

Bayer HealthCare Pharmaceuticals



October 3, 2012

Joan McClure, MS
Senior Vice President, Clinical Information and Publications
National Comprehensive Cancer Network (NCCN)
275 Commerce Dr., Suite 300
Fort Washington, PA 19034

Re: Request for addition of Stivarga® (regorafenib) to the NCCN Guidelines for metastatic colorectal cancer (mCRC) and gastrointestinal stromal tumors (GIST).

Dear Ms. McClure:

Bayer HealthCare Pharmaceuticals is pleased to provide you with the current literature available regarding Stivarga® (regorafenib) as therapy with metastatic colorectal cancer and GIST. We respectfully request NCCN Colon Cancer and Sarcoma Committees review the enclosed data for inclusion of regorafenib as treatment for patients with metastatic colorectal cancer, and GIST respectively.

FDA Clearance: The FDA has approved Stivarga® treatment for metastatic colorectal cancer patients 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. The GIST NDA is currently under priority review.

Specific changes:

- 1.) Recommend Stivarga® for metastatic colorectal cancer patients who have been previously treated.
- 2.) Recommend Stivarga® for the treatment of previously treated GIST.

Regorafenib is an oral tumor deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumor angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumor microenvironment (PDGFR, FGFR). In preclinical studies regorafenib has demonstrated potent antitumor activity in a broad spectrum of tumor models including colorectal tumor models which is mediated both by its antiangiogenic and antiproliferative effects. In addition, regorafenib has shown anti-metastatic effects *in vivo*. Major human metabolites (M-2 and M-5) exhibited similar efficacies compared to regorafenib in *in vitro* and *in vivo* models.

Rational CRC: The following supporting data are submitted with the full prescribing information in support of the proposed colorectal cancer addition. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributor of some of these studies.

- Stivarga® (regorafenib) PRESCRIBING INFORMATION, Distributed by Bayer Healthcare Pharmaceuticals, September 2012
- Strumberg et al described colon cancer patients treated in a Phase I dose escalation and extension trial. Twenty-six of 38 heavily pretreated colon cancer patients were treated with 160 mg daily. Patients had a median of 4 previous therapies (range 0-7) with Eastern Oncology Cooperative Group (ECOG) Performance Status (PS) of 0-2. The most common treatment related toxicities were: hand foot skin reaction, fatigue, voice change and rash. Of 27 patients evaluable for response, there was 1 partial response and 19 with stable disease. Median progression-free survival was 107 days (95% CI, 66-161)
- Dr. Axel Grothey (Mayo Clinic) presented the results from the pivotal CORRECT (Colorectal cancer treated with regorafenib or placebo after failure of standard therapy) at ASCO 2012. The multicenter, international double blind placebo controlled study met its primary endpoint, showing statistically significant improvement in overall survival (OS) by 29% (HR=0.77, p=0.0052, median OS: 6.4 months vs. 5.0 months for the placebo group) in patients with metastatic colorectal cancer whose disease had progressed after approved standard therapies. Additionally, findings from the secondary endpoints of the CORRECT study showed statistically significant improvement in progression-free survival (PFS) (HR=0.49, p<0.000001, median PFS: 1.9 months vs. 1.7 months) and an improvement in disease control rate (44.8% vs. 15.3%) in patients treated with regorafenib compared to those treated with placebo. The difference in objective response rate between the two arms (1.0% vs. 0.4%) did not reach statistical significance. The most common drug-related treatment-emergent adverse events included fatigue (47.4% vs. 28.1%), hand-foot skin reaction (46.6% vs. 7.5%), diarrhea (33.8% vs. 8.3%), anorexia (30.4% vs. 15.4%), hypertension (27.8% vs. 5.9%), oral mucositis (27.2% vs. 3.6%) and rash/desquamation (26.0% vs. 4.0%) for patients receiving regorafenib as compared to placebo. Please note the CORRECT manuscript has been submitted for publication and will be forwarded upon acceptance.

Rational GIST: The following supporting data are submitted in support of the GIST addition.

- George et al published their Phase II evaluation of regorafenib in metastatic GIST of 34 patients treated in this multi-institutional trial. Clinical benefit rate (defined as SD or better for 16 weeks or more) was 79% (95% CI, 61% to 91%) and progression-free survival was 10.0 months. The most commonly observed toxicities were hand-foot-skin reaction 85%, fatigue 79%, hypertension 67% and diarrhea 61%. The majority of toxicities were grade 1 or 2.
- Dr. George Demetri et al presented positive data from the Phase III GRID (GIST – Regorafenig In Progressive Disease) trial evaluating regorafenib in patients with metastatic and/or whose disease had progressed despite prior treatment with imatinib and sunitinib. Regorafenib significantly improved progression-free survival

(PFS) over placebo (HR=0.27, $p<0.0001$). The median PFS was 4.8 months in the regorafenib arm versus 0.19 months in the placebo arm. Furthermore, regorafenib demonstrated a significantly greater disease control rate (DCR, defined as rate of partial response {PR} plus durable stable disease {SD} lasting for at least 12 weeks) compared to placebo (52.6% vs 9.1%; $p<0.000001$). There was a positive trend in the regorafenib group in improving overall survival (OS) (HR=0.77, $p=0.20$). The OS results were not statistically significant, which was expected due to the cross-over design of the study. The most common drug-related, treatment-emergent adverse events included hand-foot-skin reaction (56.1% vs 15.2%), hypertension (48.5% vs 16.7%), diarrhea (40.9% vs 7.6%), fatigue (38.6% vs 27.3%) and oral mucositis (37.9% vs 9.1%) for patients receiving regorafenib as compared to placebo. Please note the GIST CORRECT manuscript has been submitted for publication and will be forwarded upon acceptance.

Should you have any questions regarding the content of this letter, please do not hesitate to contact us.

Sincerely,



Joseph F. Germino, Ph. D, M.D.
Vice President, Medical Affairs, Oncology
Bayer HealthCare Pharmaceuticals

References:

1. Mross, Frost A, Steinbild S, et al. A Phase I Dose-Escalation Study of Regorafenib (Bay 73-4506), An Inhibitor of Oncogenic, Angiogenic and Stromal Kinases, in patients with advanced solid tumors. *Clin Cancer Res*, online, March 15, 2012
2. Strumberg D et al. Regorafenib (Bay 73-4506) in advanced colorectal cancer: a phase I study. *British Journal of Cancer*, online 8 May 2012, 2012, 1-6
3. George S, et al. Efficacy and Safety of regorafenib in Patients with Metastatic and/or Unresectable GI Stromal Tumor After Failure of Imatinib and Sunitinib: A Multicenter Phase II Trial. *J Clin Oncol* 30. 2012
4. Eisen T, et al. Phase II trial of the oral multi kinase inhibitor regorafenib (BAY 73-4506) as first-line renal cell carcinoma (RCC) *Abstract BSP098 Tim Eisen poster final*
5. Bolondi L et al. Phase II safety study of the oral multikinase inhibitor regorafenib (BAY 73-4506) as second-line therapy in patients with hepatocellular carcinoma (HCC) *Abstract BSP099 HCC poster final*
6. Demetris G et al. Randomized Phase III Trial of Regorafenib in Patients (pts) with Metastatic and/or Unresectable Gastrointestinal Stromal Tumor (GIST) Progressing Despite Prior Treatment with at least Imatinib (IM) and Sunitinib (SU): The GRID Trial ASCO 4 June 2012 *Abstract*
7. Grothey A et al. Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer (mCRC) who have progressed after standard therapies ASCO GI, 21 Jan 2012 *Abstract*