PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Regorafenib (Stivarga) for Metastatic Colorectal Carcinoma

November 15, 2013

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Stivarga® (regorafenib) mCRC
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback:	Bayer Inc.

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ Agrees ____ agrees in part X Disagree

Bayer disagrees with the pCODR initial recommendation concerning Stivarga in mCRC. pERC must reconsider its initial assessment of the value of Stivarga in this clinical area of unmet need on the following grounds:

- pERC's assessment of efficacy and safety is incongruent with pCODR's CGP report, and the opinions of treating physicians.
- Bayer disagrees with the EGP's cost-effectiveness estimate provided to pERC. The EGP's method of dealing with uncertainty and extrapolation of Stivarga's survival benefit misrepresents the clinical data.
- The resulting EGP analysis is misleading in the Stivarga assessment. Unfortunately, as pCODR cancelled Part 1 of the Checkpoint Meeting process, Bayer was provided no opportunity to clarify information in the submission and address the EGP's concerns which led to this misinformed recommendation.

Clinical Benefit Assessment

Stivarga is the first agent to show an improvement in life expectancy in mCRC patients who have progressed on earlier lines of therapy.[1,2] The magnitude of Stivarga's survival benefit is consistent with existing mCRC treatments funded by Canadian payers. Collectively, these modest gains have improved median survival from 5 months in the 1970's to >20 months.[2]

Despite the fact that 48% of patients had received ≥ 4 previous metastatic anticancer therapies, CORRECT demonstrated a 1.4 month (6.4 vs 5.0) increase in median OS with a 0.77 HR. This represents a 23% reduction in the risk of death and is in the range of HRs from recent earlier line mCRC studies (0.75 to 0.85).[3-5]

Stivarga addresses an unmet need as there are no other proven agents in this setting. The treatment of mCRC is not one single treatment but a campaign of multiple consecutive treatments with an accumulation of benefits. Delaying or failing to treat leads to rapid progression, decline in quality life and ultimately death. The therapeutic value of Stivarga in mCRC is supported by the CGP assessment and is included in established clinical guidelines (NCCN, ESMO, WC5 and EC5).[6-8] The survival benefit achieved by Stivarga has also been deemed to be sufficiently meaningful by regulatory bodies resulting in priority approvals from Health Canada and the FDA.

Safety and Tolerability Assessment

Regorafenib's adverse events are generally predictable, manageable and reversible. Trial investigator's noted, the safety profile of regorafenib in the CORRECT trial was consistent with early clinical experience, and is typical of the TKI class.[1,9,10] The most common grade 3 adverse drug reactions were hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash or

desquamation. Most events occurred early in the course of treatment (within 1–2 cycles) and were readily manageable with dose modifications leading to a low discontinuation rate due to AEs (8.2% regorafenib vs 1.2% placebo).

The pERC highlighted the incidence of liver dysfunction (any grade): 5.6% regorafenib vs 3.6% placebo. It is important to note that the vast majority of mCRC patients suffer from liver metastases. Within that context, drug related AEs for liver dysfunction (any grade) were infrequent: 1.8% regorafenib vs 0% placebo. Although 8 fatal hepatic events were referenced by pERC, all of these deaths were associated with disease progression. Grothey et al reported only 1 fatal hepatic event to be related to study drug.[1] Across all trials, investigators linked drug induced liver injury with fatal outcome in 0.3% of 1,200 regorafenib-treated patients. Hepatotoxicity is a recognized risk associated with TKIs and mCRC treatments. Management strategies for these risks are recommended across the class and include labeling, diligent surveillance, appropriate patient selection, and dose modifications.[9,11] Bayer pharmacovigilance continues to monitor globally all reported adverse events.

Patient Based Values and Quality of Life

Bayer disagrees with pERC's statement that "regorafenib only partially aligns with patient values". In mCRC, as noted by the EGP, patients seek "…to maintain their quality of life." For patients entering the CORRECT trial baseline EQ-5D utilities in both arms, demonstrated high function status of patients entering the trial despite previous progression on multiple lines of therapy. Improvements in QoL in this population would be unexpected. The expectation with treatment is to maintain QoL.

The EGP report states "there is a high likelihood that QALY loss due to AEs is not adequately reflected in the EQ-5D results". This statement does not consider the EORTC (a cancer specific instrument) analysis in the trial. The EORTC analysis did not find a significant difference in quality of life at the end of treatment, nor did a time-adjusted AUC analysis (p31 of the CGP report).[1] Receiving regorafenib did not adversely affect QoL based on EQ-5D and EORTC analysis. With clinically meaningful declines in EQ-5D observed at end of treatment in both arms, coupled with regorafenib's significant improvement in PFS (HR = 0.49), patients have a reduced risk of deterioration in QoL compared with BSC alone.

Based on the balance of Stivarga's clinical efficacy and safety profile, Bayer disagrees with pERC's statement "palliation is still the most reasonable treatment option for these patients". Individual patient decisions need to be balanced with their oncologist's considerations and efforts to manage their disease. Untreated, mCRC patients face the certainty of disease progression, and worsening of symptoms resulting in a rapid decline in QoL.

Economic Assessment

Bayer does not agree with the EGP's method of survival extrapolation from 10 months onward and the resulting ICER and ranges reported by the EGP as the "best estimate".

The manufacturer's HE model was based on a statistical model of OS for both BSC and Stivarga using the full data from the 2nd interim analysis; the same dataset as submitted for approval to Health Canada. The methodology for extrapolation is fully described in Appendix 1 of Bayer's HE Report and was validated through comparison to mCRC reported survival datasets.

Bayer was unable to reproduce the EGP ICER following the method described in their report. As the methodology is not fully described, based on exploratory analyses by Bayer, it appears the following approach was taken[a]:

- First, the EGP's regorafenib OS curve (fig4 from the EGR) beyond 1-year averages the Bayer extrapolations for regorafenib and BSC, which reduces intercept and slope of the regorafenib OS curve. The EGP curve then draws an almost straight line from day 315 of the Bayer regorafenib OS curve to day 364 to meet the EGP post 1-year extrapolation. This adjustment reduces Stivarga's observed benefit before 12 months.
- It appears the BSC curve was also adjusted to the average of the BSC and regorafenib curves

[a] For transparency Bayer requests that Figures 2, 3 and 4 of the EGR be disclosed. Bayer also requests that the EGP's equivalent of Figure 2 be provided and disclosed in the final recommendation documentation.

beyond 1 year. This would require adjustment between 315 and 364 days improving BSC survival predictions. The slope of the BSC curve was then reduced by ~2% to obtain the estimated ICER. Although our attempt to reproduce the analysis may not be precisely the same as the undisclosed method, the results using the above adjustments closely match the EGP analyses.

Based on data at the 2nd interim analysis, the number of individuals at risk at 12 months is 7 and 3 in the regorafenib and placebo arms respectively, constituting less than 2% of the study population. Thus, there is considerable uncertainty regarding the survival probabilities, and any trends in the mortality rate, in this region of the OS curve. It is therefore not appropriate to modify the extrapolation of OS used in the model based solely on data from this region as that corresponds to an over-interpretation and over-fitting of limited data which could lead to erroneous findings. However, the EGP reanalysis uses this approach.

The EGP extrapolation is also inconsistent with final OS data included in Section f) "New Data Generated after NDS" of the submission. The additional data confirms the benefit of regorafenib beyond 1 year, with 17 months of follow-up.[1] In the table below, the final OS data are consistent with Bayer's submitted extrapolation (7.1% vs 6.4%), but the survival benefit in the EGP extrapolation shows a substantial underestimate (7.1% vs 1.2%).

Survival at 12 months	**CORRECT Results**		**OS Extrapolation**	
Study Arm	**Interim Data**	**Final Data**	**Bayer**	**EGP***
Stivarga	24.2% (n at risk=7)	24.1% (n at risk 59)	26.2%	23.0%
BSC	24.0% (n at risk=3)	17.0% (n at risk 17)	19.8%	21.8%
Difference	**0.2%**	**7.1%**	**6.4%**	**1.2%**

*EGP is Bayer's estimate of the EGP extrapolation as the EGP's method of extrapolation for both arms was not provided. Bayer's method to generate the EGP estimate is described above.

The economic model submitted by the manufacturer incorporated an extrapolation of OS using all of the clinical trial data and the best fitting log-normal curve. The extended follow-up data showed that the OS curves for regorafenib and placebo remained separate for up to 17 months. The OS extrapolation in the submitted economic model was more consistent with the observed data from the extended follow-up than the OS projections produced by the EGP using limited data at 12 months.

Contrary to the ultimately observed clinical data, the EGP extrapolation beyond 1-year suggested almost no additional benefit for regorafenib over placebo during the remainder of the 5 year period. The EGP analysis is equivalent to truncating the time horizon in the Bayer model at 1-year (no extrapolation of the clinical trial data). Consequently, the resulting EGP model only produces 0.07 LYs gained whereas Bayer's model produced 0.15 LYs utilizing the trial data. This >50% reduction in projected LYs has a significant impact on the resulting ICER.

The other observations raised by the EGP regard model time horizon, dose intensity, and inclusion of markup. We acknowledge the alternative assumptions made by the EGP (markup removed, 90% dose intensity and 5-year time horizon) result in an ICER of $205,489/QALY. This ICER, though <10% higher than that submitted remains similar to published ICERs for other mCRC treatments. We request that pERC reconsider the initial recommendation by considering the clarification of information provided when finalizing their recommendation.

pERC's Assessment of Adoption Feasibility

The budget impact is expected to be modest as only those patients who meet the criteria for prior treatments and appropriate performance status would be eligible for coverage. It is unlikely 100% of mCRC patients would receive and progress through all lines of treatment and subsequently receive Stivarga.[12] As regorafenib is an oral tablet supplied in a three week supply, waste associated with discontinuation will be minimal.

References

1. Grothey A, Cutsem EV, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-12.

2. Vickers MR. Slow and steady: incremental survival improvements in advanced colorectal cancer. Oncology Exchange 2013;12(1):4.
3. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012;30:3499-506.
4. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539-44.
5. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:4706-13.
6. Benson AB, 3rd, Bekaii-Saab T, Chan E, et al. Metastatic colon cancer, version 3.2013: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw 2013;11:141-52; quiz 52.
7. Casado-Saenz E, Feliu J, Gomez-Espana MA, Sanchez-Gastaldo A, Garcia-Carbonero R. SEOM Clinical guidelines for the treatment of advanced colorectal cancer 2013. Clin Transl Oncol 2013.
8. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 2012;23:2479-516.
9. Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug Saf 2013;36:491-503.
10. Festino L, Fabozzi A, Manzo A, et al. Critical appraisal of the use of regorafenib in the management of colorectal cancer. Cancer Manag Res 2013;5:49-55.
11. Iacovelli R, Palazzo A, Procopio G, et al. Incidence and relative risk of hepatic toxicity in patients treated with antiangiogenic tyrosine kinase inhibitors for malignancy. Br J Clin Pharmacol 2013.
12. Hedden L, Kennecke H, Villa D, et al. Incremental cost-effectiveness of the pre- and post-bevacizumab eras of metastatic colorectal cancer therapy in British Columbia, Canada. European Journal of Cancer 2012;48:1969-76.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____	Support conversion to final recommendation.	__X__	Do not support conversion to final recommendation.
	Recommendation does not require reconsideration by pERC.		Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.