PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Regorafenib (Stivarga) for Metastatic Colorectal Cancer

July 16, 2015

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

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.

INQUIRIES

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

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Bayer** compared regorafenib plus best supportive care to placebo plus best supportive care for patients with metastatic colorectal cancer (mCRC) 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 is administered orally.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate as there is no standard of care for these patients.

Patients considered the following factors important in the review of regorafenib, which are relevant to the economic analysis: adverse events, the impact of adverse events on quality of life, disease stability, and having a choice of therapy in advanced lines. The economic model incorporated these factors as adverse events, quality of life, overall survival and progression-free survival.

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.

Potential enablers to the implementation of regorafenib include:

- Availability of another treatment option;
- Ease of dose adjustments, if necessary; and
- Oral drug that can be delivered to patients more easily than intravenous therapy.

Potential barriers to the implementation of regorafenib include:

- Safety profile, including a black box warning and subsequent monitoring of patients for these adverse events;
- Potentially large patient population, with the possibility of indication creep; and
- Possibility of wastage given that the tablets are only stable for 28 days after opening.

The above enablers and barriers have been accounted for in the economic model and budget impact analysis.

At the list price, regorafenib costs $72.62 per 40 mg tablet. At the recommended dose of 160 mg daily for 21 days of a 28-day cycle, the average cost per 28-day course is $6,100.08. At the confidential price provided by the submitter, regorafenib costs $[redacted] per 40 mg tablet. At the recommended dose of 160 mg daily for 21 days of a 28-day cycle, the average cost per 28-day course is $[redacted]. (*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*.)

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is $188,537 when regorafenib plus best supportive care is compared with placebo plus best supportive care.

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 $15,660 (ΔC). The factors that most influence cost in this economic analysis are treatment duration, dose intensity and drug cost.
- the extra clinical effect of regorafenib is 0.083 (ΔE). The factors that most influence effects in this economic analysis are overall survival, treatment duration and the time horizon.

The EGP based these estimates on the model submitted by Bayer and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- The overall survival hazard of regorafenib equals that of the placebo group after 518 days (when trial follow-up has ended), the extra cost of regorafenib is $13,146 ($\Delta C_1$) and the extra effect is 0.078 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $168,711 (from $158,283).
- Treatment duration is until disease progression or death (instead of the observed treatment duration in the clinical trial), the extra cost of regorafenib is $15,923 ($\Delta C_2$) and the extra effect is 0.090 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $177,215 (from $158,283).
- The best case estimate of the above two parameters is $188,537.

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Bayer, when regorafenib plus best supportive care is compared with placebo plus best supportive care:

- the extra cost of regorafenib is $13,409 (ΔC). Costs considered in the analysis included treatment cost, medical resource utilization, and adverse events.
- the extra clinical effect of regorafenib is 0.085 quality-adjusted life years and 0.128 life years gained (ΔE). The clinical inputs considered in the analysis were based on overall survival, progression-free survival, adverse events, dose intensity, treatment duration, wastage and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $158,283.

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 ICER differs because the EGP incorporated two changes. The first change is the inclusion of a parameter where survival following the end the trial is equal for both regorafenib and the placebo. This allowed the EGP to incorporate uncertainty in the overall survival estimate, given that follow-up was not complete at the data cut off point.

The second change is the incorporation of treatment duration being until progression or death, and not based solely on the treatment duration observed in the clinical trial.

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

Yes, factors that are important to patients were adequately addressed in the submitted economic analysis. These factors include adverse events, quality of life, and survival (both progression-free and overall).

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

Yes, the design and structure of the model are adequate for summarizing the evidence. The EGP was able to manipulate the model structure to examine the uncertainty in the data inputs.

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?

Many of the inputs in the economic model came from the clinical trial, with scenario analyses provided. The submitter assumed that subsequent treatments should not be included; the CGP confirmed that this is an appropriate assumption. Medical resource utilization was based on expert opinion, however, these costs had little impact on the ICER.

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?

Yes. The clinical inputs came from a head-to-head clinical trial. However, survival data was not complete at data cut off. The EGP tried to account for some of this uncertainty in their best estimate, by having the survival benefit between the two treatment arms be equal once follow-up from the trial was done. Further, though a clinical trial is an adequate source of data, given that a trial setting does not always reflect real world setting, the EGP, based on feedback from the CGP, incorporated a change in treatment duration. The cost inputs were adequate, and the EGP did not need to change any for the best estimate.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

Aside from cost of regorafenib, the factors that most strongly influence the budget impact analysis include the percentage of people aged 18-64 who are eligible for coverage if funding were recommended for regorafenib, and the market share of regorafenib. Other factors that also influence the budget impact analysis are the distribution of new diagnosed cases of colorectal cancer and the % of patients with an performance status of less than or equal to 1.

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

In addition to the assumptions noted above, the key limitations included that data on the number of prevalent cases of Stage IV CRC were not available, and therefore incidence and mortality rates were estimated. The BIA also assumes that 40% of patients are KRAS mutation positive tumors and 60% are KRAS wild type tumors. These parameters were able to be modified and explored by the EGP.

1.5 Future Research

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

Given the side effects of regorafenib, incorporating dose reductions into the structure of the model could be a potential improvement. The impact on quality of life from side effects could also be modeled by incorporating utility decrements.

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

It is always preferable to wait until data collection is complete on survival data given that this data is then extrapolated, which introduces further uncertainty.

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 Endocine 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 for mCRC. A full assessment of the clinical evidence of Regorafenib for mCRC 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.cadth.ca/pcodr).

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. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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.cadth.ca/pcodr). 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.

REFERENCES

1. Grothey A, Van Cutsem E Fau - Sobrero A, Sobrero A Fau - Siena S, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. 20130128 DCOM- 20130207 (1474-547X (Electronic)).

2. National Centre for Pharmacoeconomics Ireland. *Regorafenib (Stivarga®) for mCRC.* 2014.