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Colon Cancer Guidelines Panel:
Submission Request c/o Mary Anne Berman
National Comprehensive Cancer Network (NCCN)
275 Commerce Drive, Suite 300
Fort Washington, PA 19043

RE: Request for addition of Stivarga ® (regorafenib) Regorafenib plus nivolumab an open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO) in patients with advanced gastric (GC) or colorectal cancer (CRC) in the NCCN Clinical Practice Guidelines in Oncology™ – Colon Cancer

On behalf of Bayer HealthCare Pharmaceuticals, I respectfully request the NCCN Colon Cancer panel to review the enclosed data to support the addition of Stivarga ®(regorafenib) in combination with nivolumab to category 2b listing for patients with metastatic colorectal cancer based on recently presented results of an open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO,EPOC1603). The data from this study were presented at American Society of Clinical Oncology (ASCO) 2019.

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 an open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO), a total of 50 pts with previously treated colorectal cancer (CRC) or advanced gastric (GC) were enrolled (25 CRC; 25 GC) until October 2018. The patients received regorafenib plus nivolumab in a dose-finding phase to estimate the maximum tolerated dose (MTD). Additional patients were enrolled in a dose-expansion phase to further establish the safety and determine the preliminary efficacy. Regorafenib of 80 to 160 mg was administered once daily for 21 on 7 days off with intravenous nivolumab 3 mg/kg every 2 weeks. The primary endpoint was dose-limiting toxicity (DLT) during cycle one (4 weeks) to estimate the MTD and the recommended dose. The secondary objectives were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), disease control rate (DCR).

This study results[2] are summarized below:

- The median prior treatment line was 3 (range 2-8).
- During the dose-escalation, 3 DLTs were observed with regorafenib 160 mg, including grade (G) 3 maculopapular rash, mucositis and proteinuria. There was no DLT observed with 80 or 120 mg.

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- In the dose expansion cohort with regorafenib 120 mg, the dose was reduced to 80 mg due to frequent G3 skin toxicities. Grade ≥ 3 treatment related adverse events occurred in 17 pts; the common events (> 5%) being rash (14%), palmar-plantar erythrodysesthesia (10%), and proteinuria (8%).

- Objective response rate was 40% (95% CI:26-55)
  - 36% with colorectal cancer and 44% with gastric cancer
  - Objective tumor response was observed in 19 pts (38%) including 11 microsatellite stable (MSS) gastric cancer, 7 microsatellite stable (MSS) CRC and one microsatellite instable tumors (MSI-H) CRC for response rates of 44% in GC and 29% in MSS CRC. Three of the 7 A-PD1 pretreated GC pts achieved a partial response.
- Disease control rate was 88% (95% CI:76-96)
- Median PFS for CRC was 6.3 months and for GC was 5.8 month
- Median duration of treatment was 6.1 months (range 0.7- 14.9 months)
  Please note: At the time of the presentation in June 2019, the study treatment was ongoing in 21 patients.

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

1. Stivarga [prescribing information]. Wayne, NJ: Bayer U.S. LLC
   https://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf
2. Shota Fukuoka at el Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): An open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO, EPOC1603). J Clin Oncol 37, 2019 (suppl; abstr 2522)
   http://abstracts.asco.org/239/AbstView_239_265149.html