pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Regorafenib (Stivarga)

Submitted Funding Request:
The treatment of 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

Submitted By:
Bayer Inc.

Manufactured By:
Bayer Inc.

NOC Date:
March 11, 2013

Submission Date:
March 22, 2013

Initial Recommendation Issued:
August 29, 2013

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) does not recommend funding regorafenib (Stivarga) in patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. The Committee made this recommendation because, compared with placebo, regorafenib had only a modest overall survival and progression-free survival benefit, no quality of life improvement, significant toxicities and was not cost-effective.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

pERC noted that metastatic colorectal cancer is the second most commonly diagnosed malignancy. pERC noted that there are limited effective treatment options for these patients at a late stage of disease after exhausting all other standard treatment options. pERC noted that patients would currently be given best supportive care after being treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. pERC discussed that patients who are not KRAS wild type have fewer treatment options. pERC discussed that the life expectancy of these patients from the time of diagnosis is approximately two years and is even shorter once all treatment options have been exhausted. Therefore, pERC considered there is a need for more effective treatments that extend overall survival while improving quality of life.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

One double-blind randomized controlled trial (CORRECT, Grothey 2013) compared regorafenib plus best supportive care with placebo plus best supportive care in patients with metastatic colorectal cancer. pERC noted that these were patients who had been previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. pERC acknowledged that the pCODR Clinical Guidance Panel considered that there was a net clinical benefit. However, pERC discussed that the magnitude of the absolute benefit in median overall survival (6.4 months versus 5.0 months, respectively) and in median progression-free survival (1.9 months versus 1.7 months, respectively) was modest for regorafenib compared with placebo. pERC also considered that quality of life measures were similar between the regorafenib and placebo groups. pERC discussed the toxicity profile of regorafenib based on the results of the CORRECT study. It was noted that there were more grade 3 treatment-related adverse events and more fatal hepatic events with regorafenib compared with placebo. Other adverse events that were more common with regorafenib included fatigue, hand-foot syndrome, hypertension, diarrhea and rash. Therefore, considering all of these factors, pERC was unable to conclude that there was an overall net clinical benefit associated with regorafenib.

pERC deliberated upon patient advocacy group input, which indicated that patients value extending life while maintaining quality of life. pERC acknowledged that as an oral therapy, regorafenib could provide patients easier access than intravenous therapies. However, pERC considered that the magnitude of overall survival and progression-free survival benefit from the CORRECT study was very modest. pERC also discussed that the CORRECT study demonstrated that regorafenib did not improve quality of life compared with placebo and that there were important side effects associated with regorafenib. Therefore, pERC considered that regorafenib only partially aligned with patient values.

pERC deliberated upon the cost-effectiveness of regorafenib. pERC reviewed the incremental cost-effectiveness estimates provided by both the manufacturer and the pCODR Economic Guidance Panel (EGP) and noted that regorafenib was not cost-effective in both estimates. However, pERC noted that the EGP estimates were considerably higher than the manufacturer's estimates and discussed the assumptions upon which the EGP estimates were based. The EGP estimates had assumed a 5 year time horizon compared with a 10 year time horizon in the manufacturer's analysis. pERC agreed that given the short life expectancy of this patient population, 5 years was more appropriate and considered that an even shorter time horizon such as two years could also be considered. The EGP estimates also accounted for potential wastage of regorafenib. In considering input from the pCODR Provincial Advisory Group, pERC agreed that wastage could occur, as with all oral medications, but could be greater for regorafenib due to how it is packaged. Therefore, pERC considered that this would lead to slightly higher estimates of the incremental cost effectiveness ratio than the manufacturers' estimates. pERC further discussed that one of the main factors affecting the EGP's cost-effectiveness estimates was the extrapolation of survival after the first 12 months. This led to a lower estimate of incremental effect compared with the manufacturer's estimate (0.05 versus 0.09 QALYs gained). pERC noted that these small changes in the

estimates of incremental effect had a large impact on the ICER estimates. pERC discussed the uncertainty associated with estimating the overall survival after 12 months and agreed that the survival benefit was likely not as favourable as the manufacturer had estimated. Therefore, considering all these factors, the incremental cost-effectiveness ratio is likely higher than the manufacturer's estimate.

pERC discussed factors that could impact the feasibility of implementing a funding recommendation for regorafenib and noted that regorafenib is likely to be an additional, sequential therapy in the treatment of patients with metastatic colorectal cancer. Therefore, it will not likely replace other therapies and overall treatment costs could be expected to increase if it were funded. pERC also noted that in provinces where anti-EGFR therapies (cetuximab and panitumumab) are not currently funded, the budget impact of regorafenib would be larger. pERC further discussed input from the pCODR Provincial Advisory Group that due to the packaging of regorafenib in 28-tablet bottles, the potential for wastage was higher than for oral drugs that are blister-packed. However, pERC noted that this wastage was still likely less than what would be observed with intravenous drugs.

EVIDENCE IN BRIEF

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing clinical context, an evaluation of the manufacturer's economic model and budget impact analysis, guidance from pCODR clinical and economic review panels, input from one patient advocacy group (Colorectal Cancer Association of Canada) and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of regorafenib compared to standard care options or placebo in 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

Studies included: one randomized controlled trial

The pCODR systematic review included one double-blind randomized controlled trial (RCT), the CORRECT study (Grothey et al 2013), which evaluated the safety and efficacy of regorafenib (N=505) compared with placebo (N=255). Regorafenib 160mg was given once daily for 3 weeks followed by 1 week off treatment. All patients received best supportive care (BSC). No crossover was permitted between treatment groups until after the pre-specified efficacy criteria were met at the second interim analysis.

Patient populations: patients with ECOG performance status 0 or 1

Patient characteristics appeared to be balanced between the two groups in the CORRECT study. Patients had a median age of 61 years and an ECOG performance status of 0 or 1. pERC discussed that patients with ECOG performance status of 2 or greater were not included in the study but noted that due to the unfavourable toxicity profile of regorafenib, treatment with regorafenib would not be likely in patients with a lesser performance status.

All patients in the study had previously been treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti VEGF therapy and, if KRAS wild type an anti-EGFR therapy. Fifty four percent and 63% of patients had a KRAS mutation in the regorafenib and placebo arms, respectively. The majority of patients had also received ≥4 prior systemic anti-cancer therapies.

Key efficacy results: modest overall survival and progression-free survival benefit

Key outcomes deliberated on by pERC included overall survival, the primary endpoint of the CORRECT study, and progression free survival (PFS). pERC noted that at the second interim analysis, the pre-specified conditions for efficacy and for stopping the study were met. The median overall survival was 6.4 months and 5.0 months in the regorafenib and placebo group, respectively (HR=0.77, 95% confidence interval (CI) 0.64 to 0.94). The median PFS was 1.9 months and 1.7 months in the regorafenib and placebo

group, respectively (HR=0.49, 95% CI 0.42 to 0.58). pERC acknowledged the pCODR Clinical Guidance Panel's conclusions that there was a net clinical benefit to the use of regorafenib. However, pERC discussed the magnitude of the benefit in overall survival and PFS conferred with regorafenib (1.2 and 0.2 months, respectively) and considered that this benefit was very modest.

Quality of life: no improvement in quality of life compared with placebo

Health related quality of life was assessed in the CORRECT study using EORTC QLQ-C30 and EQ-5D measures. pERC noted that results at end of treatment indicated a similar decline in patients' quality of life in both the regorafenib and placebo groups. pERC acknowledged that based on patient advocacy group input, quality of life was an outcome important to patients and that a similar decline in quality of life in both the regorafenib and placebo arm only partially aligned with patient values.

Safety: hepatic toxicity and dose modifications due to adverse events required

pERC deliberated on the safety data available from the CORRECT study. It was noted that adverse events that occurred more frequently in patients treated with regorafenib included hand-foot skin reaction, fatigue, diarrhea, hypertension and rash or desquamation. pERC also discussed that there were serious toxicities associated with regorafenib and that dose modifications were frequently required. Fatal hepatic adverse events were 2.1% (n=8) and 0.6% (n=1) in the regorafenib and placebo groups respectively. Serious hepatobiliary adverse events were 5.4% (n=27) and 3.6% (n=9) in the regorafenib and placebo groups, respectively. Grade 3 treatment-related adverse events occurred in 51% (n=253) and 12% (n=31) patients in the regorafenib and placebo groups, respectively. pERC considered these data to be indicative of an unfavourable toxicity profile for regorafenib.

Adverse events leading to dose modification occurred in 76% and 38% patients in the regorafenib and placebo groups respectively while withdrawals due to adverse events occurred in 18% and 13% patients in the regorafenib and placebo groups respectively. In patients requiring dose modifications, 20.0% and 3.2% received dose reductions while 70.4% and 37.5% received dose interruptions in the regorafenib and placebo groups, respectively. The majority of these patients received one dose interruption or reduction with the duration of the interruption or reduction lasting more than 5 days. pERC considered input from pCODR's Provincial Advisory Group and agreed that dose interruptions would have a greater impact on regorafenib wastage than dose reductions, which could be more easily managed by adjusting prescriptions.

Need: effective therapies for patients who have exhausted all other treatments

pERC noted that colorectal cancer represents the second most common cause of cancer death in Canadian males and the third most common cause of cancer death in Canadian females. With established cytotoxic chemotherapy (i.e., fluoropyrimidines, oxaliplatin, irinotecan) and targeted agents (i.e., bevacizumab, cetuximab, panitumumab), median survivals are now reliably measured in the 20-24 month range. Despite these significant improvements, long-term survival remains rare and cures are still not anticipated in patients with unresectable metastatic colorectal cancer. Therefore, there is a need for new effective therapies in this patient population, who are currently treated with best supportive care when treatment options are exhausted. pERC noted that an extra line of therapy is available in the fourth line setting for patients with KRAS wild type status, while patients with the KRAS mutation have only three lines of therapy available to them. While pERC considered that there is a need for new therapies, pERC further discussed that regorafenib provides only a very modest overall survival and PFS benefit, while being associated with unfavourable toxicities and no improvement on quality of life. As a consequence, palliation is still the most reasonable treatment option for these patients.

PATIENT-BASED VALUES

Values of patients with metastatic colorectal cancer: additional treatments

Input from one patient advocacy group indicated that patients with metastatic colorectal cancer seek choice and flexibility in selecting treatments to manage their disease and to maintain their quality of life. Important symptoms of metastatic colorectal cancer (mCRC) which patients would like help in managing include severe abdominal pain, shortness of breath, cough, fatigue, bloating and loss of appetite. pERC noted that patients value access to additional treatments even if they provide only short term benefit and have associated adverse effects. However, pERC noted that based on the CORRECT study, regorafenib

provides only a very modest benefit in overall survival and progression-free survival and has serious toxicities; therefore, pERC considered that regorafenib would only partially align with patient values of having new effective treatment options.

Patient values on treatment: prolong progression-free survival and improve quality of life
pERC noted that patients are looking for treatments that will prolong progression-free survival, improve quality of life and allow for extended periods of disease control. pERC acknowledged that as an oral therapy, regorafenib could provide patients easier access than intravenous therapies. However, pERC noted that based on the CORRECT study, regorafenib provides only a modest benefit in overall survival and progression-free survival and does not improve quality of life; therefore, pERC considered that it only partially aligned with these patient values.

ECONOMIC EVALUATION

Economic model submitted: cost utility
The pCODR Economic Guidance Panel assessed a cost utility analysis comparing regorafenib (Stivarga) to best supportive care (BSC) for patients with metastatic colorectal cancer (CRC) who had been previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. The comparison was based on the results of the CORRECT study.

Basis of the economic model: clinical and economic inputs
Costs included in the analysis included drug costs, cost of routine care, adverse event management, treatment administration and dispensing fees.

The clinical effect considered in the analysis was based on the overall survival and progression-free survival from the CORRECT trial. PFS and OS were extrapolated beyond the end of the CORRECT trial follow-up. The model's clinical effect estimates are greatly affected by the methods and assumptions used in the extrapolation.

Drug costs: confidential price submitted
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]. (Non-disclosable information was provided to pERC in the pCODR guidance reports for deliberation on a recommendation 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 manufacturer that it can be publicly disclosed.) At the list price, regorafenib costs $74 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 and the average cost per 28-day course is $6237.

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 as a sealed bottle of 28 tablets.

Cost-effectiveness estimates: influenced by extrapolation of overall survival, time horizon and potential for wastage
pERC deliberated upon the cost-effectiveness of regorafenib and discussed the pCODR Economic Guidance Panel's critique of the manufacturer's economic analysis. pERC reviewed the incremental cost-effectiveness estimates provided by both the manufacturer and the pCODR Economic Guidance Panel (EGP) and determined that regorafenib was not cost-effective. However, pERC noted that the EGP estimates were considerably higher than the manufacturer's estimates and discussed the assumptions upon which the EGP estimates were based. pERC agreed with the EGP's assessment that the manufacturer's estimated time horizon of 10 years was not appropriate in this patient population and while agreeing that a 5 year time horizon was more appropriate, noted that a 2 year time horizon may in

fact be considered in this palliative patient population. pERC also agreed with the EGP's consideration of wastage as potentially having an important impact on cost-effectiveness. In considering input from the PAG, pERC agreed that although wastage is a common issue with all oral treatments, there is concern for increased wastage of regorafenib due to the packaging of the drug. pERC also took into account that a large percentage of patients (75.6%) required dose modifications in the trial, many of which were dose interruptions. It further noted that wastage would likely be greater for regorafenib. pERC also discussed the EGP's concern with how the submitter had extrapolated overall survival beyond the end of the trial period. pERC agreed with the EGP's assessment that the submitter's method of extrapolating the data beyond the first 12 months would overestimate overall survival in favor of the regorafenib group. The EGP's estimates adjusted for this, which led to a lower estimate of incremental effect compared with the manufacturer's estimate (0.05 versus 0.09 QALYs gained). pERC noted that these small changes in the estimates of incremental effect had a large impact on the ICER estimates. Therefore, pERC considered that the incremental cost-effectiveness ratio was likely higher than the manufacturer had estimated.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: additional therapy, potential for wastage

pERC discussed the feasibility of implementing a funding recommendation for regorafenib and noted that regorafenib is likely to be an additional, sequential therapy in patients with metastatic colorectal cancer. pERC discussed that as a new line of therapy where there wasn't one available previously, regorafenib would incur additional pharmacy dispensing workload. Regorafenib will not likely replace other therapies and overall treatment costs would increase if it were funded. pERC also noted that in provinces where anti-EGFR therapies (cetuximab and panitumumab) are not currently funded, the budget impact of regorafenib would be larger.

pERC discussed pCODR's Provincial Advisory Group's input regarding the availability of regorafenib in sealed bottles with a 28-day shelf life once opened. Based on the trial data from the CORRECT study, pERC agreed that patients are likely to receive dose modification due to toxicities and as such wastage is likely to have an important budget impact. pERC agreed that in the event of a dose interruption, tablets would likely be wasted as patients would not be able to re-use tablets on their next cycle. pERC noted that the availability of a blister pack would have been preferable to extend the shelf life of the tablets. However, pERC noted that this wastage was still likely less than what would be observed with intravenous drugs. pERC also noted that regorafenib may require increased monitoring of patients for hepatic toxicity.

DRUG AND CONDITION INFORMATION

Drug Information	• multiple kinase inhibitor • 40 mg film coated tablet • 160 mg (4 tablets, orally) daily for 3 weeks, followed by 1 week off treatment
Cancer Treated	• metastatic colorectal cancer
Burden of Illness	• second most common cause of cancer death in Canadian males and the third most common cause of cancer death in Canadian females
Current Standard Treatment	• best supportive care
Limitations of Current Therapy	• median survivals are now reliably measured in the 20-24 month range • long-term survival remains rare and cures are still not anticipated in patients with unresectable metastatic colorectal cancer • there is an unmet need for those patients who still retain a good performance status despite exhausting all of their standard therapies

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist;
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Lister, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

Dr. Maureen Trudeau chaired the meeting in her capacity as Vice-Chair of pERC. All members participated in deliberations and voting on the initial recommendation except:

- Dr. Mario de Lemos and Dr. Scott Berry who were not present for the meeting
- Dr. Anthony Fields who was excluded from chairing and voting due to a conflict of interest
- Carol McMahon who did not vote due to her role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website

and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of regorafenib (Stivarga) for metastatic colorectal cancer, through their declarations, eight members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, two of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Bayer Inc. as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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