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26 January, 2018

Colorectal 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) ReDOS phase II randomized cycle 1 weekly dose escalation strategy data in the NCCN Clinical Practice Guidelines in Oncology™ – Colorectal Cancer

On behalf of Bayer HealthCare Pharmaceuticals, I respectfully request the NCCN Colorectal Cancer panel to review the enclosed data for inclusion of Stivarga®(regorafenib) cycle 1 weekly dose escalation strategy for patients with metastatic colorectal cancer (mCRC) based on recently presented results of the phase II randomized Regorafenib Dose Optimization (ReDOS) trial. ReDOS evaluated a regorafenib cycle 1 weekly planned dose escalation strategy (80 mg/daily week 1, then 120 mg/daily week 2, then 160 mg/daily week 3, week 4 rest) compared to regorafenib standard starting dose (160 mg daily for 21 days followed by 1 week rest) in refractory mCRC (1).

Specific Changes: Recommend the inclusion to the NCCN Colorectal Cancer Guidelines and Compendium to add regorafenib cycle 1 weekly dose escalation strategy (80 mg/daily week 1, then 120 mg/daily week 2, then 160 mg/daily week 3, week 4 rest) as tolerated for metastatic colorectal cancer and add the ReDOS phase II randomized cycle 1 weekly dose escalation strategy compared to cycle 1 standard starting dose regorafenib in refractory mCRC supporting data.

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. (2)
- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously been treated with imatinib mesylate an sunitinib malate. (3)
- hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.(4)

Rationale: In patients with metastatic colorectal cancer patients treated with planned cycle 1 weekly dose escalation strategy (80 mg/daily week 1, then 120 mg/daily week 2, then 160 mg/daily week 3, week 4 rest) demonstrated statistically significant increased percentage of patients starting cycle 3 and a trend towards increased overall survival compared to starting regorafenib at standard dose (160 mg/d). Study results from this trial were presented at the American Society for Clinical Oncology Gastrointestinal Cancers Symposium (ASCO-GI) in 2018.

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This multi-center, randomized, phase II study was conducted in the United States.

The ReDOS randomized phase II study results are summarized below:

- The primary endpoint in this study was met with and a higher percentage of patients starting cycle 3 were observed in the cycle 1 weekly dose escalation strategy regorafenib arm. Planned cycle 1 weekly dose escalation regorafenib treated patients demonstrated a significant increase (43%) in starting cycle 3 compared to regorafenib patients treated at standard dose (24%); p.028.
- Secondary endpoints included progression-free survival (PFS), overall survival (OS), and quality of life (QOL)
  - There was increased median OS for weekly planned dose escalation strategy regorafenib of 9.0 months compared to 5.9 months for patients starting at standard dose regorafenib with HR 0.65, p =.094.
  - PFS trended to favor weekly planned dose escalation regorafenib treated patients compared to those at standard dose with a median of 2.5 compared to 2 months HR =0.89, p = .55
  - A trend towards improved QOL was noted in the planned weekly dose escalation arm
- There were slightly lower toxicities in the planned weekly dose escalation arm compared to standard dose. Most common grade 3 or 4 toxicities for the weekly planned dose escalation regorafenib arm compared to standard dose were fatigue (13%/0% v 17.7%/0), HFSR (14.8%/0 v. 16.1%/00%), abdominal pain (16.7%/0% v. (6.5%/0%), and hypertension (7.4%/0%) v. (14.5%/0%).

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. TS Bekaii-Saab et al. Regorafenib dose optimazation study (REDOS) randomized phase II trial to evaluate dosing strategies fo regorafenib refractory metastatic colorectal cancer (mCRC0 – an ACCRU Network study. JCO suppl 4S; abstr 611, 2018
2. Grothey et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international multicenter, randomized, placebo-controlled, phase III trial. Lancet (381:3863), 2013
3. Demetri GD et al. Efficacy and Safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicenter, randomized, placebo-controlled, phase 3 trial. Lancet 381, 2013
4. Bruix J et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet 389, 2017
5. Stivarga [prescribing information]. http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf