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Colon Cancer Guidelines Panel:
Submission Request
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™ – Colon 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 metastatic colon cancer. We acknowledge that regorafenib is listed in the NCCN Guidelines® and the NCCN Compendium as a category 2a recommendation for colon cancer, based on the recent results of the phase III CORRECT trial.

Specific Changes: Recommend the update of the NCCN Colon Cancer Guidelines and Compendium to change regorafenib to a category 1 recommendation for metastatic colon cancer and add the CONCUR phase III trial as additional supporting evidence for the activity of regorafenib in metastatic colon 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 and sunitinib malate.¹

Rationale: In patients with metastatic refractory colon cancer, single-agent regorafenib has demonstrated activity in 2 phase III trials. The results of the CORRECT trial, the first phase III study of a



single agent kinase inhibitor in advanced refractory colon cancer to demonstrate an overall survival advantage for patients, were presented at the 2012 ASCO Annual Meeting.^{2,3}

The CONCUR trial was a global phase III trial primarily conducted in Asia Pacific. The CONCUR results were presented at the 2014 WCGI Annual Meeting.^{4,5} Note 40% of patients in CONCUR had not received any targeted biological therapy before randomization, in contrast to CORRECT, where all patients had previously received at least one targeted drug.

The CONCUR trial results are summarized below:

- The primary endpoint in this study was OS. Regorafenib significantly prolonged the median OS by 2.5 months compared with placebo [8.8 vs 6.3 months (HR 0.55; 95% CI 0.40–0.77), $p=0.00016$]. 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 1.5 months [3.2 vs 1.7 months (HR 0.31; 95% CI 0.22–0.44), $p<0.0001$]
 - The RR for regorafenib was 4.4% compared to 0% for placebo ($p=0.0001$). DCR, which includes CR+PR+SD+nonCR/nonPD was 51.5% vs. 4.4%
- 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,

A handwritten signature in black ink that reads "Joseph Germino".

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Enclosures (1): Stivarga® PI



Reference List

1. Stivarga® [prescribing information].
http://labeling.bayerhealthcare.com/html/products/pi/Stivarga®_PI.pdf
2. Van Cutsem E, Sobrero A, Siena S et al. Phase III CORRECT trial of regorafenib in metastatic colon cancer. J Clin Oncol 30, 2012 (suppl; abstr 3502)
3. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group. Lancet. 2013 Jan 26; 381(9863):303-12.
4. Xu J, Bai Y, Chi Y et al. CONCUR: a randomized, double-blind, placebo-controlled phase III study of regorafenib monotherapy in Asian patients with previously treated metastatic colon cancer. Annals of Oncology (2014) 25 (suppl_2)
5. J Li, S Qin, R Xu, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncology. 2015 May xx; 6(6):619-629.