
# pan-Canadian Oncology Drug Review
# Final Economic Guidance Report

# Regorafenib (Stivarga) for Metastatic Colorectal Cancer

**November 15, 2013**

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# FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Background

The main economic analysis **submitted to pCODR by Bayer Inc** compared regorafenib (STIVARGA®) to Best Supportive Care (BSC) for patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. Regorafenib 160 mg once-daily is administered orally. BSC was based on the CORRECT trial and included any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or antineoplastic chemo/hormonal/immuno-therapy during the active treatment phase of the trial.

**According to the pCODR Clinical Guidance Panel (CGP)**, this comparison is appropriate.

One **patient advocacy group**, Colorectal Cancer Association of Canada, provided input on regorafenib for the treatment of metastatic colorectal cancer. The following factors were identified as being relevant to the economic analysis: prolonging progression-free survival allowing for extended control of their disease, and an improved quality of life. Patients also stated that they are willing to tolerate moderate to significant side effects during their treatment in exchange for potential benefit. Patients also stated a preference for choice and flexibility in selecting treatments to manage their disease and to maintain their quality of life. The submitted model somewhat addresses the concerns of patients through the use of QALYs as an endpoint. The full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

The **Provincial Advisory Group (PAG)**: Input on the regorafenib review was obtained from nine of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, regorafenib is a drug that may offer a treatment options to patients that currently do not have one. PAG noted the oral route of administration may improve accessibility for patients that are already very sick. Other enablers to implementation included the potential for minimal drug wastage and the ease in dose reduction as regorafenib comes in one standard dose.

PAG noted several barriers to implementation including: the dosing schedule of regorafenib requiring 3 weeks on and 1 week off treatment, a potential for indication creep if patients and oncologists request to receive regorafenib in earlier lines of therapy, a potential for increased incremental costs in terms of increased pharmacy workload and monitoring of toxicities, and, if all patients in this setting become eligible to receive regorafenib, the size of the patient population will be large. In addition, the Black Box warning advising of severe liver toxicity and hepatic failure sometimes resulting in death was noted necessitating hepatic monitoring. Some, but not all, of the PAG concerns were addressed by the economic model.

At the confidential price provided by the submitter, regorafenib costs $[redacted] per 40 mg tablet. At the recommended dose of 160 mg (4 tablets) daily for 3 weeks, followed by 1 week off treatment, the average daily cost is $[redacted] and the average cost per 28-day course is $[redacted]. At the list price, regorafenib costs $74.25 per 40 mg tablet. At the recommended dose of 160 mg daily for 3 weeks, followed by 1 week off treatment, the average daily cost is $297.00 and the average cost per 28-day course is $6237.00. *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)*

The list price of regorafenib was not used in the manufacturer's economic model. The manufacturer's economic analysis was based on the confidential price of regorafenib, but also included an 8% mark-up on this price, which may not be observed in all provinces, and which inflates the daily cost of regorafenib. On the other hand, the analysis assumed a dose intensity of 78.9% (based on the CORRECT trial), which substantially lowers the daily cost of regorafenib but does not account for potential wastage as regorafenib is available in packages of 28 tablets.

## 1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio is **$365,830 per QALY** (between **$323,211** and **$404,227)** when regorafenib is compared with Best Supportive Care (BSC).

The incremental cost-effectiveness ratio was based on an estimate of an additional cost of $17,888 and an extra clinical effect 0.05 of regorafenib over BSC. The ICER was highly sensitive to very small changes in the incremental clinical effect.

The EGP's best estimate of:

- The extra cost of regorafenib is between **$15,804** and **$19,765**. The main factors influencing $\Delta C$ are the time horizon and dose intensity.
- The extra clinical effect of regorafenib is about 0.05 QALY. The main factors influencing $\Delta E$ are changes in time horizon and OS estimation.

**The EGP based these estimates on the model submitted by Bayer Inc. and reanalyses conducted by the EGP.** The reanalysis conducted by the EGP using the submitted model revealed that:

- When the intensity of the dose of regorafenib is changed to 90% (from 78.9% in the submission), to account for potential wastage, the extra cost of regorafenib increases from $17,493 (base case) to $19,577 per patient for patients receiving regorafenib plus BSC versus BSC alone, which increases the estimated incremental cost-effectiveness ratio to $212,539 per additional QALY

- When the model time horizon is changed from 10 years to 5 years, the extra cost of regorafenib is $17,351 and the extra clinical effect is 0.09 QALY, which slightly increases the estimated incremental cost-effectiveness ratio to $196,112 per additional QALY.

- When the estimated lognormal distribution is adjusted by changing the intercept beyond the first year to have a better fit to the trial data and considering a 5 year time horizon, the extra cost of regorafenib is $15,804 and the extra clinical effect is 0.05 QALY which increases the estimated incremental cost-effectiveness ratio to $323,211 per QALY.
- When the estimated lognormal distribution is adjusted by changing the intercept beyond the first year to have a better fit to the trial data and considering a 5 year time horizon with 100% of the intensity of the dose, the extra cost of regorafenib is $19,765 and the extra clinical effect is 0.05 QALY which increases the estimated incremental cost-effectiveness ratio to $404,227 per QALY.
- When the estimated lognormal distribution is adjusted by changing the intercept beyond the first year to have a better fit to the trial data and considering a 5 year time horizon with 90% intensity dose, the extra cost of regorafenib is $17,888 and the extra clinical effect is 0.05 which increases the estimated incremental cost-effectiveness ratio to $365,830 per QALY.

**The EGPs estimates differed from the submitted estimates.**

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

- The extra cost of regorafenib is $17,493. Costs considered in the analysis included routine care, adverse event management, treatment administration and dispensing fees.
- The extra clinical effect of regorafenib is 0.09 quality-adjusted life years or 0.15 life years gained (approx. 1.8 months). The clinical effect considered in the analysis was based on the overall survival and progression-free survival from the CORRECT trial.(1) PFS and OS were extrapolated beyond the end of the CORRECT trial follow-up. The model's clinical estimates are greatly affected by the methods and assumptions used in the extrapolation.

As such, the submitter estimated that the incremental cost-effectiveness ratio was $189,914 per QALY gained or $124,338 per LY gained.

According to the probabilistic sensitivity analysis submitted by the manufacturer, the chance that incremental cost-effectiveness ratio for regorafenib is less than $100,000 per QALY is 3% and the probability of this ratio being less than $150,000 per QALY is approximately 28%.

## 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?**

- In reanalysis, the time horizon was shortened from 10 years to 5 years as per recommendations from the Clinical Guidance Panel (CGP)

- As is discussed below, the log-normal function used to extrapolate OS beyond the end of the CORRECT trial follow up doesn't fit the observed data in the trial beyond one year. Rather than make an assumption based on a super-imposed distribution (log-normal) as in the manufacturer's model, the EGP attempted a sensitivity analysis by manually fitting the survival curve using available CORRECT trial data. As such, the EGP adjusted the log-normal distribution to get a better fit to the observed data by changing the intercept to more closely match the trial data after the 350 days. The intercept was systematically adjusted by 1-3% at various time points to get a smooth fit to the actual data. The resulting change in QALYs was small but had a large impact on the ICER because the ICER was highly sensitive to very small changes in the incremental effect.

- EGP has changed the dose intensity from 78.9 % to 90%. The EGP considered that patients would likely be dispensed more medication than they would use in situations of non-adherence, dosage reduction, or discontinuation of the medication. As such, this medication would be wasted and higher dosage intensity was used to take this into account.

- In addition, the manufacturer added an 8% mark-up to the cost of regorafenib, which inflates the cost per package. This mark-up will not be present in all provinces and increases the over-all cost of the therapy. However, reanalyses by the EGP removing this mark-up did not significantly impact the ICER.

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

For the most part, important factors to patients are adequately addressed in the submitted model. These important factors for patients are overall survival, progression free survival and quality of life. Overall survival beyond the clinical trial follow-up has been extrapolated to the time horizon of 10 years but the method used to extrapolate overestimated OS.

For quality of life, utility weights from the EQ-5D data in the CORRECT trail have been used in the model and there is high likelihood that QALY loss due to adverse events associated with regorafenib is not adequately reflected in the EQ-5D data.

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

The submitted Excel file lacks a comprehensive input sheet which made it difficult for the EGP reviewer(s) to change the model parameters and study the effect of changes on model outcome. As such, the model supplied was not flexible enough to do full testing by the EGP. However, the EGP was able to conduct reanalyses on the key variables in the economic 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?**

***(1) Overall survival extrapolation (see figures, section 2):***

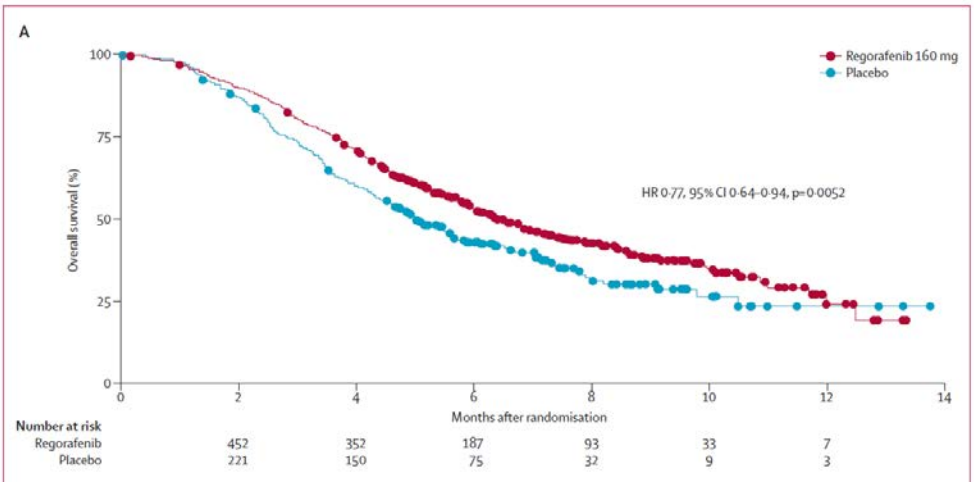
The manufacturer's model applied an extrapolation to estimate PFS and OS beyond the end of the CORRECT trial (1) follow-up using a log-logistic distribution for PFS and a log-normal distribution for OS. Based on AIC that they present in Table A1.2 on page 71 of the Economic Model Technical Report, the lognormal distribution was deemed to be the best fit (lowest AIC value) compared to the Weibull, log-logistic and exponential distributions.

However, the lognormal distribution used to estimate the OS data doesn't fit the observed data (appendix fig 2) in the trial. It can be seen from the CORRECT trial published paper (1) that after 12 months the survival rates for regorafenib and BSC arms are equal. But in the submitted model, the fitted log normal function consistently overestimates OS for regorafenib and applies a survival advantage over BSC. To further illustrate this point, please consider the following:

- The CORRECT trial has a time horizon of 413 days for BSC and 401 days for regorafenib. The submitted analysis estimates PFS and OS beyond the end of the CORRECT trial follow-up using the observed 12 month data using a log-logistic distribution for PFS and the log-normal distribution for OS.

- However, as we can see from the survival curve from the CORRECT trial (Fig1 below), at 12 months, the survival rates for regorafenib and BSC arms are equal and after 12 months, the survival is worse for regorafenib than BSC.

Fig1:OS curve from CORRECT trial




- However, the same trend in estimated log-normal function is not presented in the model. In Fig 2, the OS estimated in the submitted model always shows better survival rate for regorafenib compared to BSC over the whole period (even beyond 12 months) (Fig-2). This result is because only the first 12 months (371 days) of data is used to fit the survival function.

- When the fitted cure is compared to the estimated curve for survival rates, beyond 12 months there is a consistent overestimation of the OS rate of regorafenib (Fig3). As such, we have adjusted the fitted curve to allow a better

estimate for overall survival rate of regorafenib compared to BSC (Fig4) across the entire time period (ie. beyond 371 days).

The Submitter expressed concerns with the reanalyses conducted by the EGP since the submitted model had incorporated an extrapolation of OS using all of the clinical trial data (17 month of follow-up) and the best fitting log-normal curve. The EGP reviewed additional data reported in an ESMO abstract that uses the 17 months of follow-up. However, the EGP concluded that this data did not change the EGPs estimates because the key issue is that the log-normal distribution that was applied still does not fit the observed Kaplan-Meier survival data. In the manufacturer's extrapolations of OS, the estimates of survival for regorafenib are always optimistic post one-year. However, as can be seen in Figure 1, the observed survival data from the trial suggest that there may be scenarios where survival is worse for regorafenib than BSC. The EGP reanalyses were intended to explore this uncertainty in the model.

The ESMO abstract reported an OS rate of 24.1% at 12 months for regorafenib while the fitted distribution used by the manufacturer is more optimistic and predicts that the OS rate at 12 months (364 days) would be 26.2%. In the manufacturer's analysis, this higher survival rate is further perpetuated by the leveling off of the extrapolated survival curve. However, the EGP considered that based on the Kaplan-Meier survival curves provided by the manufacturer, OS for regorafenib drops to 19% at 375 days. This potential decline in survival is never captured in the submitter's modeling. Therefore, the EGP determined it was important to conduct sensitivity analyses around these OS assumptions.

Because this potential decline in survival was still not captured in the submitter's economic analysis, the EGP considered that the data presented in the ESMO abstract does not impact the EGP's estimates of the ICER by an appreciable amount and would remain at approximately $340,000 per QALY.

***(2) Dose intensity and potential for wastage***

There is no real world evidence to support the assumption in the model to use a dose intensity of 78.9% as observed from the trial. This value doesn't represent clinical practice as the issue of waste has not been factored into the analysis. As such, the EGP has conducted a sensitivity analysis for different levels of dose intensity as follows:

| Dose intensity | ICER |
|---|---|
| 78.90% | $323,211 |
| 85% | $346,632 |
| 90% | $365,830 |
| 95% | $385,028 |
| 100% | $404,227 |

***(3) Adverse events (AEs)***

Regorafenib has extensive adverse events (AEs) which are listed in Table 3 of the manufacturer's report. It is reported in both the HE model and CORRECT trial that the death rate due to AEs (not associated with disease progression) is 1.6% for regorafenib comparing to 1.2% for BSC. However, the manufacturer's model does not consider QALY detriments due to higher AEs associated with regorafenib compare to BSC. The report argues that "the utilities were derived from EQ-5D data obtained throughout the CORRECT trial, which were completed

by patients who were receiving treatment. Therefore, the effect of treatment-related AEs is already reflected in their responses."

There is a high likelihood that QALY loss due to AEs is not adequately reflected in the EQ-5D results of the CORRECT trial. The reason for this is twofold: 1) the EQ-5D lacks specific domains that might be impacted by the adverse events; 2) the EQ-5D was only administered at set times of the trial and has a one-day reflection period (i.e. "How is your health today"). A recent report conducted in HIV showed that this recall period can be problematic in assessing adverse events in clinical trials.(2)

**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?**

No. For clinical effectiveness, the manufacturer's model does not consider QALY loss due to higher AEs associated with regorafenib compare to BSC. Also the method used to extrapolate overall survival doesn't fit the actual data from the CORRECT trial beyond one year.

Unsupported assumptions and issues in methods used in extrapolating OS data that form the bases of regorafenib's advantages over BSC make the submitted model results highly uncertain. Very small changes in the incremental effect, when estimated as quality-adjusted life years, have a large impact on the ICER. Based on the results observed in the CORRECT trial, a 1.4 months survival advantage (or about 0.12 LY gained) was demonstrated for regorafenib. However, the manufacturer's economic analysis estimated a greater advantage of 0.15 LY gained.

## 1.4 Summary of Budget Impact Analysis Assessment

**What factors most strongly influence the budget impact analysis estimates?**

Regorafenib market size (number of eligible patients), market shares and drug costs estimates and assumptions regarding eligibility for coverage under provincial drug plans are the factors that the budget impact analysis is largely based upon.

The manufacturer's BIA assumes a 10% coverage rate for 18-65 year old patients. If we assume that 100% of patients will be funded, then budget impact will increase by 80%.

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

The major limitations in the BIA model are mainly due to assumptions made in calculating regorafenib market size and market shares. In the submitted BIA model, it is assumed that in order to be eligible for treatment, patients must survive for 2 years after their diagnosis. So for any each BIA model year, the number of eligible patients (market size) is based on the patient population who has been diagnosed two years prior to the BIA model year. For example, in the BIA base year 2013, the year of diagnosis is 2011 and so on. However, this assumption doesn't seem justifiable as the cohort of patients who have been diagnosed more than 2 years prior to base year (for 2013, patients who have been diagnosed in 2010 and 2009) and survived to the BIA base year are not considered. Since the 5 year survival rate for stage IV is 8%, there would be additional patients receiving therapy and this assumption will lead to an underestimate of the number of eligible patients.

Also, for market share, it is assumed that in the first year of listing regorafenib, [redacted]% of KRAS Wild Type and [redacted]% of KRAS Mutation Positive patients will undergo this therapy. Remaining patients of this year, who are not treated by regorafenib and who survive to the next year are eligible for the drug and should be added to the next year's market size. Considering that there is no other competing therapy for these patients beside BSC, it seems reasonable that many would receive regorafenib in following years. *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)*

Some other assumptions like the transition rate from early stage of disease to stage IV still need to be validated.

There is lack of evidence to support assumptions regarding the market share which the results of the BIA model are sensitive to. As a result there are lots of sources of uncertainty surrounding the BIA model's result and due to the model structure; it is very difficult for EPG to re-analyze the model considering all these changes.

## 1.5 Future Research

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

The submitted economic model could be improved in a number of ways.

- Firstly, the modeling of OS beyond the CORRECT trial time horizon should have more closely adhered to the data. As the OS in the submitted model was based upon fitting a log-normal distribution to the data, which did not reflect the observed Kaplan Meier curves from the CORRECT trial, an improvement to the economic model could be facilitated by using actual survival data beyond 12 months. The EGP attempted to use the reported CORRECT trial data for the re-analysis and manually fit the survival curve. However, there are limitations to this approach and more accurate estimates could be provided by conducting additional analyses using the underlying raw data.
- Secondly, the economic analyses should have considered the serious adverse events associated with regorafenib beyond just considering the EQ-5D clinical trial data.
- Finally, a more realistic view of dose intensity should have been implemented in the model with a full sensitivity analysis conducted around this variable.

**Is there economic research that could be conducted in the future that would provide valuable information related to regorafenib**

A prospective assessment of the long-term OS of patients receiving regorafenib would be valuable.

# 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 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 metastatic colorectal cancer. A full assessment of the clinical evidence of regorafenib (Stivarga) for metastatic colorectal cancer 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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