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10-Dec, 2018

Central Nervous System 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) phase II randomized open label study (REGOMA) in patients with relapsed glioblastoma in the NCCN Clinical Practice Guidelines in Oncology™ – Central Nervous System**

On behalf of Bayer HealthCare Pharmaceuticals, I respectfully request the NCCN Central Nervous System Cancer panel to review the enclosed data to support the addition of Stivarga® (regorafenib) listing as a single agent to category 2a for patients with relapsed glioblastoma based on recently published results of phase II randomized open label controlled study (REGOMA).

FDA Clearance: Stivarga® (regorafenib) 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.<sup>1</sup>

Rationale: In a randomized open label, phase II (REGOMA) trial, between Nov 27, 2015, and Feb 23, 2017, 124 patients were screened and 119 eligible patients were randomly assigned to receive regorafenib (n=59) or lomustine (n=60). Patients received regorafenib 160 mg once daily for the first 3 weeks of each 4-week cycle or lomustine 110 mg/m<sup>2</sup> once every 6 weeks until disease progression, death, unacceptable toxicity, or consent withdrawal. The primary endpoint was overall survival in the intention-to-treat population. Study results from this trial were published in Lancet Oncology online on -3-December 2018.<sup>2</sup>

This multi-center, randomized, open label phase II (REGOMA) study was conducted at Veneto Institute of Oncology in Italy. The study was designed to detect a 42% reduction in the hazard ratio (HR) for death based on one-sided log-rank test.

The study results at cutoff date of Dec 31, 2017 are summarized below:

- Median follow-up was 15.4 months (IQR 13.8–18.1).
- At the analysis cutoff date, 99 (83%) of 119 patients had died: 42 (71%) of 59 in the regorafenib group and 57 (95%) of 60 in the lomustine group.



- Overall survival was significantly improved in the regorafenib group compared with the lomustine group, with a median overall survival of 7.4 months (95% CI 5.8–12.0) in the regorafenib group and 5.6 months (4.7–7.3) in the lomustine group (hazard ratio 0.50, 95% CI 0.33–0.75; log-rank  $p=0.0009$ ).
- Grade 3–4 treatment-related adverse events occurred in 33 (56%) of 59 patients treated with regorafenib and 24 (40%) of 60 with lomustine.
  - The most frequent grade 3 or 4 adverse events related to regorafenib were hand–foot skin reaction, increased lipase, and blood bilirubin increased (in six [10%] of 59 patients each).
  - In the lomustine group, the most common grade 3 or 4 adverse events were decreased platelet count (eight [13%] of 60 patients), decreased lymphocyte count (eight [13%]), and neutropenia (seven [12%]).
  - No death was considered by the investigators to be drug related.

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](https://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf)
2. Giuseppe Lombardi at el Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): A multicenter, open-label, randomized, controlled, ph 2 trial  
<https://www.thelancet.com/action/showPdf?pii=S1470-2045%2818%2930675-2>