PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Regorafenib (Stivarga) for Gastrointestinal Stromal Tumours

May 2, 2014

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Bayer Inc.** compared regorafenib + BSC to placebo + best supportive care (BSC) for patients with metastatic or unresectable gastrointestinal stromal tumours (GIST), who have had disease progression on or intolerance to imatinib and sunitinib. Hereafter, the comparison is referred to as regorafenib vs. BSC. Regorafenib is administered orally.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, as there is no standard of care for the third-line setting. The Clinical Guidance Panel considered that in some jurisdictions, imatinib re-challenge may also be a clinically relevant comparator. This comparison was not included in the economic analysis.

Patients considered the following factors important in the review of regorafenib, which are relevant to the economic analysis: treatment efficacy, side effects and quality of life experienced on treatment. Efficacy and quality of life are captured in the model, as are the costs of adverse events. Patients also are concerned about availability and accessibility of treatment options.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for regorafenib, and which are relevant to the economic analysis: small patient population, dose schedule, and additional monitoring for toxicity, particularly related to the black box warning regarding hepatic toxicity. Additional monitoring costs are included in the model.

At the list price, regorafenib costs $74.25 per 40 mg tablet. At the recommended dose of 160mg daily for 21 days of a 28 day cycle, the cost of regorafenib is $222.75 per day (when adjusted for scheduled time off drug) and $6,237 per 28 day cycle. At the confidential price, regorafenib costs $[redacted] per tablet. At the recommended dose of 160mg for 21 days of a 28 day cycle regorafenib costs $[redacted] per day and $[redacted] per 28 day cycle. Patients require an average of 5 cycles, and may continue beyond progression for a further 5 cycles. The cost of regorafenib is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the *pCODR Disclosure of Information* guidelines.

Brand name imatinib costs $27.88 and $111.52 per 100mg and 400mg tablet. At the recommended dose of 400mg once daily, brand name imatinib costs 111.52 per day and $3,122.53 per 28 day cycle. Other versions of imatinib are priced at approximately 25% of the brand name product.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is $171,436 / QALY gained, and is likely between $143,317 / QALY gained and $205,299 / QALY gained when regorafenib is compared with BSC. Following feedback received from the manufacturer on the economic guidance panel's reanalysis estimates, the CGP reviewed the basis of the clinical assumptions made by the EGP in providing their re-analysis estimates and concluded that the assumptions are clinically reasonable.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- The extra cost of regorafenib is between $56,592 and $64,197 (ΔC).
- The extra clinical effect of regorafenib is between 0.310 and 0.407 QALYs (ΔE).

The estimates are affected by the overall survival (OS) benefit and total drug costs used in the model.

The EGP based these estimates on the model submitted by Bayer Inc. and reanalyses conducted by the EGP. The model was based on the phase III GRID clinical trial comparing regorafenib + BSC to placebo + BSC (the placebo arm representing BSC). A statistically significant OS benefit was not found in the trial and most patients in the BSC group (85%) crossed over to regorafenib after progression. The BSC arm was adjusted for crossover using statistical methods. The interim OS data also required substantial extrapolation.

The reanalysis conducted by the EGP using the submitted model showed that when:

- A more clinically plausible survival curve (a weibull distribution) is used for OS in the extrapolated portion of the model:
    - The extra cost of regorafenib is $57,117 (ΔC), and
    - The extra clinical effect is 0.333 QALYs.
    - This produces the EGP's **best estimate** for the ICER, $171,436 / QALY gained.

Since the submitted model is a partitioned survival analysis, the model could not be modified to address assumptions in the post-progression period only. Thus, the EGP used hazard ratios for OS to explore the relative benefit of regorafenib compared to BSC. The BSC arm was adjusted for crossover by the submitter using two similar statistical methods. The analysis produced an adjusted HR for regorafenib compared to BSC lower than that from the unadjusted HR from the trial of 0.772. As the clinical trial OS data for the regorafenib arm was best modelled with a weibull distribution, the inverse of the adjusted HR was applied to the regorafenib weibull curve to create the BSC curve.

- Using the HR from the adjusted analysis, the regorafenib OS curve and assuming the OS benefit for regorafenib continues indefinitely, the extra cost of regorafenib is $58,308 and the extra clinical effect is 0.407 QALYs, which decreases the estimated incremental cost-effectiveness ratio to $143,317 / QALY gained.
- Assuming the OS benefit for regorafenib is attenuated once treatment is discontinued (HR = 1 after 24 months, using the adjusted BSC weibull curve in this scenario), the extra cost of regorafenib is $56,592 and the extra clinical effect is 0.310 QALYs, which increases the estimated incremental cost-effectiveness ratio to $182,536 / QALY gained. Note: Regorafenib was used beyond progression in the trial and this is expected in clinical practice. The cost was included in the model. The upper limits of the 95% CIs of first and secondary progression-free survival from the clinical trial sum to 15 months.
- Using the planned dose of 160 mg daily rather than the mean daily dose of 139 mg from the trial, the extra cost of regorafenib is $64,197; the extra clinical effect is 0.333 QALYs and the ICER increases to $192,683 / QALY gained.
- Combining the above two scenarios, the extra cost is $63,649, the extra clinical effect is 0.310 QALYs, and the ICER is $205,299 / QALY gained.

Note: To reiterate, the estimate above "assuming the OS benefit for regorafenib is attenuated" is based on the more clinically plausible approach of applying a HR of 1 to the adjusted BSC weibull curve – meaning the regorafenib outcomes would decline over time, rather than BSC outcomes improve. See Section 2.2.3 for more details. The proportional hazards assumption was valid within the trial (1 year duration), however, it is unlikely that the benefits will continue indefinitely, and that proportional hazards would hold for the remainder of the model time horizon (10 years). Given that the upper limits of the 95% CIs for both PFS and secondary PFS were well below 24 months, assuming no further treatment benefits beyond 24 months (and continuing to run the model for the 10 year horizon) was considered fair and reasonable.

Lastly, **without adjusting for crossover** in the BSC arm, the extra cost is between $54,728 and $56,182 and extra clinical effect of regorafenib is between 0.185 and 0.268 QALYs, which increases the estimated ICER to between $209,310 and $295,370 / QALY gained. While the OS results in the clinical trial were not significant, it is reasonable to need to account for crossover in some way. The ICER estimates based on unadjusted survival are provided to address uncertainty in crossover adjustment methods.

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Bayer, when regorafenib is compared with BSC:

- The extra cost of regorafenib is $61,286 (ΔC). Costs considered in the analysis included drug acquisition and management costs, costs for adverse events, supportive care, and end of life costs.
- The extra clinical effect of regorafenib is 0.586 quality-adjusted life years (ΔE) or 0.820 life years gained (LY). The clinical effect considered in the analysis was based on extrapolated GRID trial data, adjustment for crossover in the BSC group, utilities for progression-free and progressed states obtained from the GRID trial, and a time horizon of 10 years.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $104,660 / QALY gained or $74,784 per LY gained.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The main difference was the OS estimates used in the model. The GRID trial reached its primary endpoint of PFS with more than 75% of patients alive, meaning that OS required substantial extrapolation in the model. To extrapolate the OS data, it was assumed in the submitted model that patients in each group would experience a constant risk of death over time (exponential distribution). The Submitter used external data from ECOG PS 0-1 patients reported in the poster by Seddon et al (2008) to justify the extrapolation. However, the Seddon study was for GIST patients starting 2nd line therapy with sunitinib. While the patient groups are similar, the timing differs; the prognosis at the initiation of an earlier line of therapy is clearly better than at the setting relevant to this review. It is not appropriate to use the survival curve from the initiation of 2nd line therapy to validate

the survival curve for patients starting 3rd line therapy. The resulting OS curves used in the submitted model appeared to be overestimated, according to the CGP and proper interpretation of the 2nd line natural history data to the context of this review. An appropriate alternative and more plausible approach to project survival (weibull distribution) was chosen to extrapolate OS for the reanalysis, and the uncertainty around the estimates of OS was explored based on this main modification.

See **Figure 4** in section 2.2.1., which demonstrates that both approaches (weibull and exponential distributions) fit the regorafenib data from the trial and the crossover-adjusted BSC data, but lead to very different long-term OS trajectories. See also the related discussion in section 2.2.1 for more detail about the appropriateness of the modification, and **Figure 6** for the implications of this modification on model outcomes.

Note: The 10 year time horizon was not changed in the model, though sensitivity analysis was conducted for a 5 year horizon, since the Clinical Guidance Panel suggested survival beyond 5 years may not be plausible. Clinical data based the SEER database suggest 5 year survival of 13% for metastatic GIST (Tran et al 2005) and the submitter estimates from diagnosis of metastatic GIST to initiation of 3rd line treatment is approximately 2 years (BIA Submission). Thus, 15% of the cohort alive in the submitted model at 5 years is not likely plausible, further suggesting the model survival curves are overestimated. The time horizon cannot be too long in a model that projects realistic survival estimates, as there are no further incremental gains to influence the results regardless of how long you look. Thus, the underlying issue is the plausibility of the OS curves used in the model. The submitted model was sensitive to the time horizon chosen, but when using the more plausible weibull OS curves, changing the time horizon did not have a large impact on the ICER, since few patients survive beyond 5 years (using weibull curves, 5 year horizon $174,082 / QALY gained, vs. 10 year horizon $171,436 / QALY gained), which further supports the EGP's best estimates. The time horizon is not described at any point in the report as potentially being as short as two years. In addition, the EGP use of the planned dose as compared to the average trial dose to provide an upper boundary in the re-analysis estimates was consistent with the approach used in previous pCODR reviews.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Patients were concerned with treatment efficacy, side effects and quality of life experienced on treatment. The model captured treatment efficacy and quality of life due to health state. Quality of life due to AEs were not included, because the quality of life data obtained from a subset of patients in the GRID trial did not find a difference in quality of life due to treatment group, within PF and progressed health states. Thus, the quality of life for each health state was captured using pooled estimates from the two treatment groups, with no other differences. Liver toxicity and hepatic failure, rare AEs associated with regorafenib, were not included in the model (either costs or outcomes).

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

The submitted partitioned survival model structure was inadequate. A partitioned survival model uses the area under the OS curves to determine the average survival durations for each treatment group. Since the GRID trial duration was short relative to the expected survival, the OS data available to inform the model were immature and required substantial extrapolation. In many cases, e.g. when most of the gains occur in the early

portion of the model, when extrapolations do not predict considerable extra benefit, or when more mature OS data exist, the partitioned survival structure may be considered. However, in this case the projected OS curves in the main analysis did not appear to be clinically plausible, predicting longer than expected survival times, particularly for regorafenib. Given that the Kaplan Meier OS curves appear to diverge but the tails cross (See **Figure 4** in Section 2.2.1), it is unclear what overall benefit would be expected over time, but at some point patients will discontinue treatment and should not continue to experience added gains. Furthermore, the analysis did not capture the uncertainty in the OS benefit, meaning that despite non-significant hazard ratios for both the unadjusted and crossover-adjusted data, the model always projects an OS benefit for regorafenib. As a result, using the partitioned survival structure to evaluate the benefits for this circumstance is challenging because it assumes the benefits while on the drug are equal to the benefits once treatment is stopped, and the outcomes for patients in later stages (i.e. following treatment discontinuation) cannot be modified separately. In short, it is not possible to address the implicit assumption that there are continued long-term OS gains. The EGP modified the structure to explore the impact of extrapolated portion of the model on the benefits obtained from regorafenib, using hazard ratios (see above for modifications to the main analysis, as well as section 2.2.3). The modifications produced higher ICER estimates than the submitted model.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The assumptions about the shapes of the extrapolated OS curves have the largest impact on the results. The submitter used estimates that assumed constant risks of death and that the benefits of regorafenib continued throughout the duration of the model. Changing these assumptions increased the ICER and produced more clinically plausible OS estimates.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

The data sources appeared to be appropriate. The GRID clinical trial was used for clinical outcome and utility data. Health state and management costs were based on an economic evaluation of sunitinib, which did not describe the costing in detail, but generally seemed reasonable. The regorafenib drug costs were modified by the EGP to include the planned dose rather than the mean daily dose from the clinical trial to address potential wastage. The estimates for survival in the BSC arm were based on crossover adjustment using two similar statistical techniques (main estimate formed using Iterative Parameter Estimation). The EGP could not fully assess or reproduce the approaches used to adjust for crossover, and the adjusted HR was also not statistically significant, so there is some uncertainty in the estimates of adjusted BSC curves. Of note, the Seddon natural history data used for external validation of the survival estimates are not appropriate, as they represent survival from the initiation of 2nd line therapy, which has a better prognosis than the 3rd line setting relevant to this review.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The estimates for incidence of GIST (age-adjusted rate of 0.68/100,000), market share (90% of eligible patients) and the duration of treatment (7.7 months) have large impacts on the model.

What are the key limitations in the submitted budget impact analysis?

The estimates for incidence of GIST, based on a US study, were on the lower end of the global range and are the most influential to the model. It is assumed that 50.4% of patients diagnosed and surviving two years would be eligible for treatment (70% of patients failing sunitinib); these estimates may be validated directly using local treatment volumes for imatinib and sunitinib.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

Use of a Markov model and incorporation and additional exploration of the uncertainty in the OS estimates would improve the economic evaluation.

Is there economic research that could be conducted in the future that would provide valuable information related to regorafenib for metastatic GIST?

The model would benefit from more mature OS data to reduce the uncertainty in the OS estimates.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Final Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Gastrointestinal Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of regorafenib (Stivarga) for GIST. A full assessment of the clinical evidence of regorafenib (Stivarga) for GIST is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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