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

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Hepatobiliary 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 category change of Stivarga®(regorafenib) in the NCCN Clinical Practice Guidelines in Oncology™ – Hepatobiliary Cancer**

On behalf of Bayer HealthCare Pharmaceuticals, I am pleased to provide to you with updated literature available regarding Stivarga®(regorafenib) as therapy for patients with unresectable hepatocellular cancer (HCC) based on the recent results of the phase III RECOURSE trial.

Specific Changes: Recommend the inclusion to the NCCN Hepatobiliary Cancer Guidelines and Compendium to add regorafenib as a category 1 recommendation for unresectable hepatocellular cancer and add the RECOURSE phase III trial as supporting evidence for the activity of regorafenib in unresectable hepatocellular cancer.

FDA Clearance: Stivarga ®(regorafenib) is a kinase inhibitor indicated for the treatment of patients with:

- Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and if KRAS wild type , an anti-EGFR therapy.
- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously been treated with imatinib mesylate an sunitinib malate.<sup>1</sup>

Rationale: In patients with metastatic refractory colon cancer, single-agent regorafenib has demonstrated activity in a phase III trial. The RECOURSE (REgorafenib after SOrafenib in patients with hepatoCELLular carcinoma) trial, is the first phase III study in advanced refractory HCC to demonstrate an overall survival advantage for patients after prior sorafenib, were presented at the 2016 WCGI meeting.

RECOURSE is a global, randomized, placebo-controlled, double-blind phase III trial conducted in Europe, Asia Pacific, and the United States. The CONCUR results were presented at the 2016 WCGI Annual Meeting.<sup>2</sup> Note the trial inclusion criteria included Child-Pugh A HCC patients with documented



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radiological progression to sorafenib. Patients must have received a minimum of 400 mg daily sorafenib for at least 20 days of the last 28 days of treatment.

The RECOURSE trial results are summarized below:

- The primary endpoint in this study was OS. Regorafenib significantly prolonged the median OS by 2.8 months compared with placebo [10.6 vs 7.8 months (HR 0.692; 95% CI 0.50–0.78),  $p=0.0001$ ]. The OS benefit was maintained in all predefined subgroups.
- The main secondary efficacy endpoints included progression free survival (PFS), response rate (RR) and disease control rate (DCR).
  - PFS was significantly prolonged in regorafenib patients compared to placebo by 1.6 months [3.1 vs 1.5 months (HR 0.46; 95% CI 0.37–0.56),  $p<0.001$ ]
  - The RR for regorafenib was 10.6% compared to 04.1% for placebo ( $p=.01$ ) by modified RECIST. DCR was 65.5% vs.36.1%
- Safety profile was consistent with the known safety profile of regorafenib. No new safety signals were identified.

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

Enclosures (1): Indicated in blue in Reference List below

## Reference List

1. Stivarga [prescribing information].  
[http://labeling.bayerhealthcare.com/html/products/pi/Stivarga\\_PI.pdf](http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf)
2. Bruix J et al. Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: results of the international, randomized phase 3 RESORCE trial, WCGI 2016