 3 and 4 adverse events reported in 40% of patients.
  - The most common toxicities were hypophosphatemia (40%), hyperbilirubinemia (26%), hypertension (23%), and hand-foot skin reaction (7%).

We appreciate your review and consideration of this recommendation. Should you have any questions regarding the content of this letter, please do not hesitate to contact me.

Sincerely,

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Reference List
2. Weijing Sun et al. “A Phase 2 Trial of Regorafenib as a Single Agent in Patients With Chemotherapy-Refractory, Advanced, and Metastatic Biliary Tract Adenocarcinoma” Cancer 2018;0:1-8