pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Initial Clinical Guidance Report

Regorafenib (Stivarga) Resubmission for Metastatic Colorectal Cancer

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy 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.

Regorafenib is a multiple kinase inhibitor. The Health Canada recommended dose is 160 mg (4 x 40mg tablets) taken orally, once daily for 3 weeks in a 4-week cycle[1] The funding request is aligned with the Health Canada approved indication with the specification for patients with ECOG performance status of ≤1.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two multicentre 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 (160mg, 4 x 40mg tablets orally) once daily compared to a matching dose of placebo given for 3 weeks of each 4 week cycle.[2,3] In addition, all patients received best supportive care (BSC).The CORRECT study randomized patients in a 2:1 ratio between regorafenib (N=505) and placebo (N=255). Reported patient characteristics appeared to be balanced between the two groups. No crossover was permitted between treatment groups. The CONCUR study had a similar design as the CORRECT study, patients were randomized in a 2:1 ratio between regorafenib (N=136) and placebo (N=68).

There were notable differences between the two studies, 100% and 51% of patients in the CORRECT study received prior anti-VEGF (bevacizumab) or anti-EGFR therapy, compared to patients in the CONCUR study, where 60% of patients received prior anti-VEGF or anti-EGFR therapy before randomization, respectively. Furthermore, a smaller proportion of patients in the CONCUR study compared to the CORRECT study had first diagnosis of mCRC ≥18 months before randomization, known KRAS mutation, and ECOG PS of 0.

Efficacy

The primary endpoint for both studies was overall survival (OS). In the CORRECT study, at the second interim analysis (July 2011), 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 and placebo group, respectively (HR: 0.77, 95% confidence interval (CI): 0.64 to 0.94), indicating a gain of 1.4 months in OS for the regorafenib group. In the updated analysis (November 2011), the median OS value remained unchanged with a HR of 0.79 (95%CI: 0.66-0.94).[4] In the CONCUR study, the median OS was 8.8 and 6.3 months in the regorafenib and placebo group, respectively (HR: 0.55, 95%CI: 0.40-0.77), indicating a gain of 2.5 months in OS for the regorafenib group.

For the secondary outcome of progression-free survival (PFS), in the CORRECT study, the median PFS was 1.9 and 1.7 months in the regorafenib and placebo group, respectively (HR: 0.49, 95%CI: 0.42-0.58). For the CONCUR study, the median PFS was 3.2 and 1.7 months in the regorafenib and placebo group, respectively (HR: 0.31, 95%CI: 0.22-0.44).

Health related quality of life (HRQoL) was assessed using EORTC QLQ-C30 and EQ-5D measures in both studies.[2,5] Overall results at the end of treatment and from one cycle to the next, indicated a similar decline in patients' HRQoL in both the regorafenib and placebo groups. In the CORRECT

study, using the Global Health Status (GHS)-based 3-component endpoint, time to deterioration was significantly longer in the regorafenib group compared to the placebo group.[6] However, a significant difference was not observed when other endpoints were applied. Similar results were seen when an analysis of time-adjusted area under the curve (AUC) was conducted for EORTC QLQ-30, EQ-5D index, and EQ-5D VAS in both the CORRECT and CONCUR studies.

Harms

Updated data (January 2014) from the CORRECT study confirmed results from the interim analysis, with similar incidences of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) occurring in the regorafenib and placebo groups. The overall incidence of SAEs was lower in CONCUR than CORRECT, however, the rate of SAEs was similar between treatment groups. SAEs occurred in 46.2% and 40.3% of patients in the regorafenib and placebo group of CORRECT, respectively. In CONCUR, they occurred in 31.6% and 26.5% of the regorafenib and placebo groups, respectively. Grade 3 AEs frequently occurred in patients treated with regorafenib in the CONCUR study, these included hand-foot skin reaction (16%), hypertension (12%), and hypophosphatemia (9%). Hepatic failure occurred in 1% of patients in the CORRECT study, it was not reported as one of the SAEs in the CONCUR study.

1.2.2 Additional Evidence

pCODR received input on regorafenib from one patient advocacy group (Colorectal Cancer Association of Canada). Provincial Advisory Group input was obtained from nine of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

No supplemental issues were identified during the development of the review.

1.2.3 Interpretation and Guidance

Regorafenib is an oral, small-molecule multi-kinase inhibitor targeting angiogenic, stromal and oncogenic pathways including VEGFR, PDGFR and KIT. Regorafenib was approved by Health Canada in March 2013 for the treatment of patients with mCRC who have previously been treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy and, if KRAS wild-type, an anti-EGFR therapy. Following a review by pCODR based primarily on the results of the CORRECT phase III trial, a recommendation to not fund was issued in November 2013. Since that time, access to regorafenib for Canadian patients has been limited to those patients with third-party-insurance, capacity to self-pay and patients eligible for the Bayer ABC Stivarga Program. This resubmission is now under consideration in light of further evidence including an updated analysis of the CORRECT trial and confirmatory positive results reported in a second phase III trial conduced in Asian patients (CONCUR).

<u>Effectiveness</u>

As highlighted in the systematic review, CORRECT was an international randomized trial which enrolled 760 patients with treatment-refractory mCRC and a performance status of 0-1, assigned in a 2:1 ratio to receive regorafenib 160mg orally daily for 3 of 4 weeks versus placebo. The median participant age was 61 years, approximately 60% were male, 40% were KRAS mutant, and 100% of participants had received prior bevacizumab therapy.[2] In the updated efficacy analysis, the primary endpoint of OS was superior in the regorafenib arm (median 6.4 vs 5.0 months, HR=0.79, p=0.0038)[4] As well, PFS was also improved in the regorafenib versus placebo arm (median 1.9 vs 1.7 months, HR=0.49, p<0.0001). Disease control was reported in 41% of patients

on regorafenib vs 15% on placebo (p<0.0001). No differences were observed in the HRQoL analysis as measured by EORTC QLQ-C30 or EQ 5D. The rate of SAEs and withdrawal due to AEs was relatively high with 46.2% and 19%, respectively of those in the regorafenib group, compared to 40.3% and 12.3% respectively, of those in the placebo group, reflecting the general disposition and limited toxicity tolerance of these heavily-pretreated patients.

CONCUR was a randomized phase III trial with similar study design in 204 patients.[3] Unlike in the global CORRECT study (78% white, 15% Asian and 7% other), CONCUR was conducted exclusively in Asian patients. The median age was younger at 58 years, KRAS status was unknown in 30%, and of note, 40% of patients had received prior bevacizumab therapy. OS was superior with regorafenib (median 8.8 vs 6.3 months, HR=0.55, p=0.0002). PFS was also improved with regorafenib (median 3.2 vs 1.7 months, HR=0.31, p<0.0001).

In both CORRECT and CONCUR, the HRQoL changes were similar in the regorafenib and placebo groups, including magnitude of end-of-treatment deterioration and time to deterioration. A post-hoc analysis of CORRECT suggested that time to deterioration with regorafenib was significantly longer than placebo when assessed using a GHS-based 3-component endpoint, however, a significant difference was not observed when the other endpoints were applied.[6]

Safety

The most common toxicities in both studies included hand-foot skin reaction, fatigue, diarrhea, hypertension, rash, and anorexia. While clinical utilization of regorafenib in Canada has been limited, medical oncologists have nonetheless gained some experience with its use. There is an appreciation of its TEAEs, which are not unlike those seen with other multi-kinase inhibitors in common use. The importance of appropriate patient-selection and the use of alternative dosing strategies may help to mitigate severe toxicities and early withdrawal. However, there are no identified patient subgroups or clinical predictors of toxicity and efficacy to assist in rationale therapeutic decision-making. In addition, no validated predictive or pharmacogenomics biomarkers have yet been identified to determine which patients are most likely to benefit from regorafenib.

Need and Burden of Disease

As the second and third most common cause of cancer death in Canadian males and females respectively, colorectal cancer (CRC) represents a significant disease burden in Canada. Due in large part to the availability of newer and novel systemic therapies, notable progress has been made in recent years in extending the survival of patients diagnosed with CRC, both in terms of extending the probability of cure for patients with earlier-stage and resectable disease, and extending survival and QoL for patients living with mCRC.

Patient advocacy group input based upon patient surveys and updated interviews with patients who have been on regorafenib therapy, highlights that prolonging PFS and allowing for extended control of their disease and improved QoL are important aspects when consideration is given to treatment. Patients are aware that all treatments for metastatic cancer carry risk and are willing to tolerate moderate to significant side effects during their treatment. Oral therapy in late stage disease, QoL and the ability to access treatment at home are important factors; patients seek choice and flexibility in selecting treatments to manage their disease. The balance between the efficacy and safety tradeoff needs to be an individual patient decision. With respect to implementation of regorafenib therapy, the Provincial Advisory Group has acknowledged concerns that the eligible patient population may be large and there will be a need for regular and early toxicity monitoring. The possibility of drug wastage would also need to be considered.

In summary, regorafenib is an oral agent that offers a modest yet statistically superior disease control rate, progression free survival and overall survival when compared to best supportive care, as demonstrated in two randomized, placebo-controlled phase III studies. The demonstration of survival benefit is consistent but the absolute median survival benefit is modest, shown to be a gain of 1.4 months (HR=0.79) in CORRECT and 2.5 months (HR=0.55) in CONCUR. There is no evidence of quality of life improvement and toxicities are common, requiring close supervision and early management. In the opinion of the Clinical Guidance Panel, regorafenib provides a treatment option for selected patients with treatment-refractory mCRC with a preserved performance status. Given the lack of alternative therapeutic options, this indication represents an important unmet medical need.

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit with the use of regorafenib over best supportive care alone in patients with treatment-refractory metastatic colorectal cancer.

In making this conclusion, the Clinical Guidance Panel considered:

- **Effectiveness:** The efficacy of regorafenib has been demonstrated in two similarly-designed, multi-centre RCTs, CORRECT and CONCUR, with a modest but consistent and statistically significant improvement in OS. There was no associated significant improvement in QoL measures. These trials include patients from Western and Asian populations and are considered generalizable to Canadian patients with treatment-refractory mCRC with an ECOG PS of 0-1.
- **Safety:** Regorafenib introduces the risk of toxicities such as hand-foot skin reaction, fatigue, diarrhea, hypertension, rash, and anorexia. These toxicities can be managed with early intervention and there is an increasing awareness among the Canadian oncology practitioner community regarding the profile and management of such toxicities. Patient advocacy input suggests that patients would be willing to tolerate moderate to significant treatment-related side effects in the hopes of controlling their disease.
- **Need and Burden of disease:** As a leading cause of cancer-related morbidity and mortality, the burden of mCRC among Canadians is significant. Regorafenib fulfills an unmet need for the treatment of patients with mCRC who have exhausted all currently available systemic therapies yet are still well enough to consider further treatment.
- In reaching this conclusion the panel was unable to comment on the use of regorafenib in earlier lines of therapy. To the panel's knowledge, there is no evidence currently supporting the use of regorafenib in earlier lines of therapy.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding regorafenib (Stivarga) for metastatic colorectal cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.cadth/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding regorafenib (Stivarga) for metastatic colorectal cancer conducted by the Gastrointestional Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from a patient advocacy group; and input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted patient advocacy group input on regorafenib (Stivarga) for metastatic colorectal cancer and a summary of submitted Provincial Advisory Group Input on regorafenib (Stivarga) for metastatic colorectal cancer are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Colorectal cancer (CRC) is the second and third most common form of cancer among men and women, respectively, in Canada.[4] The Canadian Cancer Society estimated newly diagnosed CRC cases in 2014 to be 24,400.[4] About 25% of patients present with metastases at the time of primary diagnosis and over the course of their disease more than 50% of CRC patients develop metastases.[1,3]

Non-surgical treatment options for mCRC include chemotherapy, targeted therapy, and radiation therapy.[7] Chemotherapy treatments involve the sequential use of fluoropyrimidines, oxaliplatin and irinotecan, which may be used alone or in combination as first-line therapy depending on the individual patient's needs. Current Health Canada approved targeted therapies for use in mCRC are bevacizumab (an anti-vascular endothelial growth factor [VEGF]); and cetuximab, and panitumumab, both of which are anti-epidermal growth factor receptor (EGFR) therapies used in patients with KRAS wild-type tumors. They have specific indications to be used alone or in combination with chemotherapy as a first-line therapy (bevacizumab) or as second-line or third-line therapy.[8]

Regorafenib was approved in 2013 by Health Canada for the treatment of patients with 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. It is an oral medication with a recommended daily dose of 160 mg to be taken for 3 weeks in every 4-week cycles. Regorafenib is an inhibitor of multiple protein kinases, including kinases involved in tumor angiogenesis, oncogenesis, and the tumor microenvironment.[9]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of regorafenib (Stivarga) on patient outcomes 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. See Table 2 in Section 6.2.1 for outcomes of interest and comparators.

2.1.3 Highlights of Evidence in the Systematic Review

The review included two phase III, double-blind randomized controlled trials (RCTs),[2,10] the CORRECT and CONCUR studies, which compared regorafenib at a once daily dose of 160 mg with matching placebo given for the first 3 weeks of each 4 week cycle in patients with metastatic colorectal cancer (mCRC) who have failed standard therapies. The CORRECT study included patients from 16 countries although the majority (78%) were white, while the CONCUR study was conducted in 5 countries with only Asian patients.

For each study, patients' demographic and disease conditions were generally balanced between treatment groups. The median age of study participants ranged from 56 to 61 years and most patients were male. The ECOG PS at baseline suggested that majority of patients in the CONCUR study reported impact on their daily life as a result of their disease, with an ECOG PS of 1 in 74% and 78% of patients in the regorafenib and placebo groups, respectively. The converse was true in the CORRECT study in which at baseline, 52% and 57% of patients in the regorafenib and placebo groups respectively, had an ECOG PS of 0 (little impact on daily living activities due to their disease).

Patients were randomized in a 2:1 ratio in both studies. In the CORRECT study, 505 and 225 patients to the regorafenib and placebo arms, respectively. In the CONCUR study, 136 and 68 patients to the regorafenib and placebo arms, respectively. In both the CORRECT and CONCUR studies, patients in each treatment arm also received best supportive care (BSC) which included any appropriate concomitant medications or treatments such as antibiotics, analgesics, radiation therapy for pain control, corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC. Other investigational anti-tumour agents or anti-neoplastic chemotherapy were not allowed.[11]

The primary endpoint was overall survival (OS) in both studies with the CORRECT study reporting a median OS of 6.4 months in the regorafenib group and 5.0 months in the placebo group, while the CONCUR study reported respective median OS of 8.8 months and 6.3 months (Table 1). Thus, treatment with regorafenib resulted in OS gain over placebo of 1.4 months (HR: 0.79, 95%CI: 0.66-0.94, p=0.0038) and 2.5 months (HR: 0.55, 95%CI: 0.40-0.77, p=0.0002) in the CORRECT and CONCUR studies, respectively.

Progression-free survival (PFS) results from both studies indicated regorafenib reduced the risk of disease progression. The median PFS was 1.9 and 1.7 months in the regorafenib and placebo group, respectively (HR: 0.49, 95%CI: 0.42-0.58, p<0.0001). For the CONCUR study, the median PFS was 3.2 and 1.7 months in the regorafenib and placebo group, respectively (HR: 0.31, 95%CI: 0.22-0.44, p<0.0001). There was no significant difference in health related quality of life (HRQoL) outcomes between regorafenib and placebo (Table 1).

In both studies, the proportion of patients who reported serious adverse events (SAEs), adverse events (AEs), and AEs leading to withdrawal/discontinuation of treatment (WDAEs), was generally similar between the regorafenib and placebo groups.

Table 1: Highlights of Key Outcomes

	CORRECT [a 2,12,13,14]		CONCUR[3,15,16]	
	REG (N=505)	PL (N=255)	REG (N=136)	PL (N=68)
Median OS (95% CI) in months	6.4 (5.8, 7.0)	5.0 (4.4, 5.9)	8.8 (NR)	6.3 (NR)
HR* (95% CI)	0.79 (0.66, 0.94)		0.55 (0.40-0.77)	
p-value	0.0038		0.0002	
Median PFS (95% CI) in months	1.9 (1.9, 2.1)	1.7 (1.7, 1.7)	3.2 (NR)	1.7 (NR)
HR* (95% CI)	0.49 (0.42, 0.58)		0.31 (0.22-0.44)	
p-value	<0.0001		<0.0001	
HRQoL - EOT			N=131	N=63
EORTC QLQ-30C, [b,†] LSM difference (95% CI)	−1.19 (−3.13, 0.75)		−0.40 (−3.53, 2.72)	
EQ 5D Index, [†] LSM difference (95% CI)	0.00 (−0.03, 0.03)		−0.03 (−0.08, 0.01)	
EQ 5D VAS, [†] LSM difference (95% CI)	−1.21 (−3.04, 0.61)		−1.18 (−4.01, 1.66)	
Harms Outcomes n (%)	(N=500)	(N=253)		
SAE	231 (46.2)	102 (40.3)	43 (31.6)	18 (26.5)
AE (any grade)	498 (99.6)	245 (96.8)	136 (100.0)	60 (88.2)
WDAE	95 (19.0)	31 (12.3)	19 (14.0)	4 (5.9)

AE= adverse event, **CI**= confidence interval, **EORTC QLQ-C30**= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, **EQ5D**= European Quality of Life 5 Dimensions, **HR**= hazard ratio, **HRQoL**= health-related quality of life, **NR**= not reported, **OS**= overall survival, **PFS**= progression free survival, **PL**= placebo, **REG**= regorafenib, **SAE**= serious adverse event, **SD**= standard deviation, **VAS**= visual analog scale, **WDAE**= withdrawal due to adverse event

*HR < 1 favours regorafenib

[a] Updated data are in bold font and are different from those reported in the second interim analysis

[b] Global health status at the end of treatment

[†] Higher scores indicate better HRQoL and better health status

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify any further relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) input, respectively.

Patient Advocacy Group Input

One patient advocacy group, Colorectal Cancer Association of Canada (CCAC), provided input on regorafenib (Stivarga) for the treatment of 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; for patients with ECOG status of ≤ 1, and their input is summarized below.

CCAC conducted two separate online surveys on March 12, 2013 to April 4, 2013 of colorectal cancer patients (n=3) and caregivers (n=1) in Canada and abroad to gather information about patient and caregiver experiences with the drug under review. These patients were contacted through the CCAC Medical Advisory Board medical oncologists as well as through expert medical oncologists within and outside of Canada who treat metastatic colorectal cancer. The survey used free-form commentary and scoring options (ten point scale) and limited closed-ended questions (agree/disagree, yes/no, patient/caregiver). CCAC also included a Quality of Life (QoL) survey of 1,001 Canadians aged 18 and over of which 82% of the respondents had a close family member or friend with cancer, or personally have or had cancer that was conducted in March 2011. A copy of the surveys were provided to pCODR. In addition to the above, to better provide the patient perspective, CCAC conducted interviews in November and December 2014 with three (3) patients who have used regorafenib who were not previously surveyed.

From a patient perspective, prolonging progression-free survival and allowing for extended control of their disease and an improved quality of life are important aspects when consideration is given to treatment. CCAC reported that for patients who exhaust currently approved treatments, accessing an additional therapeutic option would allow for increased progression free survival and extended disease control (i.e., tumour shrinkage or disease stability) with anticipated side effects. Patients are aware that all treatments for metastatic cancer carry risk and are willing to tolerate moderate to significant side effects during their treatment. CCAC noted that patients have found that early intervention in the management of these known side effects allows for a better tolerance; and thereby, allowing for them to stay on treatment for a longer period of time. Additionally as an oral therapy in late stage disease, quality of life and the ability to access treatment at home are important factors. CCAC indicated that current available treatment options in Canada are not suitable for all patients; therefore, patients with metastatic colorectal cancer seek choice and flexibility in selecting treatments to manage their disease and to maintain their quality of life.

PAG Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of regorafenib:

Clinical factors:

- Treatment option for patients who have previously been treated or are not candidates for intravenous chemotherapy
- Potential for use in earlier lines of therapy

Economic factors:

- Potentially large patient population
- Regular monitoring for serious adverse events and treatment of serious adverse events
- Drug wastage a possibility

2.2 Interpretation and Guidance

Regorafenib is an oral, small-molecule multi-kinase inhibitor targeting angiogenic, stromal and oncogenic pathways including VEGFR, PDGFR and KIT. Regorafenib was approved by Health Canada in March 2013 for the treatment of patients with mCRC who have previously been treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy and, if KRAS wild-type, an anti-EGFR therapy. Following a review by pCODR based primarily on the results of the CORRECT phase III trial, a recommendation to not fund was issued in November 2013. Since that time, access to regorafenib for Canadian patients has been limited to those patients with third-party-insurance, capacity to self-pay and patients eligible for the Bayer ABC Stivarga Program. This resubmission is now under consideration in light of further evidence including an updated analysis of the CORRECT trial and confirmatory positive results reported in a second phase III trial conduced in Asian patients (CONCUR).

Effectiveness

As highlighted in the systematic review, CORRECT was an international randomized trial which enrolled 760 patients with treatment-refractory mCRC and a performance status of 0-1, assigned in a 2:1 ratio to receive regorafenib 160mg orally daily for 3 of 4 weeks versus placebo. The median participant age was 61 years, approximately 60% were male, 40% were KRAS mutant, and 100% of participants had received prior bevacizumab therapy.[2] In the updated efficacy analysis, the primary endpoint of OS was superior in the regorafenib arm (median 6.4 vs 5.0 months, HR=0.79, p=0.0038)[4] As well, PFS was also improved in the regorafenib versus placebo arm (median 1.9 vs 1.7 months, HR=0.49, p<0.0001). Disease control was reported in 41% of patients on regorafenib vs 15% on placebo (p<0.0001). No differences were observed in the HRQoL analysis as measured by EORTC QLQ-C30 or EQ 5D. The rate of SAEs and withdrawal due to AEs was relatively high with 46.2% and 19%, respectively of those in the regorafenib group, compared to 40.3% and 12.3% respectively, of those in the placebo group, reflecting the general disposition and limited toxicity tolerance of these heavily-pretreated patients.

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In both CORRECT and CONCUR, the HRQoL changes were similar in the regorafenib and placebo groups, including magnitude of end-of-treatment deterioration and time to deterioration. A post-hoc analysis of CORRECT suggested that time to deterioration with regorafenib was significantly longer than placebo when assessed using a GHS-based 3-component endpoint, however, a significant difference was not observed when the other endpoints were applied.[6]

Safety

The most common toxicities in both studies included hand-foot skin reaction, fatigue, diarrhea, hypertension, rash, and anorexia. While clinical utilization of regorafenib in Canada has been limited, medical oncologists have nonetheless gained some experience with its use. There is an appreciation of its TEAEs, which are not unlike those seen with other multi-kinase inhibitors in common use. The importance of appropriate patient-selection and the use of

alternative dosing strategies may help to mitigate severe toxicities and early withdrawal. However, there are no identified patient subgroups or clinical predictors of toxicity and efficacy to assist in rationale therapeutic decision-making. In addition, no validated predictive or pharmacogenomics biomarkers have yet been identified to determine which patients are most likely to benefit from regorafenib.

Need and Burden of Disease

As the second and third most common cause of cancer death in Canadian males and females respectively, colorectal cancer (CRC) represents a significant disease burden in Canada. Due in large part to the availability of newer and novel systemic therapies, notable progress has been made in recent years in extending the survival of patients diagnosed with CRC, both in terms of extending the probability of cure for patients with earlier-stage and resectable disease, and extending survival and QoL for patients living with mCRC.

Patient advocacy group input based upon patient surveys and updated interviews with patients who have been on regorafenib therapy, highlights that prolonging PFS and allowing for extended control of their disease and improved QoL are important aspects when consideration is given to treatment. Patients are aware that all treatments for metastatic cancer carry risk and are willing to tolerate moderate to significant side effects during their treatment. Oral therapy in late stage disease, QoL and the ability to access treatment at home are important factors; patients seek choice and flexibility in selecting treatments to manage their disease. The balance between the efficacy and safety tradeoff needs to be an individual patient decision. With respect to implementation of regorafenib therapy, the Provincial Advisory Group has acknowledged concerns that the eligible patient population may be large and there will be a need for regular and early toxicity monitoring. The possibility of drug wastage would also need to be considered.

In summary, regorafenib is an oral agent that offers a modest yet statistically superior disease control rate, progression free survival and overall survival when compared to best supportive care, as demonstrated in two randomized, placebo-controlled phase III studies. The demonstration of survival benefit is consistent but the absolute median survival benefit is modest, shown to be a gain of 1.4 months (HR=0.79) in CORRECT and 2.5 months (HR=0.55) in CONCUR. There is no evidence of quality of life improvement and toxicities are common, requiring close supervision and early management. In the opinion of the Clinical Guidance Panel, regorafenib provides a treatment option for selected patients with treatment-refractory mCRC with a preserved performance status. Given the lack of alternative therapeutic options, this indication represents an important unmet medical need.

2.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit with the use of regorafenib over best supportive care alone in patients with treatment-refractory metastatic colorectal cancer.

In making this conclusion, the Clinical Guidance Panel considered:

- **Effectiveness:** The efficacy of regorafenib has been demonstrated in two similarly-designed, multi-centre RCTs, CORRECT and CONCUR, with a modest but consistent and statistically significant improvement in OS. There was no associated significant improvement in QoL measures. These trials include patients from Western and Asian populations and are considered generalizable to Canadian patients with treatment-refractory mCRC with an ECOG PS of 0-1.

- **Safety:** Regorafenib introduces the risk of toxicities such as hand-foot skin reaction, fatigue, diarrhea, hypertension, rash, and anorexia. These toxicities can be managed with early intervention and there is an increasing awareness among the Canadian oncology practitioner community regarding the profile and management of such toxicities. Patient advocacy input suggests that patients would be willing to tolerate moderate to significant treatment-related side effects in the hopes of controlling their disease.
- **Need and Burden of disease:** As a leading cause of cancer-related morbidity and mortality, the burden of mCRC among Canadians is significant. Regorafenib fulfills an unmet need for the treatment of patients with mCRC who have exhausted all currently available systemic therapies yet are still well enough to consider further treatment.
- In reaching this conclusion the panel was unable to comment on the use of regorafenib in earlier lines of therapy. To the panel's knowledge, there is no evidence currently supporting the use of regorafenib in earlier lines of therapy.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Colorectal cancer represents the second most common cause of cancer death in males and third most common cause of cancer death in females. The Canadian Cancer Society estimates that, in 2014, 24,400 Canadians were diagnosed with, and 9,300 Canadians died as a consequence of, colorectal cancer.[17] Approximately 20% of patients present with metastatic disease while another 30% of those presenting with early-stage disease will go on to develop metastatic recurrence. As such, the burden of metastatic colorectal cancer (mCRC) remains significant.

3.2 Accepted Clinical Practice

Aside from a minority of cases where resection of isolated liver and/or lung metastasis is possible, mCRC is considered incurable. Untreated, historical series describe a median survival in the range of six to ten months.[18] As such, the goal of treatment in this setting is to extend survival, reduce disease-related symptoms and improve quality of life. With the subsequent 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 with a 5 year survival rate of less than 10%.[19]

The current paradigm for the systemic treatment of mCRC is based upon the delivery of sequential lines of combination chemotherapy. In Canada, the preferred strategy includes first-line doublet chemotherapy with a fluoropyrimidine and irinotecan (FOLFIRI) with or without bevacizumab or a fluoropyrimidine and oxaliplatin (FOLFOX or CAPOX) with or without bevacizumab with a switch to the alternate doublet in second-line. Third-line treatment is predicated upon the molecular KRAS status of a tumour with wild-type KRAS disease (representing 50-60%) amenable to treatment with an EGFR inhibitor (i.e. cetuximab or panitumumab). No further funded therapeutic options are currently available in Canada for patients who have failed anti-EGFR therapy or for patients with mutant KRAS disease; these patients may be offered clinical trials if available, or more commonly, are transitioned to best supportive care only. This represents an important unmet need for a meaningful proportion of patients who maintain an acceptable performance status yet have exhausted all standard therapies. It is in this context that regorafenib may be considered as an additional therapeutic option.

Regorafenib is an oral, small-molecule multi-kinase inhibitor targeting angiogenic, stromal and oncogenic pathways including VEGFR, PDGFR and KIT. The CORRECT study was an international randomized, placebo-controlled, phase III trial conducted at 114 centres in North America, Europe, Asia, and Australia in treatment-refractory mCRC.[20] This trial included patients meeting eligibility criteria of a performance status of ECOG 0 or 1, a life expectancy of over three months, and a pathologically confirmed advanced adenocarcinoma of the colon or rectum. Disease progression during or within three months of prior standard therapy was required and patients were to have been exposed to all of the available standard therapies (i.e. fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab and either panitumumab or cetuximab if KRAS wild-type). Subjects were randomized in a 2:1 fashion to receive best supportive care plus either regorafenib

160 mg orally daily for three of four weeks or matching placebo until disease progression, death, unacceptable toxicity, withdrawal of consent, or decision by the treatment physician.

When compared to best supportive care plus placebo, the additional of regorafenib to best supportive care resulted in a statistically significant improvement in overall survival (6.4 versus 5.0 months, HR=0.77, 95%CI: 0.64-0.94, p=0.0052) in addition to an improved disease control rate (41% versus 15%, p<0.0001) and progression-free survival (1.9 months versus 1.7 months, HR=0.49, 95%CI: 0.42-0.58, p<0.0001). The rate of grade 3/4 treatment-related adverse events with regorafenib was 54% versus 14% on placebo. Adverse events leading to permanent discontinuation were 19% vs 12% respectively. The associated common toxicities (hand-foot skin reaction, fatigue, diarrhea, hypertension, rash) occur early and were manageable with dose reductions or interruptions.[21] A planned quality of life (QoL) analysis using EORTIC QLQ-C30 and EQ-5D revealed a similar decline in QoL in both the regorafenib and placebo arms. A post-hoc QoL analysis using time to deterioration indicated that regorafenib was associated with a reduced risk of deterioration compared to placebo (HR=0.77, 95%CI: 0.65–0.91; p<0.01).[6] A final updated efficacy analysis confirmed the median OS was 6.4 months for regorafenib versus 5.0 months for placebo (HR=0.79, 95% CI 0.66-0.94).[4] These findings led to an expedited review and subsequent Notice of Compliance issued by Health Canada in March 2013 with approval of regorafenib for the treatment of patients with refractory mCRC.[1]

The survival benefit of regorafenib in this setting was confirmed in a subsequent phase III trial of similar design in Asian patients. The CONCUR trial included 204 patients (from China, Hong Kong, South Korea, Taiwan and Vietnam) with chemo-refractory mCRC.[3] Failure on prior biologic therapy was not mandated. The results presented at the World Congress of GI Cancers in June 2014 demonstrated a statistically significant improvement in OS (8.8 versus 6.3 months, HR=0.550, p<0.001) and progression-free survival (3.2 versus 1.7 months, HR=0.311, p<0.0001). The grade ≥3 toxicity rate was 71.3% vs 44.2% for placebo, most commonly related to hand-foot syndrome/rash, hypertension, liver function abnormalities, diarrhea and fatigue. The treatment discontinuation rate was similar to CORRECT (14% vs 5.9%).

The use of regorafenib as a treatment option in this setting of treatment-refractory mCRC has since been endorsed in the guidelines of the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO).[22,23]

3.3 Evidence-Based Considerations for a Funding Population

The population under consideration are patients with mCRC who have previously been treated with a fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy (bevacizumab) and, if KRAS wild-type, an anti-EGFR therapy (cetuximab or panitumumab).

Given the potential for toxicity, their performance status would be well maintained (ECOG 0 or 1).

Assuming that there is a 30% drop-off for each line of therapy administered, this would suggest that about 3,200 Canadians would be considered appropriate for treatment with regorafenib annually.

Currently, there are no biomarkers that predict for a response to regorafenib.

3.4 Other Patient Populations in Whom the Drug May Be Used

No additional patient populations would be considered for regorafenib therapy. The benefit of regorafenib in earlier lines of therapy for mCRC or in the adjuvant setting is not known.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Colorectal Cancer Association of Canada (CCAC), provided input on regorafenib (Stivarga) for the treatment of 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; for patients with ECOG status of ≤1, and their input is summarized below.

CCAC conducted two separate online surveys on March 12, 2013 to April 4, 2013 of colorectal cancer patients (n=3) and caregivers (n=1) in Canada and abroad to gather information about patient and caregiver experiences with the drug under review. These patients were contacted through the CCAC Medical Advisory Board medical oncologists as well as through expert medical oncologists within and outside of Canada who treat metastatic colorectal cancer. The survey used free-form commentary and scoring options (ten point scale) and limited closed-ended questions (agree/disagree, yes/no, patient/caregiver). CCAC also included a Quality of Life (QoL) survey of 1,001 Canadians aged 18 and over of which 82% of the respondents had a close family member or friend with cancer, or personally have or had cancer that was conducted in March 2011. A copy of the surveys were provided to pCODR. In addition to the above, to better provide the patient perspective, CCAC conducted interviews in November and December 2014 with three (3) patients who have used regorafenib who were not previously surveyed.

From a patient perspective, prolonging progression-free survival and allowing for extended control of their disease and an improved quality of life are important aspects when consideration is given to treatment. CCAC reported that for patients who exhaust currently approved treatments, accessing an additional therapeutic option would allow for increased progression free survival and extended disease control (i.e., tumour shrinkage or disease stability) with anticipated side effects. Patients are aware that all treatments for metastatic cancer carry risk and are willing to tolerate moderate to significant side effects during their treatment. CCAC noted that patients have found that early intervention in the management of these known side effects allows for a better tolerance; and thereby, allowing for them to stay on treatment for a longer period of time. Additionally as an oral therapy in late stage disease, quality of life and the ability to access treatment at home are important factors. CCAC indicated that current available treatment options in Canada are not suitable for all patients; therefore, patients with metastatic colorectal cancer seek choice and flexibility in selecting treatments to manage their disease and to maintain their quality of life.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission and have not been corrected.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with mCRC

CCAC reported that the symptoms of metastatic colorectal cancer (mCRC) include but are not limited to: severe abdominal pain, shortness of breath, coughing, fatigue, bloating and loss of appetite. The symptoms experienced by patients with mCRC are dependent upon the metastatic site. CCAC noted that mCRC is a fatal disease for which there is no known cure other than tumour control or reduction coupled with surgery in some cases. CCAC also noted that there are limited reimbursed treatment options depending on the province in which they live.

First and second line therapy (FOLFIRI/FOLFOX) in combination with a biologic therapy (bevacizumab) can successfully shrink tumours and stop the progression of the disease for a period of time for a subset of patients. Unfortunately, for other patients the cancer may become resistant to these lines of therapy and the question arises as to whether to treat beyond progression with bevacizumab or to treat with a new line of therapy. For the patient population (approximately 60%) identified to be KRAS wild type, third line therapy may be prescribed to provide quality of life benefit and additional overall survival. The balance, however, (approximately 40%) are left without a treatment alternative. Eventually, even patients with KRAS wild type disease exhaust third line therapy and are left without a treatment option in fourth line. Without treatment options in third line (for KRAS mutant) and fourth line (KRAS wild type), patients face certainty of disease progression including worsening of symptoms such as increasing shortness of breath, severe fatigue, abdominal pain, lung disease, painful bone metastases, peritoneal disease, liver failure and/or brain metastases.

According to the patient survey conducted by CCAC and conversations CCAC had with patients, the most frequently reported disease-related symptoms were: fatigue, bloody stools, painful diarrhea/constipation all of which impacted a patient's quality of life significantly.

> "*Fatigue was the most difficult aspect to control of colorectal cancer; and wanting to get back to be able to do some work*."

CCAC indicated that patients who have progressed to third or fourth line treatments are in need of an additional therapeutic option to help manage their disease and side effects, help maintain quality of life and prolong overall survival.

4.1.2 Patients' Experiences with Current Therapy for mCRC

Current therapies such as FOLFIRI and FOLFOX administered in first and second line in combination with a biologic therapy have proven to successfully shrink tumours and provide progression free survival for a limited period of time. However, resistance eventually develops which necessitates an additional treatment option in these patients with treatment-refractory mCRC.

Current treatment-related toxicities often necessitate discontinuation of therapy. For example, neurotoxicity is the most frequent dose-limiting toxicity of oxaliplatin. A cumulative sensory peripheral neuropathy may also develop with prolonged treatment with oxaliplatin. Patients report tingling or a feeling of pins and needles in hands and feet with severe numbness and find it difficult to do small tasks with their hands such as, buttoning a shirt. In some cases, neuropathy can cause pain and difficulty with daily life, including walking or balancing. Diarrhea, nausea and vomiting are the most frequently reported side effects of irinotecan which can cause dehydration and necessitate cessation of therapy. Serious adverse reactions to 5-FU are chest pain, ECG changes and increases in cardiac enzymes - which may indicate problems with the heart. An additional treatment option may ensure continued clinical benefit.

According to CCAC, respondents indicated it would be very important to access additional treatments whose benefits might only be short term despite treatment adverse effects. The survey conducted by the CCAC showed that patients were interested in treatment even in end of life situations when the benefit was just a few weeks provided there was a good quality of life. The results of the CCAC survey determined that part of maintaining quality of life is linked to providing greater access to therapies that treat mCRC.

CCAC noted that disparities exist across Canada as they relate to access to treatments both to the therapy itself and in some cases, the line of treatment in which it is available. Over 50% of

respondents surveyed in the Quality of Life survey conducted by the CCAC of the general public believe that geographical location impacts the quality of treatment when diagnosed with cancer.

For the KRAS wild type population, third line therapy is not funded in some provinces and, therefore, not accessible to all patients. Moreover, there is also an unmet clinical need for the KRAS mutation positive patients who have exhausted first and second line therapy. Current provincial reimbursement eligibility criteria is perceived to be too restrictive or limited by many patients. In view of the above, CCAC believes that funding of an additional therapeutic option would help to increase access for both these patient populations and to manage the progression of this disease.

4.1.3 Impact of mCRC and Current Therapy on Caregivers

Patient advocacy group input indicated that the impact of mCRC on caregivers and families is significant. Caregivers provide supportive care to the patient in managing adverse side effects, providing emotional support and assuming additional unpaid work duties in the home. Additionally, caregivers of mCRC patients are fraught with financial challenges relating to disability and cost of accessing treatments in those provinces that do not currently fund third line therapy.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Regorafenib

Based on the information collected by CCAC, patients have repeatedly expressed their desire to continue accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival. For patients who exhaust currently approved treatments, accessing an additional therapeutic option would allow for increased progression free survival and extended disease control (i.e., tumour shrinkage or disease stability) with anticipated side effects. Additionally as an oral therapy in late stage disease, quality of life and the ability to access treatment at home are important factors.

One respondent who participated in the CCAC survey reported he "*feels very fortunate to be on regorafenib as opposed to more chemo*". Respondents also reported that in the absence of tumour shrinkage, disease stability would be highly welcomed for their progressive, treatment-refractory mCRC. There is a gap or unmet patient need in current therapy that regorafenib would help alleviate, particularly, in the KRAS mutant and treatment refractory population.

CCAC reported that patients are aware that all drug therapies have associated risks. Regorafenib has significant adverse events, such as hand-foot skin reaction, fatigue and diarrhea; side effects with which patients are well acquainted from previously administered therapies. CCAC noted that patients have found that early intervention in the management of these known side effects allows for a better tolerance; and thereby, allowing for them to stay on treatment for a longer period of time. As an oral therapy, regorafenib is not administered in a hospital setting and, therefore, allows the patient ease of use often associated with clinic visits and having to endure hours of treatment infusions and infusion-related adverse events. Fewer clinic/hospital visits can help alleviate some of the cancer patient's stress. As an orally administered monotherapy, regorafenib offers patients the opportunity to access an additional line of therapy in the comfort of their own homes.

CCAC interviewed three (3) mCRC patients currently receiving regorafenib. Below is a summary of the key observations that were reported by the respondents.

Patient #1 is a 55 year old female whose metastatic disease is confined to the spleen. CCAC reported that she has been receiving regorafenib for 18 months as of November 2014 with virtually no toxicity issues. The respondent reported excellent QoL, no dosage adjustments and has achieved disease stabilization throughout the entire 18 month period. In her own words, "*the only negative effect from the drug is the fact that I need to take a nap in the afternoons while on the drug*". In addition to the above, the respondent expressed an appreciation for an oral medication which can be administered in the comfort of her own home, thus saving her the time, effort and expense of travel to the cancer centre.

Patient #2 is a 79 year old male with metastatic disease to the liver, abdomen and rectum. CCAC reported that he has been receiving regorafenib for five (5) months as of December 2014. The respondent experienced severe Hand & Foot syndrome and fatigue throughout the first cycle of the therapy; however, it was reported that a 25% dose reduction resolved these toxicity issues. The respondent has not experienced any other medication-related adverse events. His most recent CT scan revealed disease shrinkage/stabilization and is tolerating the therapy, in his words, "*quite well*". The respondent claims to prefer an oral medication to an infusional therapy and is pleased with having reduced the number of visits to the cancer centre. He noted it makes for "*a less stressful life*" for his wife (who is the primary caregiver) and himself.

Patient #3 is a 66 year old female with metastatic disease to liver and lungs. CCAC reported that she has been receiving regorafenib for three and half (3.5) months as of December 2014. According to CCAC, her latest CT scan showed disease shrinkage in both organs. A 25% dose reduction was necessary after the first cycle to address the Hand & Foot Syndrome. The respondent maintains her QoL was being compromised due to regorafenib –induced toxicity: "*painful hands and feet, blisters on hands and feet, difficulty walking, fatigue kept me from living my life*". According to the respondent, a 25% dosage reduction completely addressed the toxicity issues and was able to resume her daily routine. The administration of an oral medication in the comfort of her own home also spared her costly parking (and other) expenses borne out of trips to the Cancer Centre. In her words: "*I'm a big fan of this chemo pill. Not only is it therapeutic, but it's also convenient for me and my family*."

4.3 Additional Information

Patients and physicians are in agreement that an additional line of therapy is required for the treatment-refractory mCRC population. The KRAS mutant population is underserved and would benefit from regorafenib therapy, allowing them access to a third line therapy that is currently non-existent. In the metastatic setting, long term health is relative and is viewed by patients in small increments. Any reasonable extension of life is considered desirable by mCRC patients and caregivers.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of regorafenib:

Clinical factors:

- Treatment option for patients who have previously been treated or are not candidates for intravenous chemotherapy
- Potential for use in earlier lines of therapy

Economic factors:

- Potentially large patient population
- Regular monitoring for serious adverse events and treatment of serious adverse events
- Drug wastage a possibility

Please see below for more details.

5.1 Factors Related to Comparators

The current standard treatment for patients with mCRC who have previously been treated with, or are not candidates for, intravenous chemotherapy is best supportive care. PAG noted that the availability of another treatment option as an enabler to implementation.

5.2 Factors Related to Patient Population

If all patients in the third and fourth line setting become eligible to receive regorafenib, the patient population could be large. PAG also recognised a potential for indication creep in that as an oral therapy, patients and oncologists may request to receive regorafenib in earlier lines of therapy, over the current evidence-based intravenous therapies.

5.3 Factors Related to Dosing

PAG noted that the dosing of regorafenib requires 4 pills once daily. As regorafenib comes in 40mg tablets, PAG noted that dose adjustments will be easy if needed. There are concerns with drug wastage due to dose adjustments because the 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. Regorafenib is supplied in a bottle of 28 tablets which requires 3 bottles of 28 to be dispensed for a 21 days supply. Patients could and likely will open more than one bottle, so they could have three bottles opened at any one time. If the patient has been dose reduced to two tablets daily for 21 days of a 28 day cycle, up to 42 tablets from the 84 issued, could be wasted if the patient has opened multiple bottles.

Although the once daily regimen will increase patient compliance, PAG noted that the dosing schedule of 3 weeks on and 1 week off may potentially result in dosing errors.

5.4 Factors Related to Implementation Costs

As a potential barrier to implementation, PAG noted that the availability of a new treatment where patients previously would have received best supportive care could increase incremental costs. These may include increased pharmacy workload for dispensing of a new drug and increased monitoring of patients for drug interactions or managing toxicities.

PAG noted that the Black Box Warnings and other adverse events associated with regorafenib therapy would require additional health care resources to regularly monitor and treat the toxicities.

5.5 Factors Related to Health System

PAG noted that regorafenib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

It is also important for pharmacy staff to be aware that regorafenib should not be repackaged in unit dose blister packaging but remain in its original container for dispensing. This is a barrier as many of these patients have their medications repackaged into blister packages.

5.6 Factors Related to Manufacturer

Regorafenib is supplied in a bottle of 28 tablets, which at 4 tablets a day is a one week supply. The tablets are only stable for 28 days once the bottle has been opened and it is important for patients and their caregivers be taught to only open one bottle at a time otherwise this could lead to drug wastage.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of regorafenib (Stivarga) on patient outcomes 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. See Table 2 in Section 6.2.1 for outcomes of interest and comparators.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 2: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished DB RCTs	Patients with mCRC who have been previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if KRAS wild-type, anti-EGFR therapy. **Subgroups:** **Age** • <65 years • ≥65 years **KRAS mutation** • KRAS wild type • KRAS mutant	Regorafenib plus BSC	Placebo plus BSC	Efficacy • **OS** • **PFS** • **HRQoL** • **DCR** AEs • SAEs • **AEs** • WDAEs • Dose modification **AEs of Special Interest** • **HFSR** • Hypertension • **Diarrhea** • Liver toxicity

AE = adverse events; **BSC** = best standard care; **DB** = double-blind; **DCR** = disease control rate; **EGFR** = epidermal growth factor receptor; **HFSR** = hand-foot skin reaction; **mCRC** = metastatic colorectal cancer; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression-free survival; **QOL** = quality of life; **RCT** = randomized controlled trial; **SAE** = serious adverse event; **VEGF** = vascular endothelial growth factor; **WDAE** = withdrawal due to adverse event.

Note: the underlined sections under the Patient Population and Outcomes criteria were the only changes made to the original systematic review protocol for the regorafenib resubmission.
* Standard and/or relevant therapies available in Canada (may include Drug and non-drug interventions)

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2014, Issue 12) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were regorafenib and Stivarga.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of April 1, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Cancer Trials registry) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

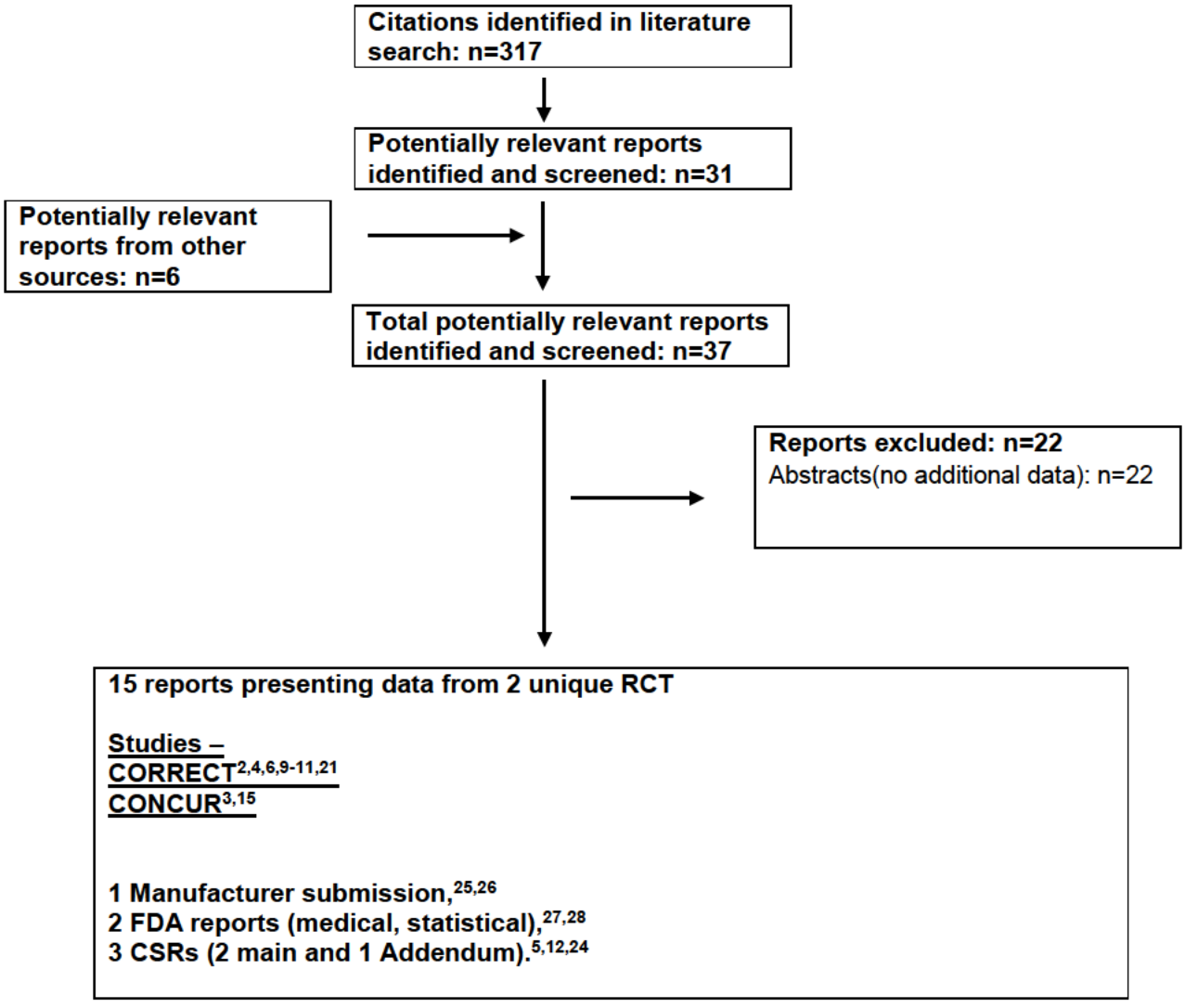
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental issues.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information, the interpretation of the systematic review and wrote guidance and conclusions for the report.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 37 potentially relevant reports identified, 15 reports presenting data from 2 unique RCTs were included in the pCODR systematic review[2-6,9-12,15,21,24] and 22 reports were excluded. Reports were excluded because they were abstracts with no additional data.

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

Included studies for the Resubmission

Updated overall survival (OS) and safety data for the CORRECT trial (OS data cut-off dates of July 21, 2011 and November 13, 2011; safety data cut-off date of January 22, 2014), which was the sole study included in the initial review, was provided by the manufacturer.[4,24] In addition, the manufacturer provided data from an ongoing placebo controlled study (CONCUR),[3,5,15] evaluating efficacy and safety of regorafenib in Asian patients with metastatic colorectal cancer (mCRC) who progressed during or within 3 months following the last administration of approved standard therapies. The CONCUR study is similar in design to the CORRECT study (see Table 3). No additional study that met the inclusion criteria of this review was identified by the pCODR literature search.

6.3.2.1 Detailed Trial Characteristics

Table 3: Summary of Trial Characteristics of the Included studies (CORRECT and CONCUR)

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
CORRECT[2] 114 centres in 16 countries in North America (including five centers in Canada), Europe, Asia and Australia Patient enrollment: 30 April 2010 to 22 March 2011. Data cut-off was on July 21, 2011 n=760 randomized, n=753 treated Phase III, double- blind, placebo controlled RCT Randomization was stratified by previous treatment with VEGF-targeting drugs, time from diagnosis of metastatic disease to randomization, and geographical region Funded by Bayer HealthCare Pharmaceuticals	Patients ≥ 18 years with histological or cytological documentation of metastatic adenocarcinoma of the colon or rectum Disease progression during or within 3 months after last administration of approved standard therapies or standard therapy discontinued due to unacceptable toxic effects Measurable or non-measurable disease according RECIST v1.1 ECOG PS ≤1 Life expectancy≥ 3 months Adequate bone-marrow, liver and renal function Patients were excluded if they had prior treatment with regorafenib, were pregnant or breast-feeding or had uncontrolled medical disorders	Oral regorafenib (160 mg) once daily plus BSC versus placebo plus BSC First 3 weeks of each 4 week cycle	<u>Primary</u> OS <u>Secondary</u> PFS, ORR, DCR, safety <u>Tertiary</u> Duration of response and stable disease, HRQL (EORTC, QLQ-C30, EQ-5D)

Table 3: Summary of Trial Characteristics of the Included studies (CORRECT and CONCUR)

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
CONCUR (Study 15808)[3,5,15] 25 centres in 5 countries in Asia (Mainland China, Hong Kong, Taiwan, Vietnam, and South Korea) Data cut-off was on Nov. 29, 2013 Study Start date: April 2012 Estimated Completion: June 2015.[29] n=243 enrolled, n=204 randomized, n=204 treated Phase III, double- blind, placebo controlled RCT Randomization was stratified by single organ metastasis versus multiple organ metastasis), and time from diagnosis of metastatic disease to randomization (≥ 18 months versus < 18 months. Funded by Bayer HealthCare Pharmaceuticals	Asian male or female patients 18 years of age or older with mCRC (Stage IV) who have failed at least two lines of prior treatment. Disease progression during or within 3 months following the last administration of approved standard therapies. Measurable or non-measurable disease according to RECIST criteria, version 1.1 ECOG PS ≤1 Life expectancy≥ 3 months Adequate bone-marrow, liver and renal function Patients were excluded if they had prior treatment with regorafenib, were pregnant or breast-feeding or had uncontrolled medical disorders	Oral regorafenib (160 mg) once daily plus BSC versus placebo plus BSC First 3 weeks of each 4 week cycle	Primary OS Secondary PFS, ORR, and DCR, Tertiary Duration of response, duration of stable disease, HRQL (EORTC QLQ-C30, EQ-5D) Safety variables SAE, and AE

AE= adverse events, **BSC=** best supportive care, **DCR**= disease control rate, **ECOG PS**= Eastern Cooperative Oncology Group performance status, **EORTC**= European Organization for Research and Treatment of Cancer, **EQ-5D**= EuroQoL five dimensions, **HRQoL**= health-related quality of life, **ORR**= objective tumour response rate, **OS**= Overall Survival, **PFS**= progression free survival, **RCT**= randomized controlled trial, **RECIST**= Response Evaluation Criteria in Solid Tumors, **SAE**= serious adverse events

Source: Grothey, 2013,[20]; Li, 2014[3] and Kim et al., 2015,[15]

a) Trials

CORRECT, a multicentre phase III, double-blind RCT[2,20] was included in this review. Patients were randomized in a 2:1 ratio between regorafenib (N= 505) and placebo (N=255).

Major eligibility criteria for inclusion into the study have been listed in Table 3. Approved standard therapies included fluoropyrimidine, oxaliplatin and irinotecan.[5] When oxaliplatin was used as adjuvant therapy, patients must have progressed during or within 6 months of completion of adjuvant therapy. Patients who progressed more than 6 months after completion of therapy in which oxaliplatin was used as adjuvant must have been retreated with oxaliplatin-based therapy to be eligible.[5]

The study was designed to have 90% power to detect a hazard ratio (HR) of 0.75 for regorafenib versus placebo, with a one-sided alpha (α) of 0.025 and 2:1 randomization, assuming a median

overall survivals of 4.5 months and 6 months for the placebo and regorafenib groups respectively. It was estimated that 582 deaths were needed for the final analysis and this could be expected from accrual of 690 patients. Besides the final analysis, two interim analyses of overall survival were performed. The first interim analysis was for futility and was planned at approximately 174 (30%) deaths and a second interim analysis of futility and efficacy was planned at approximately 408 (70%) deaths. The study was to be stopped at the second interim analysis, if for efficacy the one-sided p-value was ≤ 0.0093, approximately corresponding to HR≤0.7864. The LanDeMets alpha spending function with an O'Brien-Fleming type of stopping boundary was used to adjust for inflation of type 1 error rate for the second interim analysis of efficacy. Patients were enrolled between April 30, 2010 and March 22, 2011.The second interim analysis cut-off date was July 21, 2011 and at that time the efficacy boundary had been crossed and the trial was stopped for efficacy.[2,30,31] The study was unblinded after completing this analysis and four patients in the placebo group crossed over to receive regorafenib. An updated final analysis cut-off date was dated for November 13, 2011 with updated safety data for January 22, 2014.

New data: CONCUR

The CONCUR trial had a similar design as the CORRECT study.[5] Two hundred and four (204) patients were randomly assigned on a 2:1 basis in a blinded fashion to be treated with regorafenib 160 mg daily (N=136) or matching placebo (N=68), for 3 weeks of every 4 week cycle, 3 weeks on treatment with 1 week off. The sample size calculation was based on an overall 1-sided α of 0.2 assuming a 33.3% increase in the median OS (HR=0.75), with 154 death events providing 80% power.[3,15]

Randomization was stratified by occurrence of metastasis (single organ versus multiple organ metastasis), and time from diagnosis of metastatic disease (≥18 months versus <18 months).[5]

In both the CORRECT and CONCUR studies, patients in each treatment arm also received best standard care (BSC) which included any appropriate concomitant medications or treatments such as antibiotics, analgesics, radiation therapy for pain control, corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC. Other investigational anti-tumor agents or anti-neoplastic chemotherapy were not allowed.[5]

b) Populations

Of the 1052 patients screened in the study CORRECT, 760 were randomized in a 2:1 ratio to receive regorafenib (n=505) or placebo (n=255). The median age was 61 years. The proportion of males was higher compared with females (61% versus 39%). Majority of the patients were white (78%). For most patients (82%), the time from diagnosis of metastases was ≥18 months. Details of patient characteristics in the two groups are shown in Table 4.

New Data: CONCUR

The population characteristics of the CONCUR study are also summarized in Table 4. In general, patients' characteristics at baseline were similar between the regorafenib and placebo groups as it was in the CORRECT study. It is noteworthy that unlike the CORRECT study, the CONCUR study allowed the inclusion of patients who had not been pre-treated with targeted therapies such as bevacizumab and/or cetuximab. According to the manufacturer, real-life-situation in Asia had revealed that not all patients had access at study entry to these drugs even if these drugs were approved.[5,15] Overall, 40% of patients in the CONCUR study did not receive prior anti-VEGF or anti-EGFR targeted therapy before randomization, as opposed to the CORRECT study in which 100% of

patients had received prior bevacizumab (anti-VEGF) and 51% received prior cetuximab and/or panitumumab (anti-EGFR).[15]

Other differences between the population characteristic of the two studies include the solely Asian population in the CONCUR study in contrast to the CORRECT study which had a multi-continental population including Asians. Although majority of patients in both studies had first diagnosis of mCRC 18 months or longer before randomization, the percentage of such patients in the CONCUR study was smaller compared to the CORRECT study. Furthermore, unlike the CORRECT study in which the distribution of patients between ECOG 0 and ECOG 1 status was similar (although a slight majority had ECOG 0 in both arms), the status of patients in CONCUR was predominantly EGOG 1 (74.3% in regorafenib and 77.9% in Placebo).[3,5,15] Smaller proportion of patients in the CONCUR study were reported to have KRAS mutation than the CORRECT study. However, there were more patients with unknown KRAS status in the CONCUR study than in the CORRECT study.

Table 4: Summary of Patient Characteristics of the Included Studies

	CORRECT[5]		CONCUR[3,15]	
Characteristics	**REG (N= 505)**	**PL (N= 255)**	**REG (N= 136)**	**PL (N= 68)**
Age in years, median (IQR)	61 (54 - 67)	61 (54 - 68)	58 (31-79)	56 (30-84)
Male, n (%)	311 (62)	153 (60)	85 (62.5)	33 (48.5)
Race, n (%):				
White	392 (78)	201 (79)	0	0
Black	6 (1)	8 (3)	0	0
Asian	76 (15)	35 (14)	136 (100.0)	68 (100.0)
Other	31 (6)	11 (4)	0	0
Region, n (%):			NA	NA
1	420 (83)	212 (83)		
2	69 (14)	35 (14)		
3	16 (3)	8 (3)		
ECOG PS, n (%):				
0	265 (52)	146 (57)	35 (25.7)	15 (22.1)
1	240 (48)	109 (43)	101 (74.3)	53 (77.9)
Primary site of disease*, n (%):				
Colon	323 (64)	172 (68)	79 (58.1)	48 (70.6)
Rectum	151 (30)	69 (27)	53 (39.0)	19 (27.9)
Colon and Rectum	30 (6)	14 (5)	4 (2.9)	1 (1.5)
KRAS mutation†, n (%):				
No	205 (41)	94 (37)	50 (36.8)	29 (42.6)
Yes	273 (54)	157 (63)	46 (33.8)	18 (26.5)
Unknown	27 (5)	4 (2)	40 (29.4)	21 (30.9)
No. of previous systemic anti-cancer therapy‡, n (%):			NR	NR
1-2	135 (27)	63 (25)		
3	125 (25)	72 (28)		
≥4	245 (49)	120 (47)		
Previous anti VEGF treatment (Bevacizumab), n (%):	505 (100)	255 (100)	56 (41.2)	25 (36.8)
Prior treatment (stopped because of progression), n (%):			NR	NR
Fluoropyrimidine				
Bevacizumab	421 (83)	221 (87)		
Irinotecan	403 (80)	214 (84)		
Oxaliplatin	405 (80)	229 (90)		
Panitumumab or cetuximab or both	278 (55)	160 (63)		

Table 4: Summary of Patient Characteristics of the Included Studies				
	CORRECT[5]		CONCUR[3,15]	
Characteristics	REG (N= 505)	PL (N= 255)	REG (N= 136)	PL (N= 68)
	219 (43)	107 (42)		
Time from diagnosis of metastases, n (%):				
<18 months	91 (18)	49 (19)	54 (39.7)	28 (41.2)
≥18 months	414 (82)	206 (81)	82 (60.3)	40 (58.8)

ECOG PS= Eastern Cooperative Oncology Group performance status; **IQR**= interquartile range; **PL**= placebo, **REG**= regorafenib
Region 1= North America, western Europe, Israel and Australia, **Region 2**= Asia, **Region 3**= Eastern Europe

*Information missing from one patient in the regorafenib group in the CORRECT study.
†*KRAS* mutation status was based on historical patient record.
‡Five patients on placebo (2%) and 16 patients on regorafenib (3%) had received only one previous line of treatment for metastatic disease in the CORRECT study.

Source: Grothey, 2013,[2]; Li, 2014[3] and Kim et al., 2015,[15]

c) Interventions

Patients received oral regorafenib 160 mg (4 tablets, each 40 mg) or matching placebo once daily for the first 3 weeks of each 4 week cycle until disease progression, death, unacceptable toxic effects, withdrawal of consent, or decision of the treating physician to discontinue treatment in the best interest of the patient. All patients received in addition best supportive care.[2,32]

Common concomitant medications (≥ 25% of patients overall) included water-soluble, nephrotic, low osmolality x-ray contrast media, proton pump inhibitors, natural opium alkaloids, anilides, benzodiazepine derivatives, heparin group, corticosteroids acting locally, antipropulsives and dihydropyridine derivatives. In some instances, for the regorafenib and placebo groups there appeared to be differences in the proportion of patients receiving a particular concomitant medication. The proportions of patients in the regorafenib and placebo groups were respectively 43.0% and 29.8% for anilides, 28.5% and 17.3% for corticosteroids acting locally, 27.3% and 11.0% for antipropulsives, and 25.0% and 13.7% for dihydropyridine derivatives.[26]

Predefined dose changes were allowed for managing clinically significant treatment-related toxic effects. In patients who required dose reductions because of toxic effects, once the toxic effects were reduced to baseline levels, dose escalation up to 160 mg daily was permitted at the discretion of the investigator. Treatment was permanently discontinued if after a 4 week interruption or after dose reduction by two levels, toxic effects did not resolve. No crossover between treatment groups was permitted during the blinded phase of the study. Patients were followed every two weeks while receiving treatment and every month once treatment was stopped, until the trial data cut-off date or death. Details of extent of exposure to treatment are provided in Table 4.

New data: CONCUR

The intervention in the CONCUR study was similar to that of the CORRECT study as summarized in Table 5. The estimated final completion date of the CONCUR study is June 2015.[29] In the CONCUR study, the median overall time under treatment was 10.65 (range: 0.29-67.86) and 7.00 (0.29-39.00) weeks in the regorafenib and placebo groups, respectively. The median actual daily dose was similar with 153 mg (87-160) and 160 mg (160-160) in the regorafenib and placebo groups, respectively. In both the CORRECT and CONCUR studies, reported exposure data were generally higher in the regorafenib group than the placebo group. In terms of dose modifications, in the CONCUR study, 35 (25.7%) and 90 (66.2%) patients in the regorafenib group experienced dose reductions and dose interruptions, respectively. No patients in the placebo experienced dose reductions and 15 (22.1%) of patients had a dose interruption.

Table 5: Extent of exposure to treatment		
	CORRECT[2]	
Category	**REG (N= 500)**	**PL (N= 253)**
Overall time under treatment [b]		
Mean ± SD (weeks)	12.08 ± 9.74	7.78 ± 5.19
Median (range)	7.27 (NR)	6.98 (NR)
Number of cycles completed		
Mean ± SD	3.3 ± 2.3	2.3 ± 1.2
Median (range)	2.0 (1 - 12)	2.0 (1 - 10)
Actual time under treatment [c]		
Mean ± SD (weeks)	8.86 ± 6.82	6.29 ± 3.79
Median (range)	5.98 (NR)	5.98 (NR)
Actual daily dose (mg) [c]		
Mean ± SD	147.15 ± 18.63	159.25 ± 4.85
Median (range)	160.00 (NR)	160.00 (NR)
Total dose (mg) [c]		
Mean ± SD	8903.2 ± 6875.9	7022.5 ± 4237.3
Median (range)	6720.0 (NR)	6720.0 (NR)
Dose modification, n (%)		
Any dose modification	378 (75.6)	97 (38.3)
Dose reductions	100 (20.0)	8 (3.2)
Dose interruptions	352 (70.4)	95 (37.5)
Re-challenge at lower than protocol dose	169 (33.8)	4 (1.6)

NR= not reported, **PL**= placebo, **REG**= regorafenib **SD**= standard deviation
[b] Including time off drug/interruptions
[c] Excluding time off drug/interruptions

d) Outcome Measures

Efficacy Outcomes

Overall survival was the primary end-point in both the CORRECT and the CONCUR studies. It was defined as the time from randomization to death due to any cause.[26] Progression-free survival (PFS), defined as the time from randomization to the first observed disease progression (radiological or clinical) or death due to any cause (if death occurred before progression), was a secondary outcome in both the CORRECT and CONCUR studies.[2,3] Investigators assessed radiological or clinical PFS endpoint using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[3,5] Health related quality of life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the European Quality of Life 5 Dimensions (EQ-5D). Minimal clinically important difference (MCID) was ≥10 points for the EORTC QLQ-C30, 0.06 to 0.12 points for EQ-5D index, and 7 to 12 points for EQ-5D VAS.[2,33] Disease control rate (DCR) is another secondary outcome in the systematic review protocol, and it was defined as the sum of proportion of patients with complete response (CR) and partial response (PR) and stable disease (SD) for greater than or equal to six weeks after randomization.[26]

Safety outcomes

Safety outcomes were reported as serious adverse events (SAEs), adverse events (AEs), and AEs leading to withdrawal/discontinuation of treatment (WDAEs). A SAE was defined as any medical occurrence that was life-threatening, required hospitalization, resulted in death, resulted in significant disability or was judged by the investigator to be medically important.[26]

e) Patient Disposition

In the CORRECT study, five and two patients in the regarofenib and placebo groups, respectively, did not receive the intervention.[2] For the safety analysis, only patients who received treatment

(regarofenib or placebo) were considered. The most common reasons for discontinuation were progression of disease and adverse events (Table 6).

New data: CONCUR

All randomized patients in the CONCUR study received at least one treatment. Therefore, the full analysis set (FAS) population used to evaluate efficacy endpoints was equal to the safety analysis set (SAF) population (see Table 6).[5] Discontinuation rates were 100% and 95.6% in the placebo regorafenib groups, respectively (Table 6), with disease progression being the most common reason for discontinuation in both treatment groups. As of the data cut-off for this report (November 29 2013), only 6 (4.4%) of patients in the regorafenib treatment group were ongoing in the active treatment period.[5] Compared to the CORRECT trial, there were similar proportion of patients who discontinued treatment due to progressive disease. Slight differences were seen in the percentage of patients in the CONCUR trial who discontinued treatment for the reasons mentioned in Table 5.

Table 6: Patient Population and Disposition[2,12]

	CORRECT	
Category	**REG, n (%)**	**PL, n (%)**
Randomized	505 (100)	255 (100)
Received treatment	500 (99)	253 (99.2)
Efficacy analysis	505 (100)	255 (100)
Safety analysis	500 (99)	253 (99.2)
Discontinued	448 (88.7)	244 (95.7)
• progressive disease	336 (67)	205 (80)
• AE associated with disease progression	43 (9)	23 (9)
• AE unassociated with disease progression	42 (8)	7 (3)
• consent withdrawal	16 (3)	5 (2)
• death	7 (1)	4 (2)
• protocol violation	2 (<1)	0

AE= adverse event, **PL**= placebo, **REG**= regorafenib

f) Limitations/Sources of Bias

Limitations identified in the original submission:

- The patients in the trial had low ECOG PS [ECOG PS = 0 (54%), 1 (46%)]. Hence, it is unclear the extent to which the findings of the study will be generalizable to patients with a higher ECOG status and thus lower performance status.
- The RCT was funded by the manufacturer. The manufacturer in collaboration with the trial investigators designed the study, collected data and interpreted the results.
- There is potential of bias as assessment was conducted by the investigator and not by an independent assessor. However, the investigator was masked to treatment allocation, which is likely to reduce bias.
- Hand-foot skin reactions, diarrhea, hypertension and rash or desquamation were more frequent in the regorafenib group compared to the placebo group. There were more dose reductions and dose interruptions due to hand-foot skin reactions, diarrhea, hypertension and rash in the regorafenib group compared to the placebo group. This could have

compromised blinding and introduced detection bias as the investigator may have become aware of the treatment assigned to the patient and this may impact the assessment of outcomes.

New limitations:

- In both the CORRECT and CONCUR studies, no imputation were made for missing data. If a patient missed a scan visit and progressive disease (PD) was documented at the next available scan visit, the actual visit date of the first documented PD was used to calculate PFS and time to progression (TTP). Since mCRC is progressive in nature, this approach is conservative and unlikely to result in bias in favour of any of the treatment arms. However, the investigators reported that one of the reasons for missing data related to health status was that "the relevant questionnaire was not administered due to institution error", which raises questions about the rigour of data acquisition and processing methods that were used.
- Manufacturer-submitted materials used for the resubmission review included analyses to assess time to deterioration (TTD) of patients' health status. Since the analyses were not pre-specified (post hoc analyses) its finding could be due to chance. Secondly, HRQoL was identified as a tertiary outcome and it is unknown whether the trial was powered to detect clinically relevant difference between the treatment arms for this outcome.
- The main limitation of the CONCUR trial is that the study population was solely Asian, so that it is unknown whether its finding will be generalizable in other populations.
- Secondly, 40% of participants in the CONCUR study did not receive prior anti-VEGF or anti-EGFR targeted therapy. Therefore, a significant proportion of the study population did not meet the criteria for treatment with regorafenib as a third-line therapy, for which the manufacturer is requesting listing.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

a) Efficacy Outcomes

Efficacy analyses were based on an intent-to-treat population. Results were presented for the second interim analysis. No imputations were made for missing data. Safety analyses considered patients who had received at least one dose of treatment. Key outcomes are summarized in Table 7.

New data: CORRECT

The manufacturer submitted updated analysis data after 566 events, representing 97% of the planned total (see Table 7).[4] Harms data cover the period from the start of the study through the cut-off date of January 22nd, 2014.[24]

Efficacy Outcomes

Overall Survival

In the second interim analysis, as seen in Table 7, median OS was 6.4 months in the regorafenib group and 5.0 months in the placebo group, which indicated a gain in overall survival of 1.4 months for the regorafenib group (HR=0.77, 95%CI: 0.64-0.94, p=0.0052).

In the updated analysis, the HR for OS was reported as 0.79 (95% CI: 0.66-0.94; 1-sided p=0.0038). While the value of median OS remained unchanged from the original analysis for both treatment arms, the 95% CI improved slightly for the regorafenib group but widened slightly for the placebo group.[4]

New Data: Efficacy outcomes - CONCUR

The primary efficacy endpoint of the CONCUR trial was OS defined as the time in days from randomization to death due to any cause.[5] The formal OS analysis was performed when 154 deaths were observed.[3,5,15] The database cut-off date used for this analysis of OS was November 29 2013.[5] Patients who were alive at the time of analysis were censored at the last date they were known to be alive.[5] Median OS was 8.8 months in the regorafenib group and 6.3 months in the placebo group with estimated HR of 0.550 (95% CI: 0.395-0.765), Thus, the HR suggests a 45.0% reduction in the risk of death among patients in the regorafenib group compared with those in the placebo group. The efficacy analysis used the in the CONCUR study used the FAS population, which was defined as all randomized patients and comprised 204 patients. No imputation was performed for missing lesion assessment or tumor response data. All patients who were randomized and received at least 1 dose of study drug were included in the SAF population used for all safety analyses.[5] Key outcomes are summarized in Table 7.

Table 7: Summary of Key Outcomes from the CORRECT and CONCUR studies

	CORRECT Second interim Analysis Data[2,12,13]		CORRECT Updated Analysis Data[14]		CONCUR[3,15,16]	
	REG (N=505)	PL (N=255)	REG	PL	REG (n=136)	PL (n=68)
Overall survival, (months)						
Median (95% CI) in months	6.4 (5.9, 7.3)	5.0 (4.4, 5.8)	6.4 (5.8, 7.0)	5.0 (4.4, 5.9)	8.8 (NR)	6.3 (NR)
HR* (95% CI)	0.77 (0.64, 0.94)		0.79 (0.66, 0.94)		0.55 (0.40, 0.77)	
p-value	0.0052		0.0038		0.0002	
PFS, (months)						
Median (95% CI)	1.9 (1.9, 2.1)	1.7 (1.7, 1.7)	NR	NR	3.2 (NR)	1.7 (NR)
HR* (95% CI)	0.49 (0.42, 0.58)		NR		0.31 (0.22, 0.44)	
p-value	<0.0001		NR		<0.0001	
HRQoL - EOT					N = 131	N = 63
EORTC QLQ-30C, [a,†] LSM (95% CI)	56.93 (54.79, 59.08)	58.13 (55.72, 60.53)	NR	NR	60.76 (58.81, 62.71)	61.16, (58.48, 63.83)
LSM difference (95% CI)	−1.19 (−3.13, 0.75)				−0.40 (−3.53, 2.72)	
EQ 5D Index, [†] LSM (95% CI)	0.67 (0.64, 0.70)	0.67 (0.64, 0.70)	NR	NR	0.70 (0.67, 0.73)	0.74 (0.70, 0.78)
LSM difference (95% CI)	0.00 (−0.03, 0.03)				−0.03 (−0.08, 0.01)	
EQ 5D VAS, [†] LSM (95% CI)	60.62 (58.62, 62.63)	61.84 (59.59, 64.09)	NR	NR	69.28 (67.48, 71.08)	70.46 (68.01, 72.91)
LSM difference (95% CI)	−1.21 (−3.04, 0.61)				−1.18 (−4.01, 1.66)	
Harms Outcomes n (%)[#]	(N=500)	(N=253)	(N=500)	(N=253)		
SAE	219 (43.8)	100 (39.5)	231 (46.2)	102 (40.3)	43 (31.6)	18 (26.5)
AE (any grade)	465 (93.0)	154 (60.9)	498 (99.6)	245 (96.8)	136 (100.0)	60 (88.2)
AE (leading to any dose modification)	378 (75.6)	97 (38.3)	342 (68.4)	58 (22.9)	97 (71.3)	11 (16.2)
WDAE	88 (17.6)	32 (12.6)	95 (19.0)	31 (12.3)	19 (14.0)	4 (5.9)

AE= adverse event, **CI**= confidence interval, **EORTC QLQ-C30**= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, **EQ5D**= European Quality of Life 5 Dimensions, **HR**= hazard ratio, **NR**= not reported **PFS**= progression free survival, **PL** = placebo, **REG**= regorafenib, **SAE**= serious adverse event, **SD**= standard deviation, **VAS**= visual analog scale, **WDAE**= withdrawal due to adverse event

*HR < 1 favours regorafenib

[a] Global health status at the end of treatment

[†] Higher scores indicate better HRQoL and better health status

[#] Harms outcomes for the updated analysis for CORRECT as of January 2014

As shown in Table 8, at the time of the second interim analysis, the OS rate in the CORRECT study was numerically higher in the regorafenib group than in the placebo group at months 3, 6, and 9; but was similar in both groups at 12 months.

New data: CORRECT

Following the updated analysis, OS rates at 6 and 12 months were slightly lower than their corresponding values in the second interim analysis for both the regorafenib and placebo groups (Table 8). Although the updated data are consistent with those reported previously, they also demonstrate a more robust advantage of regorafenib over placebo at 12 months.

Table 8: Overall survival Rate

	Second Interim Analysis Data[2,12]		Updated Analysis Data[4]	
	REG (N=505)	PL (N=255)	REG (N=505)	PL (N=255)
Overall survival rate at				
3 months	80.3%	72.7%	NR	NR
6 months	52.5%	43.5%	52.2%	43.1%
9 months	38.2%	30.8%	NR	NR
12 months	24.3%	24.0%	24.1%	17.0%

IQR= interquartile range, NR= not reported, PL= placebo, REG= regorafenib

New Data: Overall Survival - CONCUR

Treatment with regorafenib demonstrated higher OS rates than placebo in the CONCUR study with the differential advantage being higher at each time point (3 to 12 months) than corresponding values in the CORRECT study. Thus, the CONCUR study confirms the reported OS rate benefit of regorafenib with more robust data.

Progression free survival (PFS)

The median PFS in the CORRECT study was 59 days (1.9 months) for the regorafenib group compared with 52 days (1.7 months) in the placebo group. The HR (95% CI) value of 0.49 (0.42, 0.58) with p<0.0001, indicate a 51% reduction of risk of disease progression in the regorafenib group compared to the placebo group.

New Data-CONCUR

In the CONCUR study, regorafenib demonstrated a significantly longer PFS than in the placebo group (HR [95% CI]: 0.311 [0.222, 0.435]; p< 0.000001), with the results indicating a 69.9% reduction in risk of disease progression or death over placebo treatment. Therefore, regorafenib demonstrated superior gains in PFS over placebo in both the CORRECT and the CONCUR studies.

New Data: Subgroup analysis of efficacy outcomes

Table 9 presents descriptive statistics and HR (95% CI) estimates for OS and PFS in protocol defined subgroups for the CORRECT and CONCUR studies.[9,34] Hazard ratio of less than 1 suggests a trend in efficacy in favor of regorafenib while HR of greater than 1 suggests a trend in favor of placebo. The HR estimates indicate that regorafenib was consistently associated with better trends in OS and PFS compared with placebo for each study and in each subgroup.

In the CORRECT study, the median OS indicated longer survival in the <65 years group that the ≥65 years group. In the CONCUR study, a higher median OS for both the regorafenib and placebo arms among the ≥65 years group indicate that patients in the ≥65 years group survived longer than those in the <65 years group Thus the median OS estimates for the age subgroup in the CONCUR

study were not consistent with that of the CORRECT study. The PFS values indicated a more favorable response trend among patients in <65 years group than those in the ≥65 years group in both the CORRECT and CONCUR studies (Table 9).

Data for the KRAS status subgroup analysis showed consistency between the two studies with both OS and PFS having more favorable results among the <65 years group that the ≥65 years group, as well as among KRAS wild-type patients than patients those with KRAS mutation.

Table 9: Subgroup data- Efficacy outcomes

	Age				KRAS Status			
	<65 years		≥65 years		KRAS WT		KRAS mutant	
	REG	PL	REG	PL	REG	PL	REG	PL
CORRECT								
Median OS (months)	6.7	5.0	6.0	5.6	NR	NR	NR	NR
OS, HR (95% CI)	0.72 (0.56, 0.91)		0.86 (0.61, 1.19)		0.65 (0.48, 0.90)		0.87, (0.67, 1.12)	
PFS, HR (95% CI)	0.42 (0.34, 0.51)		0.65 (0.50, 0.86)		0.48 (0.36, 0.62)		0.53 (0.43, 0.65)	
CONCUR								
Median OS (days)	[redacted]		[redacted]		[redacted]		[redacted]	
OS, HR (95% CI)	0.59 (0.41, 0.84)		0.61 (0.28, 1.37)		0.59 (0.34, 1.01)		0.65 (0.36, 1.15)	
Median PFS (days)	[redacted]		[redacted]		[redacted]		[redacted]	
PFS, HR (95% CI)	[redacted]		[redacted]		[redacted]		[redacted]	

CI= confidence interval, **HR**= hazard ratio, **OS**= overall survival; **PFS**= progression-free survival, **PL**= placebo, **REG**= regorafenib, **WT**= wild-type

Source: van Cutsem, 2012[9]

(*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.*)

Health related quality of life (HRQoL)

Table 10 shows baseline and end of treatment values of HRQoL for the regorafenib and placebo treatment arms of the CORRECT study with overall results at end of treatment indicating a decline in patients' HRQoL in both the regorafenib and placebo groups.

Table 10: Baseline and EOT HRQoL and health utilities values - CORRECT[2]

	REG	PL
EORTC QLQ-30C †		
Baseline score (mean± SD)	62.6± 21.7	64.7± 22.4
EOT score† (mean± SD)	48.9± 21.6	51.9± 23.9
EQ 5D Index †		
Baseline score (mean± SD)	0.73± 0.25	0.74± 0.27
EOT† (mean± SD)	0.59± 0.31	0.59± 0.34
EQ 5D VAS †		
Baseline score (mean± SD)	65.4± 19.6	65.8± 20.5
EOT (mean± SD)	55.5± 20.4	57.3± 21.6

EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, **EOT**= end of treatment, **EQ-5D**= European Quality of Life Scale, **PL**= placebo, **REG**= regorafenib **SD**= standard deviation; **VAS**= visual analog scale

†Higher scores indicate better HRQoL and better health status. Minimal important differences: 10 points for EORTC QLQ C30;[2,35,36] 0.06 to 0.12 points for EQ-5D index; and 7 to 12 points for EQ-5D VAS.[2,33]

Mean changes in scores from baseline for both the EORTC QLQ-C30 and EQ-5D scales demonstrated deterioration in the health status of the patients in both the regorafenib and placebo treatment arms of the two studies. The magnitude of decline was similar between the two treatment groups without a consistent advantage of one treatment over the other for all cycles, irrespective of the instruments applied to assess the HRQoL.

In both the CORRECT and CONCUR studies, the magnitude of end of treatment deterioration in patients' HRQoL as determined by mean changes from baseline on the EORTC QLQ-C30 scale was generally close to or greater than the MCID. The HRQoL changes were similar for each dimension assessed in the regorafenib and placebo treatment groups. In the CORRECT study, deterioration in patients' HRQoL was highest in physical function and lowest in cognitive function for both treatment arms. In the CONCUR study, physical function had the highest deterioration in the regorafenib group while the social function dimension had the highest HRQoL deterioration in the placebo group.

The placebo group had positive values for mean changes from baseline in many functional dimensions in both studies suggesting an improvement in HRQoL. The regorafenib group had no positive values except for mean changes in emotional function from baseline in cycle 4 of the CONCUR study. However, owing to the high standard deviation (SD) values for all the reported means, which indicate considerable variation in the changes from baseline, no definite conclusions about clinical relevance are possible from these observations. In the CONCUR study the investigators stated that the changes were not considered clinically meaningful because the 95% confidence intervals crossed 0.[5]

For both the CORRECT and CONCUR studies, most of the mean changes from baseline at the end of treatment were clinically important on the EQ-5D index, while changes in EQ-5D VAS did not reach the level of clinical importance.

There was consistent decline in analyzable data from baseline, and from one cycle to the next in both the CORRECT and CONCUR studies. Thus, the number of patients completing the HRQoL questionnaires decreased with time. According to the investigators, the decline is not considered unusual as over time the number of complete assessments declines due to various reasons such as patients discontinuing the study or death.[5] However, one of the reasons given for missing data related to health status was that the relevant questionnaire was not administered due to institution error.[5]

New Data: CORRECT

The manufacturer presented data from a post-hoc analysis which assessed time to deterioration (TTD) of health status as part of new information in the resubmission material (Table 11).[6] The following variables were used in the TTD analysis:

- 3-component composite of a ≥10 point reduction in EORTC QLQ-C30 global health status (GHS) score, disease progression, or death;
- 2-component composite of ≥10 point reduction in GHS score or death; and,
- ≥10 point reduction in GHS scores alone.

Additionally, these endpoints were assessed using physical functioning (PF) score in place of GHS.[6]

Using the GHS-based 3-component endpoint, regorafenib was associated with significantly longer TTD compared with placebo (HR [95% CI] 0.77; [0.65-0.91], Table 11). However a significant difference was not observed between the two treatment arms when the other endpoints were applied.

Table 11: Time to deterioration in patients' health status

	Median TTD, weeks (95% CI)		HR (95% CI)
	REG (n=505)	PL (n=255)	
3-component composite	7.0 (6.0–7.4)	7.0 (6.0–7.1)	0.77 (0.65-0.91)
2-component composite	8.1 (7.7–8.4)	8.1 (8.0–8.6)	0.91 (0.75-1.09)
GHS alone	8.0 (7.1–8.3)	8.1 (8.1–8.4)	0.96 (0.77-1.20)

GHS= global health status, **HR**= hazard ratio, **PL**= placebo, **REG**= regorafenib **TTD**= time to deterioration

Source: Chang 2013[6]

New data: HRQoL - Analysis of time-adjusted area under the curve

Analyses of time-adjusted area under the curve (AUC) for EORTC QLQ-C30, EQ 5D index and EQ 5D VAS were conducted in both the CORRECT and CONCUR studies. The overlapping confidence intervals (CI) observed in the analyses demonstrated that treatment effects were similar in both the regorafenib and placebo groups without clinically meaningful differences in the QoL of patients in the two treatment groups in both studies.

Disease control rate (DCR)

The complete and partial response rates were similar between the regorafenib and placebo groups in both the CORRECT and the CONCUR studies. However, the overall DCR was statistically significantly higher for the regorafenib group compared with the placebo group with 41% versus 15%, p<0.0001, in the CORRECT study;[2] and 51.5% versus 7.4%, p<0.0001 for the CONCUR study.[3,15] The differences were mainly driven by disease stabilization rates.

b) Harms Outcomes

Generally, the overall incidence of treatment-emergent adverse events in all the listed categories was similar between the second interim analysis and the updated analysis report. Therefore, the updated data confirm the level of demonstrated similarity of overall incidence in treatment-emergent AEs and serious adverse events (SAEs) between regorafenib and placebo as reported in the previous review.

Serious Adverse Events (SAE)

Table 12 summarizes the SAE data for the second interim analysis of the CORRECT study. Fatal hepatic adverse events occurred in 8 (2.1%) and 1 (0.6%) patients in the regorafenib and placebo groups respectively. The hepatic adverse events comprised of hepatic encephalopathy (n=1), hepatic failure (n=6), and hepatic coma (n=1) in the regorafenib group and hepatic failure (n=1) in the placebo group. Hepatic adverse events were evaluated using the Standardized MedDRA Queries (SMQs) of Hepatic failure, fibrosis, and cirrhosis and other liver damages related to conditions.[37] Serious hepatobiliary adverse events (by MedDRA system organ class and preferred term) occurred in 27 (5.4%) and 9 (3.6%) patients in the regorafenib and placebo groups respectively.[26]

The manufacturer provided updates for some safety data. The updated analysis did not identify new safety outcomes, and where updates were made, the magnitude of changes are unlikely to alter the conclusions on safety of regorafenib compared with placebo drawn from the second interim analysis.

Table 12: Serious adverse events - CORRECT (ITT)

	Second Interim Analysis[2]	
Category	**REG (N= 500)**	**PL (N= 253)**
Any SAE, n (%)	219 (44)	100 (40)
General health deterioration, n (%)	36 (7)	24 (10)
Pyrexia, n (%)	14 (3)	1 (0.4)
Abdominal pain, n (%)	12 (2.4)	2 (1)
Fatigue		
Pneumonia, n (%)	10 (2)	4 (2)
Dyspnea, n (%)	10 (2)	3 (1)
Diarrhea, n (%)	8 (2)	0
Intestinal Obstruction, n (%)	7 (1)	2 (1)

Table 12: Serious adverse events - CORRECT (ITT)		
	Second Interim Analysis[2]	
Category	REG (N= 500)	PL (N= 253)
Hepatic Failure, n (%)	7 (1)	2 (1)
Multi-organ failure, n (%)	6 (1)	4 (2)
NR= not reported, **PL**= placebo, **REG**= regorafenib		

New Data: CONCUR

The overall incidence of SAEs was lower in CONCUR than in CORRECT. However, the rate of SAEs was generally similar in the regorafenib group and the placebo groups in both studies. Hepatic failure was not reported as one of the SAEs in the CONCUR study.

Adverse events

Adverse events (AEs) frequently occurring in patients treated with regorafenib included hand-foot skin reaction (HSR), fatigue, diarrhea, hypertension and rash or desquamation. Treatment-related adverse events (TRAE) of any grade or type occurred in 465 (93%) and 154 (61%) patients in the regorafenib and placebo groups respectively (Table 13). TRAEs of Grade 3 occurred in 253 (51%) and 31 (12%) patients in the regorafenib and placebo groups respectively. TRAEs of Grade 4 were relatively few and appeared to be similar in both groups. AEs mostly occurred early in the treatment phase (cycles 1-2).

Table 13: Treatment related adverse events occurring in ≥5% of patients in either regorafenib or placebo groups from start of treatment to 30 days post treatment-CORRECT[2]						
Category	REG (N= 500)			PL (N= 253)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any event, n (%)	465 (93)	253 (51)	17 (3)	154 (61)	31 (12)	4 (2)
Fatigue, n (%)	237 (47)	46 (9)	2 (<1)	71 (28)	12 (5)	1 (<1)
Hand-foot skin reaction, n (%)	233 (47)	83 (17)	0	19 (8)	1 (<1)	0
Diarrhoea, n (%)	169 (34)	35 (7)	1 (<1)	21 (8)	2 (1)	0
Anorexia, n (%)	152 (30)	16 (3)	0	39 (15)	7 (3)	0
Voice changes, n (%)	147 (29)	1 (<1)	0	14 (6)	0	0
Hypertension, n (%)	139 (28)	36 (7)	0	15 (6)	2 (1)	0
Oral mucositis, n (%)	136 (27)	15 (3)	0	9 (4)	0	0
Rash or desquamation, n (%)	130 (26)	29 (6)	0	10 (4)	0	0
Nausea, n (%)	72 (14)	2 (<1)	0	28 (11)	0	0
Weight loss, n (%)	69 (14)	0	0	6 (2)	0	0
Fever, n (%)	52 (10)	4 (1)	0	7 (3)	0	0
Constipation, n (%)	42 (8)	0	0	12 (5)	0	0
Dry skin, n (%)	39 (8)	0	0	7 (3)	0	0
Alopecia, n (%)	36 (7)	0	0	1 (<1)	0	0
Taste alteration, n (%)	35 (7)	0	0	5 (2)	0	0
Vomiting, n (%)	38 (8)	3 (1)	0	13 (5)	0	0
Sensory neuropathy, n (%)	34 (7)	2 (<1)	0	9 (4)	0	0
Nose bleed, n (%)	36 (7)	0	0	5 (2)	0	0
Dyspnoea, n (%)	28 (6)	1 (<1)	0	4 (2)	0	0
Muscle pain, n (%)	28 (6)	2 (<1)	0	7 (3)	1 (<1)	0
Headache, n (%)	26 (5)	3 (1)	0	0	0	
Pain abdomen, n (%)	25 (5)	1 (<1)	0	10 (4)	0	0
PL= placebo, **REG**= regorafenib						

New data: CONCUR

Table 14 summarizes data for AE that occurred in at least 10% of patients in either treatment group in the CONCUR study.[3,5,15]The incidence of AEs was generally higher in the regorafenib group than in the placebo group with greater than 10% difference between the groups for all the reported AEs.

As in the CORRECT study, the regorafenib group in the CONCUR study had higher incidence of AEs with grades 3 and 4 than the placebo group, with the difference between the two groups driven mainly by grade 3 AEs while statistically insignificant differences were observed between the treatment groups in terms of grade 4 AEs (Table 14).

Table 14: Incidence rates of treatment-emergent adverse events (any grade) occurring in at least 10% of patients in any treatment group - CONCUR (SAF)

Event category	REG (N= 136) (%)			PL (N= 268) (%)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Palmar-plantar erythrodysesthesia	74.3	16.2	0	5.9	0	0
Blood bilirubin increased	48.5	7.4	4.4	20.6	1.5	0
ALT increased	31.6	8.1	0	17.6	1.5	0
Diarrhea	29.4	2.2	0	7.4	1.5	0
Voice alterations/hoarseness	28.6	0.7	0	0	0	0
Hypertension	25.0	11.8	0	5.9	4.4	0
Fatigue	22.1	2.9	0	10.3	1.5	0
Fever	18.4	0	0	0	0	0
Hypokalemia	13.2	5.9	0	0	0	0
Hypophosphatemia	11.8	8.8	0	0	0	0
Rash maculo-papular	11.8	4.4	0	1.5	0	0
Platelet count decreased	11.8	2.9	0.7	1.5	0	0
White blood cells decreased	10.3	2.2	0	0	0	0

GIT= gastrointestinal, NR= not reported, PL= placebo, REG= regorafenib

In the CORRECT study, adverse events (≥1%) leading to discontinuation of treatment or any dose modifications occurred in 88 (17.6%) and 32 (12.6%), or 378 (75.6%) and 97 (38.3%) of patients in the regorafenib and placebo groups, respectively (Table 15). Among patients in the regorafenib and placebo groups, 188 (37.6%) and 8 (3.2 %) as well as 304 (60.8%) and 55 (21.7 %) had dose reduction or dose interruption, respectively.

Table 15: Patients with AEs leading to dose modification, disruptions or discontinuation of Treatment- CORRECT[37]

Category	REG (N= 500)	PL (N= 253)
Any Event, n (%)	188 (37.6)	8 (3.2)
Dose modifications	378 (75.6)	97 (38.3)
Dose reductions	100 (20·0)	8 (3·2)
Dose interruptions	352 (70·4)	95 (37·5)
WDAE (any), n (%)	88 (17.6)	32 (12.6)
-General health deterioration	18 (4)	8 (3)
-Palmar-Plantar Erythrodysaesthesia	7 (1)	0
-Hepatic Failure	4 (1)	2 (1)
-Decreased Appetite	4 (1)	1 (0.4)
-Pneumonia	4(1)	0
-Rash	4 (1)	0

PL= placebo, **REG**= regorafenib, **WDAE**= withdrawal due to adverse events

New data: AEs leading to discontinuation, dose reduction or dose interruption-CONCUR

Table 16 summarizes the incidence of AEs leading to dose modification and discontinuation of treatment in the CONCUR study.[3,5,15] Treatment-emergent AEs leading to permanent discontinuation of treatment occurred in 14.0% of patients in the regorafenib group and in 5.9% of patients in the placebo group. Adverse events (AE) were consistent with the known safety profile of regorafenib in mCRC. As reported earlier in Table 14, the most frequently reported grade ≥3 AEs in regorafenib-treated patients included hand-foot skin reaction (16%), hypertension (12%), hypophosphatemia (9%), ALT increase (8%), and blood bilirubin increase (7%).[3,5,15]

Table 16: Percentage of Patients with AEs leading to dose modification, disruptions or discontinuation of Treatment - CONCUR[3,5,15]

Category	REG (N = 136)	PL (N = 68)
Any Grade AEs, n (%)	136 (100.0)	60 (88.2)
Dose modification, n (%)	97 (71.3)	11 (16.2)
AE leading to dose reduction, n (%)	[redacted]	[redacted]
AE leading to dose interruption, n (%)	[redacted]	[redacted]
WDAE (any), n (%)	19 (14.0)	4 (5.9)

PL= placebo, **REG**= regorafenib, **WDAE**= withdrawal due to adverse events

(*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.*)

New Data: subgroup analysis of harms outcomes

In both the CORRECT and CONCUR studies, subgroup analyses of safety outcomes, covering only treatment-emergent SAEs and AEs, were provided for age (<65 years versus ≥65 years) but not for KRAS status.

Incidence of SAEs and AEs were higher in the CORRECT study than the CONCUR study. Treatment-emergent SAEs and AEs occurred at a similar rate in the ≥65 years and the <65 years of age subgroups for the regorafenib and placebo arms in both studies with differences of <10% in each comparison except SAEs in CONCUR, where the difference between age groups was >10%.

6.4 Ongoing Trials

The CONCUR study is estimated be completed in June 2015.[29]

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestional Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on regorafenib (Stivarga) for metastatic colorectal cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information, therefore, this information was redacted from this publicly available Guidance Report.

This Initial Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

The Gastrointestional Clinical Guidance Panel is comprised of oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **Embase** 1974 to 2014 December 23, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(Stivarga* or regorafenib* or "BAY 73 4506" or "BAY73 4506").ti,ot,ab,sh,rn,hw,nm.	854
2	(755037-03-7 or 24T2A1DOYB).rn,nm.	602
3	or/1-2	854
4	3 use pmez	178
5	*regorafenib/	177
6	(Stivarga* or regorafenib* or "BAY 73 4506" or "BAY73 4506").ti,ab.	466
7	5 or 6	474
8	7 use oemezd	309
9	4 or 7	487
10	limit 9 to english language	456
11	remove duplicates from 10	324

2. Literature search via PubMed

Search	Query	Items found
#3	Search **#1 AND #2**	9
#1	Search **(regorafenib [Supplementary Concept] OR Stivarga*[tiab] OR regorafenib*[tiab] OR "BAY 73 4506"[tiab] OR "BAY73 4506"[tiab] OR Regorafenibum*[tiab] OR 24T2A1DOYB[rn])**	175
#2	Search **publisher[sb]**	471883

3. Cochrane Central Register of Controlled Trials (Central)

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There are 14 results from 843892 records for your search on 'Regorafenib* or Stivarga* or BAY 73 4506 or BAY73 4506 in Title, Abstract, Keywords in Trials'

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Stivarga or regorafenib or BAY 73 4506 or BAY73 4506

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: **Stivarga or regorafenib**

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

Search terms: Stivarga or regorafenib or **BAY 73 4506 or BAY73 4506/ last 5 years**

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