pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL 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.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC 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: August 29, 2013	**Final Recommendation:** November 15, 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 plus best supportive care, regorafenib plus best supportive care had only a very modest overall survival and progression-free survival benefit, a similar decline in quality of life, moderate but not insignificant 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 provide a clinically meaningful extension in overall survival while at the same time maintaining or 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 very modest for regorafenib plus best supportive care compared with placebo plus best supportive care. Upon reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from the manufacturer and patient advocacy groups regarding the clinical benefit of regorafenib. pERC reviewed various measures of survival and their strengths and limitations including hazard ratios and median time to survival. pERC noted that although the results were statistically significant and the relative risk reductions were large, it was uncertain if the magnitude of absolute benefit was clinically meaningful. However, pERC noted feedback indicating that in this setting where treatment options have been exhausted and no other evidence-based options remain, small incremental effects are considered important. pERC discussed that because median survival was reported, approximately half of the patients in the trial would have survived longer than the estimated 6.4 and 5.0 months. However, pERC was unable to distinguish which of the patients would survive longer than the median, and consequently benefit more from regorafenib, based on the clinical trial data or any specific patient markers. pERC also considered an analysis conducted by the manufacturer that provided 17 months of follow-up but this did not alter pERC's overall interpretation of the data. Although pERC agreed that there is a clinical benefit with regorafenib, pERC debated upon the magnitude of clinical benefit that would be required to support a funding recommendation. Various opinions were expressed, however, the majority of pERC members considered that in this specific context, the magnitude of overall survival and progression-free survival benefit that was observed with regorafenib was insufficient to recommend funding.

pERC noted that the quality of life declined from baseline to the end of treatment, although this decline was similar between the regorafenib plus best supportive care and placebo plus best supportive care groups. Upon reconsideration of the pERC Initial Recommendation, pERC considered it important to emphasize that regorafenib was unable to maintain or improve patients' quality of life, as measured in the clinical trial. pERC discussed the toxicity profile of regorafenib based on the results of the CORRECT study. It was noted that the frequency of grade 3 treatment- related adverse events was approximately 4 times higher (51% vs. 12%) and there were more fatal hepatic events with regorafenib plus best supportive care compared with placebo plus best supportive care. However, pERC acknowledged that only one of the fatal hepatic events was considered to be related to regorafenib and the others were disease-related. pERC also acknowledged that adverse events appeared to be manageable for many patients through dose reductions. 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 concluded that the overall net clinical benefit associated with regorafenib was insufficient to support funding.

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 plus best supportive care did not improve quality of life compared with placebo plus best supportive care and that there were important side effects associated with regorafenib. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the patient advocacy group regarding the alignment of regorafenib with patient values. pERC noted that patients considered any extension in life meaningful, regardless of the length of this extension. Also, patients considered that an oral therapy like regorafenib could improve quality of life because patients could receive treatment at home, reducing the number of hospital visits. Therefore, considering this feedback, pERC agreed that regorafenib aligned with patient values. Despite this alignment, pERC maintained that the net benefits that were observed with regorafenib were insufficient to recommend funding.

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 plus best supportive care was not cost-effective compared with placebo plus best supportive care in either analysis. 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 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 benefits 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. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from the manufacturer regarding the economic analysis. pERC noted that the manufacturer acknowledged the EGP's reanalyses regarding wastage and time horizon but disagreed with the EGP's method of extrapolating survival data in the economic analysis. pERC discussed both the manufacturer's approach to extrapolating survival and the EGP's approach. It was noted that both approaches had limitations and that the true cost-effectiveness estimate was likely somewhere in between the estimates based on the two approaches. pERC also noted additional regorafenib data based on 17 months of follow-up but agreed with the EGP that its usefulness in the economic analysis was limited without supporting patient-level data. pERC reiterated that the very small incremental effect that was observed with regorafenib made the incremental cost-effectiveness ratio (ICER) extremely sensitive to the extrapolation approach, which accounted for the wide range of possible ICER's suggested by the EGP and the manufacturer. Therefore, pERC maintained that regorafenib plus best supportive care is not cost-effective at the submitted price compared with placebo plus best supportive care. However, pERC also noted that regorafenib's lack of cost-effectiveness was not the main reason for the negative funding recommendation.

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 . Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from pCODR's Provincial Advisory Group seeking clarification on why this would occur. pERC clarified that this is because if these therapies are not funded, fewer treatment options would be available and more patients would, potentially, be eligible for treatment with regorafenib. 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)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Colorectal Cancer Association of Canada)
- the Submitter (Bayer Inc.)

The pERC Initial Recommendation was to not fund regorafenib 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. Feedback on the pERC Initial Recommendation indicated that the manufacturer and patient advocacy group disagreed with the initial recommendation and pCODR's Provincial Advisory Group agreed with the initial recommendation.

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 administered 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 poorer 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 plus best supportive care and placebo plus best supportive care arms, respectively. The majority of patients had also received ≥4 prior systemic anti-cancer therapies.

Key efficacy results: very 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 plus best supportive care and placebo plus best supportive care group, respectively (HR=0.77, 95% confidence interval (CI) 0.64 to 0.94). An additional overall survival analysis based on 17 months of follow-up data showed similar results to the second interim analysis, with a median overall survival of 6.4 versus 5.0 months in the regorafenib plus best supportive care group and placebo plus best supportive care group, respectively (HR=0.79, 95% CI: 0.66 to 0.94, P= 0.0038). The median PFS was 1.9 months and 1.7 months in the regorafenib plus best supportive care and placebo plus best supportive care 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 (1.4 and 0.2 months, respectively) and considered that this benefit was very modest.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from the manufacturer and patient advocacy groups regarding the clinical benefit of regorafenib. pERC reviewed various measures of survival and their strengths and limitations including hazard ratios and median time to survival. pERC noted that although the results were statistically significant and the relative risk reductions were large, it was uncertain if the magnitude of absolute benefit was clinically meaningful. However, pERC noted feedback indicating that in this setting where treatment options have been exhausted and no other evidence-based options remain, small incremental effects are considered important. pERC discussed that because median survival was reported, approximately half of the patients in the trial would have survived longer than the estimated 6.4 and 5.0 months. However, pERC was unable to distinguish which of the patients would survive longer than the median, and consequently benefit more from regorafenib, based on the clinical trial data or any specific patient markers. pERC also considered an analysis conducted by the manufacturer that provided 17 months of follow-up but this did not alter pERC's overall interpretation of the data. Although pERC agreed that there is a clinical benefit with regorafenib, pERC debated upon the magnitude of clinical benefit that would be required to support a funding recommendation. Various opinions were expressed, however, the majority of pERC members considered that in this specific context, the magnitude of overall survival and progression-free survival benefit that was observed with regorafenib was insufficient to recommend funding.

Quality of life: decline in quality of life similar to 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 the end of treatment indicated a similar decline in patients' quality of life in both the regorafenib plus best supportive care and placebo plus best supportive care groups when compared with the beginning of treatment. Upon reconsideration of the pERC Initial Recommendation, pERC considered it important to emphasize that regorafenib was unable to maintain or improve patients' quality of life, as measured in the clinical trial

pERC acknowledged that based on patient advocacy group input, quality of life was an outcome important to patients However, upon reconsideration of the pERC Initial Recommendation and after reviewing patient advocacy group feedback, pERC noted that patients also considered that an oral therapy like regorafenib could improve quality of life because patients could receive treatment at home and reduce the number of hospital visits.

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 plus best supportive care and placebo plus best supportive care groups respectively. However, pERC also acknowledged that only one of the fatal hepatic events was considered to be related to regorafenib and the rest were classified as disease-related. Serious hepatobiliary adverse events were 5.4% (n=27) and 3.6% (n=9) in the regorafenib plus best supportive care and placebo plus best supportive care groups, respectively. The frequency of grade 3 treatment- related adverse events was approximately 4 times higher with regorafenib plus best supportive care compared with placebo plus best supportive care (51% versus 12%, respectively). pERC considered these data to be indicative of an unfavourable toxicity profile for regorafenib. However, pERC acknowledged that adverse events appeared to be manageable for many patients through dose reductions or interruptions.

Adverse events leading to dose modification occurred in 76% and 38% patients in the regorafenib plus best supportive care and placebo plus best supportive care groups respectively while withdrawals due to adverse events occurred in 18% and 13% patients in the regorafenib plus best supportive care and placebo plus best supportive care 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 plus best supportive care and placebo plus best supportive care 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 plus best supportive care provides only a very modest overall survival and PFS benefit, while being associated with unfavourable toxicities and a decline in quality of life similar to placebo plus best supportive care.

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; Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the patient advocacy group regarding the alignment of regorafenib with patient values. pERC noted that patients considered any extension in life meaningful, regardless of the length of extension. Therefore, considering this feedback, pERC agreed that regorafenib aligned with patient values. Despite this alignment, pERC maintained that the net benefits that were observed with regorafenib were insufficient to recommend funding.

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 plus best supportive care provides only a very modest benefit in overall survival and progression-free survival and a decline in quality of life similar to placebo plus best supportive care was observed. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the patient advocacy group regarding the alignment of regorafenib with patient values. pERC noted that patients considered that an oral therapy like regorafenib could improve quality of life because patients could receive treatment at home, reducing the number of hospital visits. Therefore, considering this feedback, pERC agreed that regorafenib aligned with 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 $6,237.

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 plus best supportive care was not cost-effective compared with placebo plus best supportive care in either analysis. 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%) in the trial required dose modifications, 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. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from the manufacturer regarding the economic analysis. pERC noted that the manufacturer acknowledged the EGP's reanalyses

regarding wastage and time horizon but disagreed with the EGP's method of extrapolating survival data in the economic analysis. pERC discussed both the manufacturer's approach to extrapolating survival and the EGP's approach. It was noted that both approaches had limitations and that the true cost-effectiveness estimate was likely somewhere in between the estimates based on the two approaches. pERC also noted additional regorafenib follow-up data based on 17 months of follow-up but agreed with the EGP that its usefulness in the economic analysis was limited without supporting patient-level data. pERC reiterated that the very small incremental effect that was observed with regorafenib made the incremental cost-effectiveness ratio (ICER) extremely sensitive to the extrapolation approach, which accounted for the wide range of possible ICER's suggested by the EGP and the manufacturer. Therefore, pERC maintained that regorafenib plus best supportive care is not cost-effective at the submitted price compared with placebo plus best supportive care. However, pERC also noted that regorafenib's lack of cost-effectiveness was not the main reason for the negative funding recommendation.

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. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from pCODR's Provincial Advisory Group seeking clarification on why this would occur. pERC clarified that this is because if these therapies are not funded, fewer treatment options would be available and more patients would, potentially, be eligible for treatment with regorafenib.

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 modifications 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 • after treatment with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy
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 Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- 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
- Carole McMahon who did not vote due to her role as a patient member alternate

All members participated in deliberations and voting on the final recommendation except:

- Dr. Chaim Bell, Mario de Lemos, Dr. Bill Evans, Dr. Allan Grill, Dr. Paul Hoskins who were not present for the meeting
- Dr. Scott Berry who was excluded from voting due to a conflict of interest
- Dr. Anthony Fields who was excluded from chairing and voting due to a conflict of interest
- Carole McMahon who was not present for the meeting and who would not have voted 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, seven 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

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