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,

Joseph Germino, MD, PhD
Vice President, US Medical Affairs Specialized Therapeutics
Bayer Healthcare Pharmaceuticals
100 Bayer Boulevard, P.O. Box 915
 Whippany, N.J. 07981
(862) 404-5184

Reference List
2. Weijin Sun at el. “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