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:
Treatment of patients with metastatic colorectal cancer (CRC), and an ECOG status of ≤1, 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:
December 19, 2014

Initial Recommendation Issued:
April 30, 2015

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) does not recommend funding regorafenib (Stivarga) 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. The Committee made this recommendation because, compared with placebo plus best supportive care, regorafenib plus best supportive care had only a very modest progression-free survival and overall survival benefit, moderate but not insignificant toxicities, and a similar decline in quality of life. pERC also noted that regorafenib only partially aligned with patient values as there is a need for more effective treatment options; however regorafenib was associated with a similar decline in quality of life similar to best supportive care and had only a very modest improvement in overall survival. In addition, the Committee noted that regorafenib could not be considered cost-effective based on the manufacturer's submitted and Economic Guidance Panel's estimates of the range of incremental cost-effectiveness ratios when compared with best supportive care in this population.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

Metastatic colorectal cancer (mCRC) is the second most commonly diagnosed malignancy in Canada. pERC noted that there are limited effective treatment options for patients with late stage disease who have exhausted all other standard treatment options. pERC noted that patients are currently 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. The life expectancy of these patients from the time of diagnosis of metastatic disease is approximately two years and is much shorter once all treatment options have been exhausted. pERC agreed that there is a need for additional treatment options that extend survival and provide better symptom control.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The present review is a resubmission based on new clinical information. pERC deliberated upon two double-blind randomized controlled trials (CORRECT, CONCUR) which compared regorafenib plus best supportive care with placebo plus best supportive care in patients with metastatic colorectal cancer. pERC noted that the original pCODR submission was based on the results of the CORRECT study. Since the original submission, the CONCUR study and an updated analysis from the CORRECT study has been made available. These new data were considered in this resubmission. Both the CORRECT and CONCUR trials used the same study design; however, pERC observed that the patient populations included in the studies differed. In the CORRECT trial, prior to commencing the trial, all of the patients received anti-VEGF therapy (bevacizumab) and 51% had received anti-EGFR therapy (cetuximab or panitumumab). In the CONCUR trial, only 60% of patients had received prior anti-VEGF or anti-EGFR therapy. In the CORRECT trial, almost 50% of patients in both arms of the study had received ≥4 prior systemic anti-cancer therapies, while in the CONCUR trial, all patients had at least two lines of prior treatment. The time from diagnosis of metastases was ≥18 months for over 80% of all patients in the CORRECT trial and about 60% for all patients in the CONCUR trial. pERC concluded that the patients and the treatment patterns in the CORRECT study were more representative of the Canadian setting compared to the CONCUR study, since virtually all patients in Canada will have received prior anti-VEGF therapy with bevacizumab, would receive more prior lines of systemic therapy for mCRC before considering regorafenib, and are at a later stage of their disease.

pERC observed that the results of the CONCUR trial were consistent with those of the CORRECT trial. The improvement in median overall survival, the primary outcome, between the regorafenib arm and placebo arm was 1.4 months in the CORRECT trial and 2.5 months in the CONCUR trial. The results were statistically significant in both studies; however, the Committee considered these to be very modest improvements in overall survival.

pERC noted that patients' quality of life declined from baseline to the end of treatment in both the CORRECT and CONCUR studies. These declines were similar in both the regorafenib and placebo arms of the studies. pERC considered it important to emphasize that regorafenib was unable to maintain or improve patients' quality of life, as measured in the clinical trials. pERC discussed the toxicity profile of regorafenib based on the results of both the CORRECT and CONCUR studies. Adverse events that occurred more frequently in patients treated with regorafenib than placebo included hand-foot skin reaction, fatigue, and diarrhea. pERC noted that these toxicities were likely manageable, but not insignificant, particularly considering that many patients without treatment can be quite well with a good performance status, despite having metastatic disease and a high rate of grade 3/4 adverse effects would impair daily functioning. Therefore, despite the statistically significant improvement in overall survival and progression-free survival in patients receiving regorafenib compared to placebo, pERC concluded that there was not a net clinical benefit of regorafenib for patients with mCRC due to the very modest magnitude of the survival benefit, the inability of regorafenib to maintain or improve quality of life, and the toxicity profile of the treatment.

pERC deliberated upon patient advocacy group input, which indicated that patients value extending life while maintaining quality of life. pERC acknowledged there is a need for more options for patients with this disease; however, they concluded that regorafenib only partially aligned with patient values based on the results of the CORRECT and CONCUR studies, as there was a decline in quality of life in the context of modest disease control and not insignificant toxicities. pERC again acknowledged the input from patients that they are as individuals willing to accept treatment toxicity even in the face of small benefits.

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. pERC noted that the EGP estimates were higher than the manufacturer's estimates and discussed the assumptions upon which the EGP estimates were based.

pERC discussed factors that could impact the feasibility of implementing a positive funding recommendation for regorafenib and noted that regorafenib is expected to be an additional, sequential therapy in the treatment of patients with mCRC. It will not likely replace other therapies and overall treatment costs could be expected to increase if it were funded. Therefore the potential budget impact could be large given the prevalence of mCRC. pERC discussed and agreed with input from the pCODR Provincial Advisory Group regarding the potential for wastage since the tablets are only stable for 28 days after opening the manufacturer's bottle and dose modifications/interruptions are likely when using regorafenib.

CONTEXT OF THE RESUBMISSION

A submission for regorafenib (Stivarga) for patients with metastatic colorectal cancer was previously received by pCODR on March 22, 2013 and the pERC Final recommendation was issued on November 15, 2013.

- The pERC Final Recommendation was not to fund 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 resubmission that was made by the manufacturer provided new information on regorafenib. The new information included:
  - Updated efficacy and safety data from the randomized controlled trial included in the original submission (CORRECT)
  - Clinical data from the ongoing randomized controlled trial CONCUR
  - A revised economic evaluation

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 purpose of this review is to evaluate the efficacy and safety of regorafenib (Stivarga) 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: Two high quality RCTs

The pCODR systematic review included two phase III, double-blind randomized controlled trials (RCTs), the CORRECT study (multi-national) and CONCUR study (only Asian countries) which evaluated the efficacy and safety of regorafenib versus placebo. Regorafenib was administered at 160 mg once daily for 3 weeks followed by 1 week off treatment. All patients received best supportive care (BSC).

In both the CORRECT and CONCUR studies, the study population included patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and disease progression during or within 3 months following the last administration of approved standard therapies (fluoropyrimidine, oxaliplatin and irinotecan).

Patient populations: ECOG performance status 0-1, prior bevacizumab use in some patients

Patient characteristics appeared to be balanced between the two groups in the CORRECT and CONCUR studies. Patients had a median age of 61 and 58 years in the CORRECT and CONCUR studies, respectively. Patients had an ECOG PS of 0 or 1. pERC noted that patients with ECOG PS of 2 or greater were not included in the study but noted that due to the toxicity profile of regorafenib, treatment with regorafenib would not likely be offered to patients with a poorer performance status. In both studies, all patients had previously been treated with fluoropyrimidine-based chemotherapy, oxaliplatin, and irinotecan.

CORRECT Study: All patients had received bevacizumab, an anti-VEGF therapy, and almost 50% of patients in both arms had received ≥4 prior systemic anti-cancer therapies. The time from diagnosis of metastases was ≥18 months for over 80% of all patients. Fifty-four percent and 64% of patients had a known KRAS mutation in the regorafenib plus BSC and placebo plus BSC groups, respectively.

CONCUR Study: Only 41% and 37% of patients treated with regorafenib plus BSC and placebo plus BSC received bevacizumab, respectively. All patients had received at least two prior lines of treatment. The time from diagnosis of metastases was ≥18 months for about 60% of patients. Thirty-four percent and 27% of patients had a known KRAS mutation in the regorafenib plus BSC and placebo plus BSC groups, respectively.

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

Key efficacy outcomes deliberated on by pERC included overall survival (OS), the primary endpoint of the CORRECT and CONCUR studies, and progression-free survival (PFS).

CORRECT Study: pERC noted that at the second interim analysis, the pre-specified conditions for efficacy and for stopping the study were met. The median OS was 6.4 and 5.0 months in the regorafenib plus BSC and placebo plus BSC groups, respectively (HR=0.77, 95% confidence interval (CI) 0.64-0.94). In the updated final analysis, although the value of median OS remained unchanged, there were slightly improved confidence intervals around the HR (HR=0.79, 95%CI 0.66-0.94). The median PFS was 1.9 and 1.7 months in the regorafenib plus BSC and placebo plus BSC groups, respectively (HR=0.49 95%CI 0.42-0.58).

CONCUR Study: As noted the median OS was higher in the CONCUR study compared to the CORRECT study. In CONCUR, the median was 8.8 and 6.3 months in the regorafenib plus BSC and placebo plus BSC groups, respectively (HR=0.55, 95%CI 0.40-0.77). Similarly, the median PFS was 3.2 and 1.7 months in the regorafenib plus BSC and placebo plus BSC groups, respectively (HR=0.31, 95%CI 0.22-0.44).

pERC discussed the magnitude of benefit observed in median PFS and OS and acknowledged the pCODR Clinical Guidance Panel had concluded that regorafenib conferred a modest but consistent and statistically significant improvement in OS and that there was a net clinical benefit to the use of regorafenib. However, pERC discussed the magnitude of the benefit in OS and PFS conferred with regorafenib (1.4 and 0.2 months, respectively in the CORRECT study, which was the trial considered to be most relevant to the Canadian population; the OS and PFS were 2.5 and 1.5 months, respectively in the CONCUR study) and considered this benefit to be very modest.

Quality of life: Decline in quality of life similar to placebo

Health related quality of life (HrQoL) was assessed in the CORRECT and CONCUR studies using EORTC QLQ-C30 and EQ-5D measures. pERC noted that the HrQoL results at the end of treatment had declined to a similar degree in both the regorafenib plus BSC and placebo plus BSC groups when compared with the beginning of treatment. In a post-hoc analysis of the CORRECT study, regorafenib was associated with significantly longer time to deterioration; however, a significant difference was not observed when other end points were applied.

Safety: Dose modifications due to adverse events required

pERC deliberated on the safety data available from the CORRECT and CONCUR studies.

CORRECT Study: Grade 3 treatment-related adverse events (TRAEs) occurred in 51% and 12% of patients in the regorafenib plus BSC and placebo plus BSC groups, respectively. Rates of grade 4 TRAEs were similar between groups. Adverse events that occurred more frequently in patients treated with regorafenib included hand-foot skin reaction, hypertension, and hypophosphatemia. Hepatic failure occurred in 1% of patients. Adverse events leading to dose modifications occurred in 68% and 23% of patients in the regorafenib plus BSC and placebo plus BSC groups, respectively while withdrawals due to adverse events occurred in 19% and 12% of patients treated with regorafenib plus BSC and placebo plus BSC groups, respectively.

CONCUR Study: Adverse events that occurred more frequently in patients treated with regorafenib included hand-foot skin reaction, fatigue, diarrhea, hypertension and rash or skin desquamation. Hepatic failure was not reported as one of the serious adverse events in the study. Adverse events leading to dose modifications occurred in 71% and 16% of patients in the regorafenib plus BSC and placebo plus BSC groups, respectively while withdrawals due to adverse events occurred in 14% and 6% of patients treated with regorafenib plus BSC and placebo plus BSC groups, respectively.

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 the availability of cytotoxic chemotherapeutics (fluoropyrimidines, oxaliplatin, irinotecan) and targeted agents (i.e. bevacizumab, cetuximab, panitumumab), median survivals are now estimated to be 20-28 months. Despite these significant improvements, long-term survival is rare, with a 5 year survival rate of less than 10%, 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 a KRAS mutation have only three lines of available therapy.

PATIENT-BASED VALUES

Values of patients with metastatic colorectal cancer: Need for additional treatments
pERC deliberated upon patient advocacy group input and discussed the values of patients with mCRC. The most frequently reported disease-related symptoms are severe abdominal pain, shortness of breath, cough, fatigue, bloating and loss of appetite; all of which significantly impact a patient's quality of life. pERC acknowledged that patients indicated that there is a need for an additional therapeutic option in the third or fourth line setting that will help manage their disease and side effects, help maintain quality of life and prolong overall survival.

pERC also acknowledged that there is a considerable caregiver burden with this disease, with the most negative impacts being the management of adverse events, providing emotional support, and dealing with the financial challenges related to disability and the cost of accessing treatment in select provinces that do not currently fund third line therapy.

Patient values on treatment: Early management of toxicities and disease control
pERC noted that a small number of patients who provided input had experience with regorafenib (n=3). These patients reported awareness of significant adverse events with regorafenib, including hand-foot skin reaction, fatigue, and diarrhea, side effects which patients are well acquainted with from previously administered therapies. Patients noted that early intervention in the management of these known side effects allowed for better tolerance and longer time on treatment, leading to better disease control in terms of tumour shrinkage/stabilization. pERC noted that fewer clinic/hospital visits can alleviate patients' stress and regorafenib may provide patients a line of therapy that does not require administration in a cancer treatment facility.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis
The pCODR Economic Guidance Panel assessed an updated cost-utility analysis comparing regorafenib (Stivarga) plus best supportive care (BSC) to placebo plus BSC for patients with metastatic colorectal cancer (mCRC) 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. The submitted model was a partitioned-survival or area under the curve model.

Basis of the economic model: Clinical and economic inputs
Costs considered in the model provided by the submitter included the cost of treatment, administration, and wastage, and the costs associated with routine follow-up and adverse events.

The key clinical outcomes considered in the model provided by the submitter were overall survival, progression-free survival, and utilities.

Drug costs: Confidential price submitted

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 of 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.)*

The manufacturer's most recent economic analysis was based on a revised confidential price of regorafenib and addressed concerns in the original submission associated with drug mark-up, co-payments, dispensing fees and accounting for potential wastage as regorafenib is available as a sealed bottle of 28 tablets.

Cost-effectiveness estimates: Not cost-effective at submitted price

The EGP's reanalyses estimated the extra clinical effect of regorafenib plus BSC to be 0.083 quality adjusted life-years (QALYs). The factors found to have the greatest influence on the incremental effectiveness were the survival benefit of regorafenib plus BSC, the duration of treatment duration, and the time horizon.

pERC reviewed the incremental cost effectiveness estimates provided by both the manufacturer and the pCODR Economic Guidance Panel (EGP) and determined that regorafenib plus BSC was not cost-effective compared with placebo plus BSC in either analysis. However, pERC noted that the EGP estimates were 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 extrapolation of the data beyond the end of the follow-up period in the clinical trial may have overestimated the overall survival benefit in favor of the regorafenib group. The EGP also considered treatment duration until disease progression and death instead of the duration of treatment from the clinical trial data as the CGP felt that this would more accurately reflect real world practice. pERC noted that these small changes in the estimates of incremental effect and cost had a large impact on the ICER estimates. In conclusion, pERC determined that regorafenib plus BSC is not cost-effective at the submitted price compared with placebo plus BSC.

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 expected to be an additional, sequential therapy for patients with metastatic colorectal cancer. pERC noted that regorafenib would be a new line of therapy and as a consequence, would result in additional pharmacy dispensing workload and increased monitoring of patients for drug interactions or toxicity management. Regorafenib will not likely replace other therapies and overall treatment costs would therefore 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 given the prevalence of mCRC. pERC also noted the Provincial Advisory Group's concern that drug wastage was likely to occur as tablets are only stable for 28 days after opening the manufacturer's original bottle and cannot be repackaged to the correct number of tablets for each treatment cycle.

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 for patients with metastatic colorectal cancer are now in the 20-28 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 prior 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. Kelvin Chan, Oncologist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
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. 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. Kelvin Chan, Dr. Allan Grill, Dr. Paul Hoskins, and Dr. Tallal Younis who were not present for the meeting
- Dr. Anthony Fields who was excluded from chairing and voting due to a conflict of interest
- Dr. Scott Berry who was excluded from voting due to a conflict of interest
- Carole 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) Resubmission for Metastatic Colorectal Cancer, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, two of these members was 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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