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 Gastrointestinal Stromal Tumors

May 2, 2014

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	STIVARGA® (regorafenib, 40 mg tablet), Treatment of patients with metastatic and / or unresectable gastrointestinal stromal tumours (GIST) who have had disease progression on or intolerance to imatinib mesylate, and sunitinib malate treatment.
Role in Review (Submitter and/or Organization Providing Feedback	Manufacturer Bayer Inc.

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

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 X agrees in part ____ disagree

Bayer agrees with the pCODR initial recommendation to fund Stivarga for treatment of patients with metastatic and / or unresectable gastrointestinal stromal tumours (GIST) who have had disease progression on or intolerance to imatinib mesylate, and sunitinib malate treatment. Bayer agrees with the assessment of clinical value but disagrees with the methodology and assumptions used by the EGP to determine the best estimates of incremental cost-effectiveness ratios.

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.

X	Support conversion to final recommendation.	____	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
4	**Safety**	**Paragraph 3, line 12**	**See comment below**
Statement in initial recommendation: "Despite these concerns, the rate of treatment discontinuation due to adverse events was similar in both groups (8% versus 6%, respectively) and these…" Comment: The rates presented are reversed vs. other results presented in the same paragraph. The discontinuation rate in the GRID trial was 6% in the regorafenib arm and 8% in the BSC arm. Suggestion for clarity: The rate of treatment discontinuation due to adverse events was similar in both groups (6% vs 8% in the regorafenib vs placebo arms, respectively) and these…			
5	**Economic**	**Paragraph 6 lines 6-8**	**See comment below**

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	Evaluation		
Statement in initial recommendation: "treatment beyond progression is likely to occur in clinical practice, as agreed by the pCODR Clinical Guidance Panel, and would likely influence cost-effectiveness estimates." This statement misinterprets the findings of the EGP which noted these costs were included in the estimates provided by Bayer (page 7). When treatment beyond progression is excluded from the model the ICER in Bayer's submitted base case improved to $84,073/QALY. Suggestion for clarity: "treatment beyond progression is likely to occur in clinical practice, as agreed by the pCODR Clinical Guidance Panel, and costs for treatment beyond progression were included in Bayer's submitted base case and the EGP's best estimate."			

3.3 Additional Comments About the Initial Recommendation Document

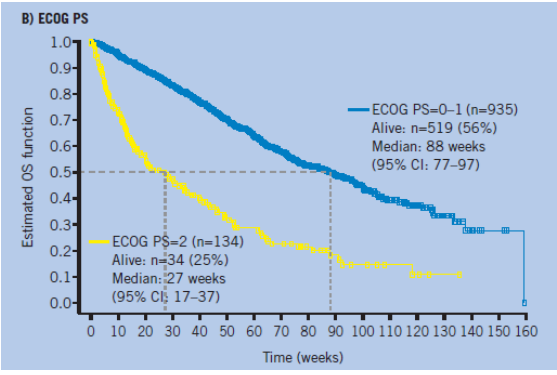
Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
2	Summary of pERC deliberations	Page 2, paragraph 4 lines 3-4.	See comment below
5	Economic Evaluation	Paragraph 6 (heading) and lines 4-5	

The pERC and EGP comments regarding over-estimation of the survival benefit are inconsistent with the trial data and the available natural history information. There are three main concerns with the EGP's re-analysis:

First, the development of Bayer's submitted economic model included internal and external validity testing for the survival projections as recommended by Latimer.(2) Internal testing included analysis of AICs to determine curves best fitting the data. Based on this testing both Weibull and exponential best-fits seemed to be reasonable. In addition to using the AIC criteria, GIST experts were consulted and initially felt the placebo Weibull projection was the expected fit for the natural history of GIST after failure / intolerance to imatinib and sunitinib. However, they expected patients from GRID to have similar survival to patients in the ECOG PS 0-1 subgroup of the Seddon study and that it was appropriate to use Seddon as an evidence-based choice for external validation of the curve fit (See Figure 1).(1)

Figure 1: Sunitinib Survival by ECOG Status (Seddon et al)(1)



The pCODR reviewers noted GIST patients in this setting may live about 6 months. While this estimate is very consistent with the prognosis for ECOG 2 patients in the Seddon study(1), it should be noted the GRID trial did not enroll ECOG 2 patients. Regardless of treatment arm, the Seddon data for ECOG 0-1 patients are the best available external validation of the potential survival extrapolations. As seen in Figure 2 the Weibull extrapolation was inconsistent with Seddon for both placebo and treatment arms; whereas, the exponential curves fit closely with the Seddon projection as seen in Figure 3. In Figure 1, the ECOG 0-1 group had a survival of approximately 70% at 1 year, consistent with the observed GRID survival further validating the Seddon ECOG 0-1 curve as appropriate for natural history.

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Figure 2 Comparison OS natural history data to Weibull extrapolations of IPE adjusted placebo and regorafenib data

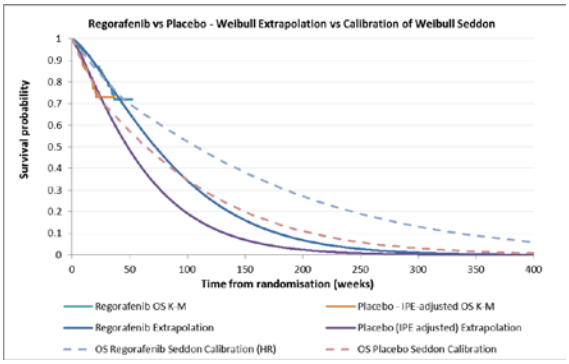
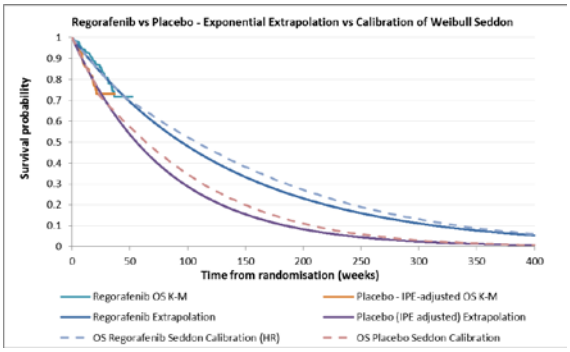


Figure 3 Comparison of OS natural history data to exponential extrapolations of IPE adjusted placebo and regorafenib data



Secondly, the EGP commented that the time horizon could be as short as two years. Even for the ECOG 2 patients from Seddon, 15% of patients remained alive beyond two years (Figure 1). Therefore it would be unrealistic to limit the model duration to such a short time horizon.

Lastly, the EGP was overly pessimistic by assuming an HR of one after an arbitrary period based on median treatment. The HR=1 method used by the EGP improves the placebo survival projection which is not plausible. The proportional hazard assumption was tested and was shown to be valid. There is therefore no justification for improving the survival of the placebo arm and thereby reducing the overall hazard ratio and extended QALY benefit of Stivarga by up to 47%. This underestimates the QALY benefit of Stivarga by using assumptions that are not externally validated and produces results at odds with available natural history evidence and clinical opinion.

EGP Report Page 2	**Summary of Results**	**Paragraph 12**	**See comment below**

The EGP recommendation to use planned dose (i.e. label dose) rather than average dose is inconsistent with previous guidance and further biases the model against Stivarga in anticipated actual use. It should be noted that in pCODR's previous evaluation of Stivarga in the treatment of mCRC the EGP recommended using the average dose in place the % of planned dose to adjust for waste. As noted by the CGP, dose reductions and interruptions are expected with Stivarga. At the % of planned dose the ICER was $95,666 / QALY.

In conclusion, overall Bayer agrees with the recommendation to fund Stivarga for the treatment of GIST. However, based on the above, the overall survival projections and resulting cost-effectiveness ratios presented in Bayer's submitted model were conservative and reasonable.

References

1. **Seddon B RP, Kang YK, et al. Detailed Analysis of Survival and Safety with Sunitinib in a Worldwide Treatment-use Trial of Patients with Advanced Imatinib-resistant/intolerant GIST. CTOS 2008.**
2. **Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Med Decis Making. 2013 Aug;33(6):743-54.**

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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.

1 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.

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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.

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