pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Regorafenib (Stivarga) for Metastatic Colorectal Cancer

November 15, 2013

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

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

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

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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 (4x 40 mg tablets) taken orally, once daily for 3 weeks in a 4-week cycle.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one multi-national, multicentre phase III, double-blind randomized controlled trial (RCT), the CORRECT study which evaluated the efficacy and safety of regorafenib (160mg, 4 x 40 mg tablets orally) once daily compared to a matching dose of placebo given for 3 weeks of each 4 week cycle.[1-3] 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). Patients had a median age of 61 years, an ECOG PS 0 or 1, were 78% white and 61% male. Reported patient characteristics appeared to be balanced between the two groups. No crossover was permitted between treatment groups.

Efficacy

The primary end-point for the study was overall survival (OS). At the second interim analysis, the prespecified 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.

For the secondary outcome of PFS, the HR for PFS was 0.49 (95% CI 0.42 to 0.58) indicating a 51% reduction of risk of disease progression or death in the regorafenib group compared to the placebo group.

Health related quality of life was assessed using EORTC QLQ-C30 and EQ-5D measures. Overall results at end of treatment indicated a similar decline in patients' HRQoL in both the regorafenib and placebo groups.

Harms

Adverse events frequently occurring in patients treated with regorafenib include hand-foot skin reaction, fatigue, diarrhea, hypertension and rash or desquamation. Non-fatal serious adverse events (SAE's) appeared to be similar in both groups. Treatment related adverse events occurred in 93% and 61% patients in the regorafenib and placebo groups, respectively. Adverse events leading to dose modification occurred in 76% and 38% patients in the regorafenib and placebo groups respectively while withdrawals due to adverse

events (WDAE) occurred in 18% and 13% patients in the regorafenib and placebo groups respectively.

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

Burden of Illness and Need

The Canadian Cancer Society estimates that, in 2012, 23,300 Canadians were diagnosed with, and 9,200 Canadians died as a consequence of, colorectal cancer. As such, colorectal cancer represents the second most common cause of cancer death in Canadian males and the third most common cause of cancer death in Canadian females.[4,5] Other than in very specific situations where resection of liver or lung metastasis is possible, metastatic colorectal cancer is considered an incurable situation. Untreated, historical series describe survivals in the range of six to ten months.[6,7]

With established cytotoxic chemotherapy[8,9] (ie. fluoropyrimidines, oxaliplatin, irinotecan) and targeted agents (ie.: bevacizumab, cetuximab, panitumumab), median survivals are now reliably measured in the twenty to twenty-four month range. Despite these significant improvements, long-term survival remains rare and cures are still not anticipated in patients with unresectable metastatic colorectal cancer. Although international collaboration to identify new and beneficial therapies continues, there remains an unmet need for those patients who still retain a good performance status despite exhausting all of their standard therapies.

Effectiveness

The CORRECT study demonstrated a clear statistical superiority in the primary (23% improvement in overall survival) and secondary (51% improvement in progression-free survival) end-points in both the intention-to-treat and predefined subgroups along with the lack of confounding that often results from significant post-progression cross-over. Thus, for patients with a preserved performance status (ECOG 0 or 1), regorafenib provides an option for further palliative systemic therapy after the currently available standard options have failed.[2]

Although Regorafenib failed to delay deterioration in quality of life based upon the EORTC QLQ-C30 and ED-5D scores when compared to placebo, the efficacy and safety are still both relevant and applicable to Canadian patients with treatment-refractory metastatic colorectal cancer.

Safety

Given that the intent of treatment is also to maintain quality of life, the efficacy benefits observed with regorafenib must be balanced against its risk of toxicities such as hand-foot skin reaction, fatigue, diarrhea, hypertension, rash, and anorexia all of which were observed more frequently in patients treated with regorafenib.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to the use of regorafenib over best supportive care alone in patients with treatment-refractory metastatic colorectal cancer. This conclusion is based upon the results of a single high-quality, well-conducted and valid randomized controlled clinical trial, CORRECT, that demonstrates superior disease control rate, progression-free survival, and overall survival with the use of regorafenib when compared to best supportive care (placebo).

In making this conclusion, the Clinical Guidance Panel considered that:

- Regorafenib fulfills an unmet need for the treatment of patients with metastatic colorectal cancer who have exhausted all other standard systemic therapies.
- Regorafenib fails to delay deterioration in quality of life and introduces the risk of relevant but manageable toxicities such as hand-foot skin reaction, fatigue, diarrhea, hypertension, rash, and anorexia.
- This impression is congruent with that of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

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.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding regorafenib (Stivarga) for metastatic colorectal cancer conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; 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

Health Canada recently approved regorafenib for treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with standard therapy.[10] The recommended dose is 160 mg (4x 40 mg tablets) taken orally, once daily for 3 weeks in a 4-week cycle.[1] Standard therapies for mCRC include chemotherapy with fluoropyrimidines, oxaliplatin, and irinotecan (used in combination and sequentially) and targeted therapy with VEGF monoclonal antibody (bevacizumab) and if KRAS wild-type, EGFR monoclonal antibodies(cetuximab and panitumumab).[1,2,11]

Regorafenib is a multiple kinase inhibitor. Kinases are involved in normal cell functions and in pathological processes such as oncogenesis, tumor angiogenesis, and maintenance of tumor environment.[12,13]

2.1.2 Objectives and Scope of pCODR Review

The objective of this review is to evaluate the effect of regorafenib on patient outcomes including overall survival, progression free survival, quality of life, and harms compared with 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.

2.1.3 Highlights of Evidence in the Systematic Review

One multi-national, multicentre phase III, double-blind randomized controlled trial (RCT)[2,3] (CORRECT) comparing regorafenib versus placebo for the treatment of patients with metastatic colorectal cancer (mCRC) who have failed standard therapies, was included in this review. Patients were randomized in a 2:1 ratio between regorafenib (N= 505) and placebo (N= 255). Patients received oral regorafenib 160 mg (4 tablets, each 40 mg)[1] or matching placebo once daily for the first 3 weeks of each 4 week cycle. All patients received in addition best supportive care (BSC). Patients were of mean age 61 years and ECOG PS 0 or 1. Majority were White (78%) and there were greater proportion of males (61%). Reported patient characteristics appeared to be balanced between the two groups.

Key outcomes from the CORRECT study[2,3] are summarized in Table1. Efficacy analyses were based on intent-to-treat population. Safety analyses considered patients who had received at least one dose of treatment.

The primary end-point was overall survival. Results from the second interim analysis are presented as at that time the prespecified condition for efficacy for stopping the study, were met. Median overall survival 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. The hazard ratio (95% confidence interval) for regorafenib versus placebo was for overall survival 0.77 (0.64, 0.94) and p=0.0052 indicating a 23% reduction in the risk of death in the regorafenib group. The data cut-off for the second interim analysis was July 21, 2011. After the second interim analysis, the study was unblinded and four patients from the placebo group crossed over to the regorafenib group. An additional analysis of overall survival was conducted at the database cut-off of November 13, 2011.[14] The additional analysis showed similar results as the second interim analysis. The median overall survival was 6.4 months in the regorafenib group and 5.0 months in the placebo group and the hazard ratio (95% confidence interval) for overall survival was 0.79 (0.66, 0.94) and p= 0.0038, for regorafenib versus placebo.[14] Unless otherwise stated, the findings reported are from the second interim analysis. The hazard ratio (95% confidence interval) for regorafenib versus placebo for progression free survival (PFS) was 0.49 (0.42, 0.58) and p<0.0001 indicating a 51% reduction of risk of disease progression or death in the regorafenib group compared to the placebo group. In the predefined subgroups (patients previously treated with VEGF-targeting drugs, patients with diagnosis of metastatic disease ≥18 months, and patients from North America, Western Europe, Israel and Australia) the risks of death and risks of disease progression were statistically significantly reduced with regorafenib compared with placebo. Overall results at end of treatment indicated a similar decline in patients' health related quality of life (HRQoL) in both the regorafenib and placebo groups. Adverse events frequently occurring in patients treated with regorafenib include hand-foot skin reaction, fatigue, diarrhea, hypertension and rash or desquamation. Non-fatal serious adverse events appeared to be similar in both groups. Treatment related adverse events occurred in 93% and 61% patients in the regorafenib and placebo groups respectively. Adverse events leading to dose modification occurred in 76% and 38% patients in the regorafenib and placebo groups respectively. Withdrawals due to adverse events (WDAE) occurred in 18% and 13% patients in the regorafenib and placebo groups respectively.

Table 1: Summary of Key Outcomes from the CORRECT study[1,2]			
Efficacy			
Outcome**	**Intervention**	**Median (95% CI) in months**	**HR* (95% CI), p-value**
Overall survival	Regorafenib	6.4 (5.9, 7.3)	0.77 (0.64, 0.94), P= 0.0052
	Placebo	5.0 (4.4, 5.8)	
Overall survival (after second interim analysis; based on database cut-off of November 13, 2011)[14]	Regorafenib	6.4 (5.8, 7.0)	0.79 (0.66, 0.94), P= 0.0038
	Placebo	5.0 (4.4, 5.9)	
PFS	Regorafenib	1.9 (1.9, 2.1)	0.49 (0.42, 0.58), P< 0.0001
	Placebo	1.7 (1.7, 1.7)	
Outcome - HRQoL	**Intervention**	**Baseline score† (mean± SD)**	**End of treatment score† (mean± SD)**
EORTC QLQ-30C	Regorafenib	62.6± 21.7	48.9± 21.6
	Placebo	64.7± 22.4	51.9± 23.9
EQ 5D Index	Regorafenib	0.73± 0.25	0.59± 0.31
	Placebo	0.74± 0.27	0.59± 0.34
EQ 5D VAS	Regorafenib	65.4± 19.6	55.5± 20.4
	Placebo	65.8± 20.5	57.3± 21.6
Harm			
Outcome	**Intervention**	**Proportion of patients (n/N)**	**Percentage of patients**
SAE	Regorafenib	219/500	44%
	Placebo	100/253	40%
AE (any grade)	Regorafenib	465/500	93%
	Placebo	154/253	61%
AE (leading to any dose modification)	Regorafenib	378/500	75.6%
	Placebo	97/253	38.3%
WDAE	Regorafenib	88/500	17.6%
	Placebo	32/253	12.6%

AE= adverse event, **CI**= confidence interval, **HR**= hazard ratio, **PFS**= progression free survival, **EORTC QLQ-C30**= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, **EQ 5D**= European Quality of Life 5 Dimensions, **HRQoL**= health related quality of life, **SAE**= serious

adverse event, **SD**= standard deviation, **WDAE**= withdrawal due to adverse event *HR < 1 favours regorafenib † Higher scores indicate better HRQoL and better health status.
**The results are from the second interim analysis (database cut-off of July 21, 2011), unless otherwise stated. At the second interim analysis, the prespecified efficacy boundary was crossed as p≤ 0.0093, approximately corresponding to HR of 0.7864 for overall survival in the regorafenib group compared to the placebo group.

2.1.4 Comparison with Other Literature

There are no health technology assessments, drug class reviews, systematic reviews, or other randomized controlled trials currently available to provide further insights into the efficacy and safety of regorafenib for the treatment of mCRC patients who have failed standard therapies.

2.1.5 Summary of Supplemental Questions

No supplemental questions were identified for 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

The Colorectal Cancer Association of Canada (CCAC) conducted a survey of colorectal cancer patients and caregivers in Canada and abroad (n=3) 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). A copy of the survey was provided to pCODR. To better provide the patient perspective, input from past conversations with patients and caregivers and a Quality of Life survey conducted by the CCAC in March 2011 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 was included.

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. Patients are aware that all treatments for metastatic cancer carry risk and are willing to tolerate moderate to significant side effects during their treatment. Current available treatment options in Canada are not suitable for all patients. 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

Input on the regorafenib (Stivarga) review was obtained from nine of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, regorafenib is a drug that may offer a treatment option to patients that currently do not have one. PAG noted the oral route of administration will improve

accessibility for patients that are already very sick. Other enablers to implementation included minimal drug wastage and the ease in dose reduction as regorafenib comes in one standard dose.

PAG noted several barriers to implementation. PAG noted that the dosing schedule of regorafenib requires 3 weeks on and 1 week off treatment and may result in dosing errors. PAG also recognised a potential for indication creep if patients and oncologists request to receive regorafenib in earlier lines of therapy. As a new treatment potentially replacing best supportive care, PAG noted potential increased incremental costs in terms of increased pharmacy workload and monitoring of toxicities. In addition, if all patients in this setting become eligible to receive regorafenib, the size of the patient population will be large.

PAG noted a particular Black Box warning advising of severe liver toxicity and hepatic failure sometimes resulting in death. PAG recognised this potential adverse effect will require hepatic monitoring of patients at baseline and during therapy.

Other

There is one ongoing randomized, double-blind, placebo-controlled phase III trial of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy[15]

Patients are currently being recruited for a multi-national, multi-centre, randomized placebo-controlled phase II trial to compare regorafenib plus FOLFIRI versus placebo plus FOLFIRI as second-line treatment for metastatic colorectal cancer.[16]

FDA recently approved regorafenib for patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumors, who have been previously treated with imatinib mesylate and sunitinib malate[17] based on a multi-national, multi-centre, randomized placebo-controlled, phase III trial (GRID).[18,19]

2.2 Interpretation and Guidance

Colorectal cancer represents the second most common cause of cancer death in Canadian males and the third most common cause of cancer death in Canadian females.[4,5] Considerable progress is being made to develop and deliver effective treatments that control advanced disease, maintain or improve quality of life, and delay death.

For patients with a preserved performance status (ECOG 0 or 1), Regorafenib provides an option for further palliative systemic therapy after the currently available standard options have failed.[2] Regorafenib is an attractive option for patients: it is an oral agent that offers a superior disease control rate (41% *versus* 15%, $p < 0.0001$), progression-free survival (1.9 months *versus* 1.7 months, HR 0.49, $CI_{95\%}$ 0.42-0.58, $p < 0.0001$), and overall survival (6.4 months *versus* 5.0 months, HR 0.77, $CI_{95\%}$ 0.64-0.94, $p = 0.0052$) when compared to best supportive care (placebo). However, given that the intent of such treatment is also to maintain quality of life, these benefits must be balanced against regorafenib's risk of toxicities such as hand-foot skin reaction, fatigue, diarrhea, hypertension, rash, and anorexia.

Patient Advocacy Groups emphasize that patients "are willing to tolerate moderate to significant side effects during their treatment" (quoted from sections 2.1.6 and 4.0.0). However, it is important that patients' wishes are balanced with their oncologists' considerations for their comorbidities, performance status, and efforts to manage their disease with the least toxicity.

Because Regorafenib has only recently become available in Canada, only a handful of medical oncologists have any direct clinical experience. With more experience, better management of the treatment-related adverse effects (93% all-grade toxicities and 54% grade 3/4 toxicities were reported on the *CORRECT* trial) and/or superior dosing schedules might transform the high number of dose modifications (76% seen in the *CORRECT* trial) and result in expanded drug use, incremental costs, and different pharmaco-economics. Further, cancer care agencies and oncologists recognize that, while oral agents are more convenient, they are also subject to problems with compliance, dose error, drug wastage, and pharmacy workload. An extra line of therapy also generates further specialist clinic visits when compared to a discharge to community palliative care. To date, there have been no validated biomarkers identified to limit the population of Canadians with metastatic colorectal cancer eligible for Regorafenib.

The evidence presented in this Clinical Guidance Report highlights the results of a single international, multicentre, phase 3 trial conducted in North America, western Europe, Israel, and Australia (*n* = 632); Asia (*n* = 104); and eastern Europe (*n* = 24). It involved a double-blind 2:1 randomization to Regorafenib plus best supportive care (*n* = 505) or to placebo plus best supportive care (*n* = 255). Thus far, no relevant health technology assessments, systematic reviews (other than a meta-analysis about hand-foot skin reaction[20]), or other randomized controlled trials have been published to corroborate this trial's efficacy and safety findings.

The strength of the evidence comes from the clear statistical superiority in the primary (23% improvement in overall survival) and secondary (51% improvement in progression-free survival) end-points in both the intention-to-treat and predefined subgroups along with the lack of confounding that often results from significant post-progression cross-over. Criticisms surround the arguably suboptimal evaluation of adverse effects (such as hand-foot skin reaction) as they pertain to their impact on quality of life. Although Regorafenib failed to delay deterioration in quality of life based upon the EORTC QLQ-C30 and ED-5D scores when compared to placebo, the efficacy and safety are still both relevant and applicable to Canadian patients with treatment-refractory metastatic colorectal cancer.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to the use of regorafenib over best supportive care alone in patients with treatment-refractory metastatic colorectal cancer. This conclusion is based upon the results of a single high-quality, well-conducted and valid randomized controlled clinical trial, CORRECT, that demonstrates superior disease control rate, progression-free survival, and overall survival with the use of regorafenib when compared to best supportive care (placebo).

In making this conclusion, the Clinical Guidance Panel considered that:

- Regorafenib fulfills an unmet need for the treatment of patients with metastatic colorectal cancer who have exhausted all other standard systemic therapies.
- Regorafenib fails to delay deterioration in quality of life and introduces the risk of relevant but manageable toxicities such as hand-foot skin reaction, fatigue, diarrhea, hypertension, rash, and anorexia.
- This impression is congruent with that of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

3 BACKGROUND CLINICAL INFORMATION

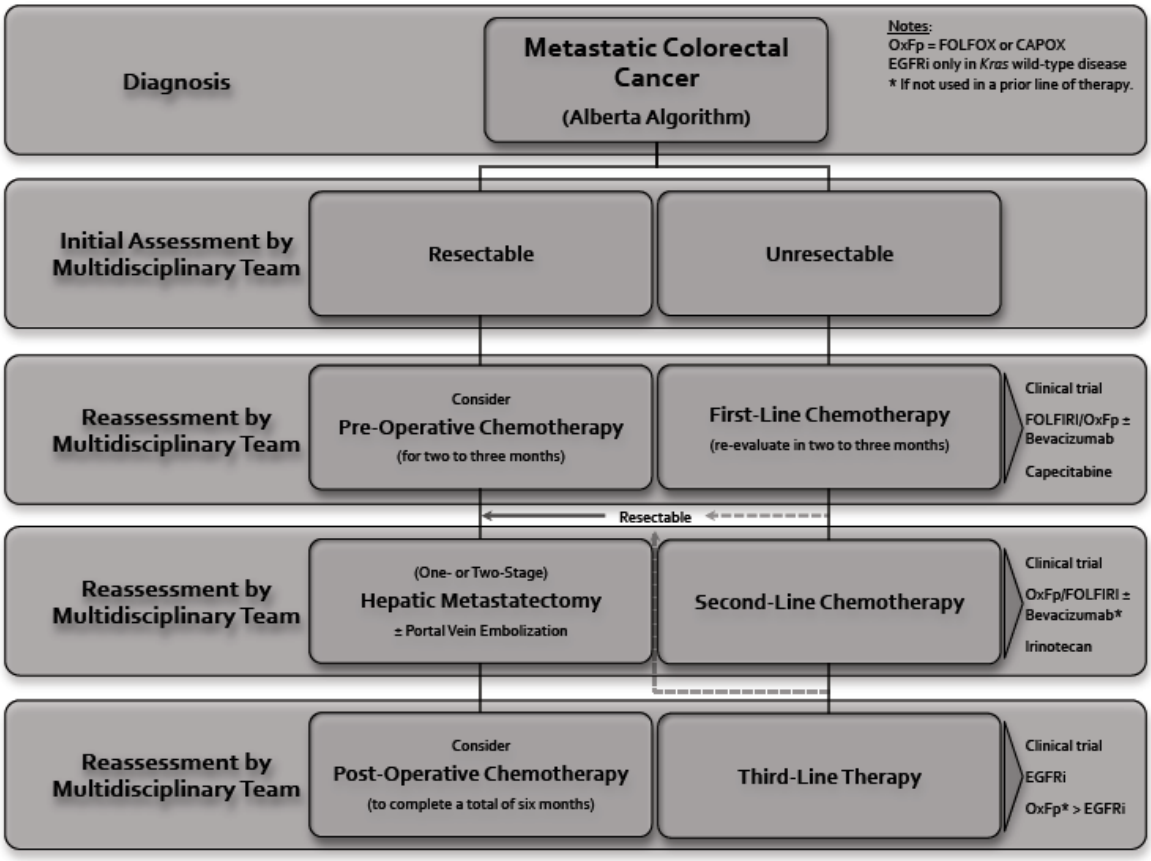
This section was prepared by the pCODR Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

The Canadian Cancer Society estimates that, in 2012, 23,300 Canadians were diagnosed with, and 9,200 Canadians died as a consequence of, colorectal cancer. As such, colorectal cancer represents the second most common cause of cancer death in males and third most common cause of cancer death in females.[4,5] It is second only to lung cancer when potential years of life lost are considered.

3.2 Accepted Clinical Practice

Other than in very specific situations where resection of liver or lung metastasis is possible, metastatic colorectal cancer is considered an incurable situation. Untreated, historical series describe survivals in the range of six to ten months.[6,7] With established cytotoxic chemotherapy[8,9] (ie. fluoropyrimidines, oxaliplatin, irinotecan) and targeted agents (ie.: bevacizumab, cetuximab, panitumumab), median survivals are now reliably measured in the twenty to twenty-four month range. In the context of treatments currently available for mCRC and in which regorafenib may be introduced, contemporary chemotherapy is cost effective,[21-25] delays the onset of tumor-related symptoms, and improves quality of life.[26,27] Despite these significant improvements, long-term survival remains rare and cures are still not anticipated in patients with unresectable metastatic colorectal cancer. Although international collaboration to identify new and beneficial therapies continues, there remains an unmet need for those patients who still retain a good performance status despite exhausting all of their standard therapies.



An algorithm summarizing the usual trajectory of care is presented in the box (Alberta Health Services Clinical Practice Guidelines)[28]

Regorafenib is an orally administered inhibitor of multiple kinases. It was evaluated in the CORRECT study,[2] a randomized, placebo-controlled, phase III trial conducted at 114 centres in North America, Europe, Asia, and Australia. This trial accrued patients with 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. The patients' disease must have progressed during or within three months of prior standard therapy. At some point in their trajectory, patients must have been exposed to all of the available standard therapies (e.g.: fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab and either panitumumab or cetuximab if Kras wild-type). Patients were randomized in a 2:1 fashion to receive best supportive care plus either Regorafenib 160 mg po QD for three in four weeks or matching placebo until disease progression, death, unacceptable toxicity, withdrawal of consent, or decision by the treatment physician that discontinuation was in the patient's best interest.

When compared to best supportive care plus placebo, best supportive care plus Regorafenib improves disease control rate (41% versus 15%, $p < 0.0001$) and prolongs both progression-free survival (1.9 months versus 1.7 months, HR 0.49, CI95% 0.42-0.58, $p < 0.0001$) and overall survival (6.4 months versus 5.0 months, HR 0.77, CI95% 0.64-0.94, $p = 0.0052$). The typical toxicities (e.g.: hand-foot skin reaction, fatigue, diarrhea, hypertension, rash) occur early and are manageable with dose reductions or interruptions.

3.3 Evidence-Based Considerations for a Funding Population

The population considered would match those that participated in the *CORRECT* study.[2] That is, they would have progressed on (or demonstrated intolerance to) fluoropyrimidine, Irinotecan, oxaliplatin, bevacizumab, and either panitumumab or cetuximab if *Kras* wild-type. 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.

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

3.4 Other Patient Populations in Whom the Drug May Be Used

It is not within the auspices of this pCODR evaluation that indications other than for the population described above be considered for Regorafenib. It is anticipated that clinical trials will be initiated to establish whether Regorafenib has utility in earlier lines of therapy as well as tolerable adverse effects when used with conventional chemotherapy. Biomarkers will be sought to better personalize therapy. Novel paradigms for treatment will be explored as we learn more about the targets Regorafenib influences.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Colorectal Cancer Association of Canada, provided input on regorafenib for the treatment of metastatic colorectal cancer and their input is summarized below.

The Colorectal Cancer Association of Canada (CCAC) conducted a survey of colorectal cancer patients and caregivers in Canada and abroad (n=3) 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). A copy of the survey was provided to pCODR. To better provide the patient perspective, input from past conversations with patients and caregivers and a Quality of Life survey conducted by the CCAC in March 2011 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 was included.

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. Patients are aware that all treatments for metastatic cancer carry risk and are willing to tolerate moderate to significant side effects during their treatment. Current available treatment options in Canada are not suitable for all patients. 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.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Colorectal Cancer

Patient advocacy group input received from the CCAC indicates 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. mCRC is a fatal disease for which there is no known cure other than tumour control or reduction coupled with surgery in some cases and limited reimbursed treatment options dependant 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 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*."

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 Metastatic Colorectal Cancer

Standard treatment for mCRC, which affects approximately 50% of the colorectal cancer population, involves chemotherapy based on fluoropyrimidines, oxaliplatin, and irinotecan used in combination i.e. FOLFIRI and FOLFOX, and sequentially; and monoclonal antibodies targeting vascular endothelial growth factor (VEGF; bevacizumab). In patients with KRAS wild type tumours (approximately 60%), monoclonal antibodies targeting epidermal growth factor receptor EGFR; cetuximab and panitumumab are also used. Patients with KRAS mutant tumours, however, do not have a third line therapy option available. Additional options are, therefore, needed for this patient population and for all patients who have disease progression despite all currently available standard therapies, because many patients maintain good performance status and might be candidates for further therapy.

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.

Patients indicate 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.

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. There is also an unmet clinical need for the KRAS mutation positive patients who have exhausted first and second line therapy. Funding of an additional therapeutic option would help to increase access for both these patient populations and to manage the progression of this disease. Current provincial reimbursement eligibility criteria is perceived to be too restrictive or limited by many patients.

4.1.3 Impact of Metastatic Colorectal Cancer 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

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 (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 patient who participated in the CCAC survey reported he "*feels very fortunate to be on regorafenib as opposed to more chemo*". Patients 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.

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. 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 was unable to secure non-anecdotal input from Canadian patients with direct experience with regorafenib. Physicians who have experience with regorafenib have noted improvement in their patients' quality of life by:

- decreasing shortness of breath brought on by lung impairment/mets
- increasing overall survival
- decreasing tumour burden

- reducing hospital/clinic visits
- decreased toxicities.

As listed in the Product Monograph: the most frequent adverse events of grade 3 or higher related to regorafenib were hand-foot skin reaction, fatigue, diarrhea, hypertension and rash. Most of these side effects, however, occurred early in the course of treatment and were readily manageable with dose reduction or interruption. mCRC patients in Canada have learned to deal with these side effects from other drugs such as capecitabine.

Currently, there are no therapeutic options approved for the treatment of patients with KRAS mutant mCRC in third line or treatment refractory patients in fourth line. Therefore, disease stabilization achieved by regorafenib in both these lines of therapy would be highly welcomed by patients and their treating oncologists. It is important for patients to have access to a choice of therapies for 3rd or 4th line treatment of mCRC and to have the following benefits of regorafenib:

- achieving stable disease
- improving quality of life
- accessing another option that provides hope for life prolongation
- decreased treatment-induced toxicities.

In the metastatic setting, long term health is relative and is viewed by patients in small increments. Any extension in life is considered an extension in long term health by mCRC patients and caregivers.

4.3 Additional Information

CCAC also surveyed medical oncologists from the CCAC Medical Advisory Board (MAB) and other affiliated experts from within Canada and abroad who treat metastatic colorectal cancer (n=11). Input was sought regarding prescribing decisions for second, third and fourth line therapy, key factors contributing to treatment choice and obstacles preventing best outcomes for their patient populations. This survey and the summary of results were provided to pCODR with the patient advocacy group's input.

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.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for regorafenib (Stivarga) for metastatic colorectal cancer (mCRC). 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).

Overall Summary

Input on the regorafenib (Stivarga) review was obtained from nine of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, regorafenib is a drug that may offer a treatment options to patients that currently do not have one. PAG noted the oral route of administration will improve accessibility for patients that are already very sick. Other enablers to implementation included minimal drug wastage and the ease in dose reduction as regorafenib comes in one standard dose.

PAG noted several barriers to implementation. PAG noted that the dosing schedule of regorafenib requires 3 weeks on and 1 week off treatment and may result in dosing errors. PAG also recognised a potential for indication creep if patients and oncologists request to receive regorafenib in earlier lines of therapy. As a new treatment potentially replacing best supportive care, PAG noted potential increased incremental costs in terms of increased pharmacy workload and monitoring of toxicities. In addition, if all patients in this setting become eligible to receive regorafenib, the size of the patient population will be large.

PAG noted a particular Black Box warning advising of severe liver toxicity and hepatic failure sometimes resulting in death. PAG recognised this potential adverse effect will require hepatic monitoring of patients at baseline and during therapy.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

The current standard treatment for patients with metastatic colorectal cancer (mCRC) is best supportive care. PAG noted that the availability of a treatment option in this patient population as an enabler to implementation.

PAG recognised a potential barrier to implementation in that treatment would be given to patients that are in the palliative setting. PAG noted that, given the small magnitude of OS benefit demonstrated in the pivotal trial, this patient population is likely to get a small incremental benefit through new available therapy.

5.2 Factors Related to Patient Population

PAG discussed that the patient population in the pivotal study, CORRECT trial, had a performance status of 0-1. However, if all patients in the 3rd and 4th line setting become eligible to receive regorafenib, the patient population could be large. PAG noted that a recommendation would need to clarify eligibility of patients and address the ECOG PS. 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.

5.3 Factors Related to Accessibility

PAG identified that as regorafenib is an oral drug it will generally be more easily accessed by patients. PAG also noted that regorafenib may potentially offer a treatment option for patients who have KRAS mutation and not eligible for treatment with cetuximab or panitumumab.

For some provinces (BC, AB, SK, MB) oral cancer therapies are fully covered. PAG did however note that in some jurisdictions, oral medications are not covered in the same way as intravenous cancer medications, which may limit accessibility. For these jurisdictions, patients 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. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of- pocket expenditure.

5.4 Factors Related to Dosing

PAG noted that the dosing of regorafenib requires 4 pills once daily with patients being on treatment for 3 weeks followed by a 1 week break. As regorafenib comes in 40mg tablets, PAG noted that dose adjustments will be easy if needed.

Although the once daily regimen will increase patient compliance, PAG noted that the dosing schedule of 3 weeks on and 1 week off may potential result in dosing errors. PAG did however recognise that the availability of an oral drug for this patient population that is in the palliative setting is an enabler.

5.5 Factors Related to Implementation Costs

As an enabler to implementation, PAG identified that the use of regorafenib will minimize drug wastage as only one tablet strength is available.

As a potential barrier to implementation, PAG noted that the availability of a new treatment where previously patients would have received BSC will require increased 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.

5.6 Other Factors

PAG noted a particular Black Box warning in this palliative population as a barrier to implementation. The warning advises of severe liver toxicity and hepatic failure sometimes resulting in death. PAG recognised this potential adverse effect will require hepatic monitoring of patients at baseline and during therapy.

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 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 160 mg QD orally for the first 3 weeks in each 4-week cycle	Placebo Best supportive care (BSC)	**OS** **PFS** **HRQoL** DCR SAE AE WDAE Dose modification due to AE
AE=adverse events; **BSC**= best supportive care, **DB**= double blind; **DCR=**disease control rate; **EGFR**= epidermal growth factor receptor, **mCRC**= metastatic colorectal cancer; **OS=**overall survival; **PFS=**progression-free survival; **QD=**once daily; **HRQoL=**health related quality of life; **RCT=**randomized controlled trial; **SAE=**serious adverse event; **VEGF**= vascular endothelial growth factor; **WDAE=**withdrawal due to adverse events				

** 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 (2013, Issue 3) 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 1 August, 2013.

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 questions.

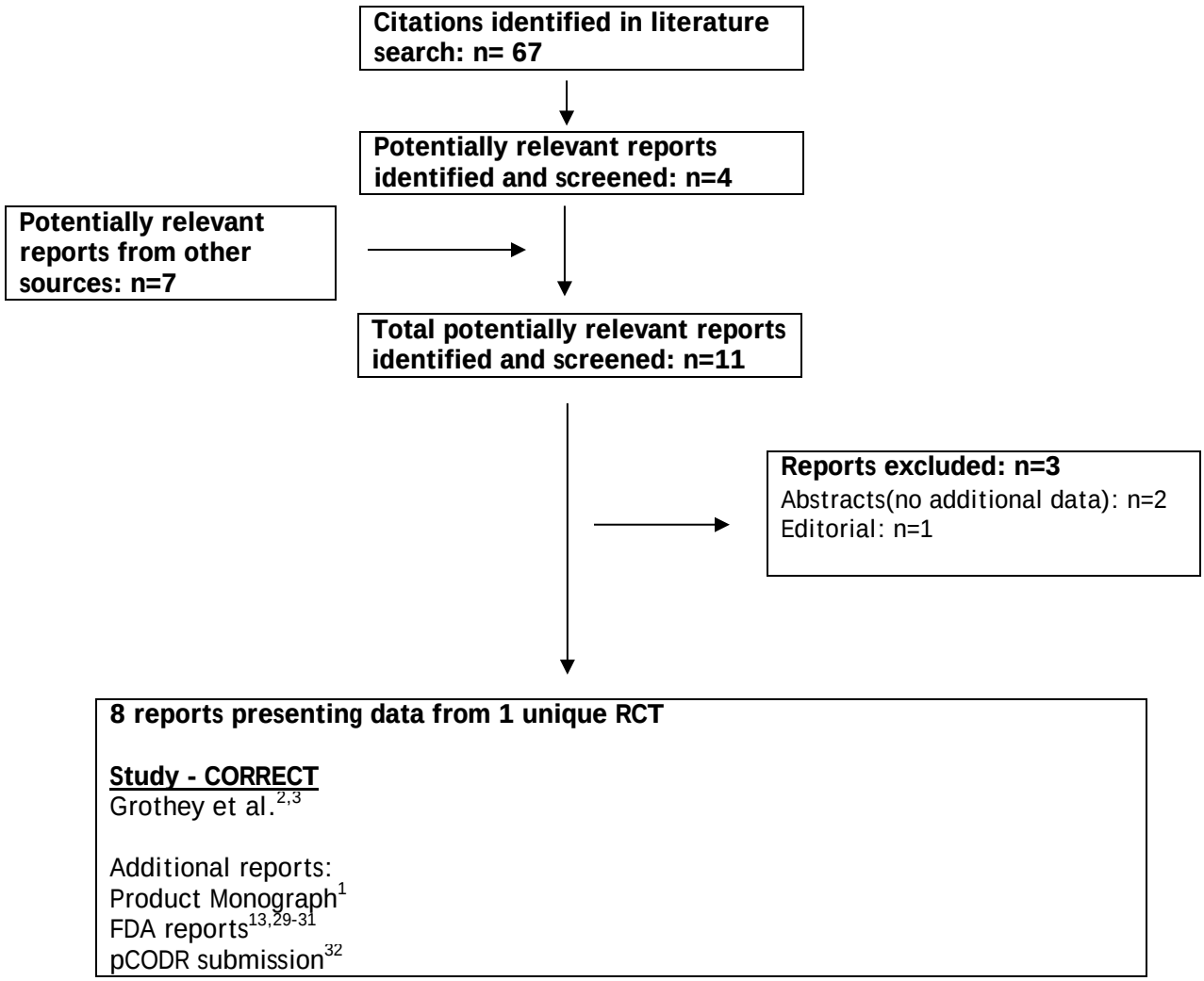
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
    - The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 11 potentially relevant reports identified, 8 reports presenting data from 1 unique RCT were included in the pCODR systematic review[1-3,13,29-32] and 3 reports were excluded. Reports were excluded because they were abstracts with no additional data[33,34] or an editorial.[35]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 3: Summary of Trial Characteristics of the Included study (CORRECT)[2]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
CORRECT[2] 114 centres in 16 countries in North America, 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 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 best supportive care versus placebo plus best supportive care 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)

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, **HRQL**= 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

a) Trials

One multicentre phase III, double-blind RCT[2,3] (CORRECT) was included in this review. The trial was conducted in 114 centres in 16 countries in North America, Europe, Asia and Australia and was manufacturer sponsored. Patients were randomized in a 2:1 ratio between regorafenib (N= 505) and placebo (N= 255).

The trial included patients 18 years or older with histological or cytological documentation of adenocarcinoma of the colon or rectum They had to have received approved standard therapies and to have disease progression during or within 3 months following the last administration of the last standard therapy or to have discontinued standard therapy as a result of unacceptable toxic effects. Patients treated with oxaliplatin in an adjuvant setting had to have progressed during or within 6 months of completion of adjuvant therapy. Patients needed to have an ECOG performance status of 0 or 1, life expectancy of at least 3 months and adequate bone-marrow, liver and renal function. Patients were not eligible to participate if they had uncontrolled medical disorders or had previously received regorafenib.

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 of 0.025 and 2:1 randomization, assuming 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 planned. 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 less than or equal to 0.0093, approximately corresponding to HR of less than or equal to 0.7864. The LanDeMets alpha spending function with an O'Brien-Fleming type of boundary was used to adjust for alpha for the second efficacy interim and final analyses. 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.[2,29,30] The study was unblinded after completing this analysis and four patients in the placebo group crossed over to receive regorafenib. An additional analysis of overall survival was conducted based on a database cut-off of November 13, 2011. It is not clear whether this additional analysis was pre-planned.

Trial procedures for randomization and allocation concealment were considered adequate. A computer generated randomization list was prepared by the study sponsor and the investigators received the randomization number for each patient via an interactive voice response system. Randomization was stratified by previous treatment, time from diagnosis of metastatic disease and geographical region. All randomized patients were included in the efficacy analyses [intent-to-treat (ITT) analysis]. Randomized patients who received at least one dose of the study medication were included in the safety analyses.

b) Populations

Of the 1052 patients screened, 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.

Table 4: Summary of Patient Characteristics of the Included Study[2]		
Characteristics	**Regorafenib (N= 505)**	**Placebo (N= 255)**
Age in years (median, IQR)	61 (54 – 67)	61 (54 – 68)
Male	311 (62%)	153 (60%)
Race:		
White	392 (78%)	201 (79%)
Black	6 (1%)	8 (3%)
Asian	76 (15%)	35 (14%)
Other	31 (6%)	11 (4%)
Region:		
1	420 (83%)	212 (83%)
2	69 (14%)	35 (14%)
3	16 (3%)	8 (3%)
ECOG PS:		
0	265 (52%)	146 (57%)
1	240 (48%)	109 (43%)
Primary site of disease*:		
Colon	323 (64%)	172 (68%)
Rectum	151 (30%)	69 (27%)
Colon and Rectum	30 (6%)	14 (5%)
KRAS mutation†:		
No	205 (41%)	94 (37%)
Yes	273 (54%)	157 (63%)
Unknown	27 (5%)	4 (2%)
No. of previous systemic anti-cancer therapy‡:		
1-2	135 (27%)	63 (25%)
3	125 (25%)	72 (28%)
≥4	245 (49%)	120 (47%)
Previous anti VEGF treatment (Bevacizumab)	505 (100%)	255 (100%)
Prior treatment (stopped because of progression):		
Fluoropyrimidine	421 (83%)	221 (87%)
Bevacizumab	403 (80%)	214 (84%)
Irinotecan	405 (80%)	229 (90%)
Oxaliplatin	278 (55%)	160 (63%)
Panitumumab or cetuximab or both	219 (43%)	107 (42%)
Time from diagnosis of metastases:		
<18 months	91 (18%)	49 (19%)
≥18 months	414 (82%)	206 (81%)
ECOG PS= Eastern Cooperative Oncology Group performance status; **IQR**= interquartile range; Region 1= North America, western Europe, Israel and Australia, Region 2= Asia, Region 3= Eastern Europe		
Data are presented as n (%) unless otherwise stated. *Information missing from one patient in the regorafenib group. †*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.		

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.[1,2]

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.[32]

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. 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 5.

Table 5: Extent of exposure to treatment[32]

Category	Regorafenib (N= 500)	Placebo (N= 253)
Overall time under treatment[a]		
Mean ±SD (weeks)	12.079 ± 9.736	7.776 ± 5.193
Median	7.270	6.980
Number of cycles completed		
Mean ±SD	3.3 ± 2.3	2.3 ± 1.2
Median	2.0	2.0
Range	1 - 12	1 – 10
Actual time under treatment[b]		
Mean ±SD (weeks)	8.861 ± 6.819	6.287 ± 3.794
Median	5.980	5.980
Actual daily dose (mg)[b]		
Mean ±SD	147.146 ± 18.634	159.253 ± 4.854
Median	160.000	160.000

SD= standard deviation
[a] Including time off drug/interruptions
[b] Excluding time off drug/interruptions

d) Patient Disposition

A total of 760 patients were randomized in a 2:1 ratio to regorafenib (n= 505) or placebo (n= 255) and were included in the efficacy analysis (intent-to-treat analyses). In the regorafenib and placebo groups five and two patients respectively did not receive the intervention.[2] For the safety analysis, only patients who received treatment (regorafenib or placebo) were considered. The common reasons for discontinuation were progression of disease and adverse events (Table 6)

Table 6: Patient Population and Disposition[2]		
Category	**Regorafenib**	**Placebo**
Randomized	505	255
Received treatment	500	253
Efficacy analysis	505	255
Safety analysis	500	253
Discontinued	448	244
Discontinued due to: • progressive disease • AE associated with disease progression • AE unassociated with disease progression • consent withdrawal • death • physician decision • protocol violation	 336 (67%) 43 (9%) 42 (8%) 16 (3%) 7 (1%) 2 (0%) 2 (0%)	 205 (80%) 23 (9%) 7 (3%) 5 (2%) 4 (2%) 0 0
AE= adverse event		

e) Limitations/Sources of Bias

- 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.
- 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.
- When concomitant medications were reviewed, there appeared to be higher proportion of patients using anilides, locally acting corticosteroids, antipropulsives and dihydropyridines in the regorafenib group compared to the placebo group. This may have impacted the results.
- The number of patients completing the QoL questionnaires decreased with time during the course of treatment. If patients with low quality of life did not complete the questionnaires, this could confound results. The average scores would be higher if sicker patients were excluded.
- The QoL tools (EORTC QLQ-30C and EQ 5D) used for assessment do not consider some of the adverse events frequently associated with regorafenib (e.g. hand-foot skin reaction, rash). However, it appears more specific validated tools are not available for such assessments.
- 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.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy analyses were based on 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. The database cut-off for the second interim analysis was July 21, 2011. After the second interim analysis, the study was unblinded and the protocol was amended to permit cross-over and four patients from the placebo group crossed over to the regorafenib group. An additional analysis for overall survival was conducted at the database cut-off of November 13, 2011.[14]

Table 7: Summary of Key Outcomes from the CORRECT study[1-3,13]

Efficacy			
Outcome**	**Intervention**	**Median (95% CI) in months**	**HR* (95% CI)**
Overall survival	Regorafenib	6.4 (5.9, 7.3)	0.77 (0.64, 0.94) P= 0.0052
	Placebo	5.0 (4.4, 5.8)	
Overall survival (after second interim analysis; based on database cut-off of November 13, 2011)[14]	Regorafenib	6.4 (5.8, 7.0)	0.79 (0.66, 0.94), P= 0.0038
	Placebo	5.0 (4.4, 5.9)	
PFS	Regorafenib	1.9 (1.9, 2.1)	0.49 (0.42, 0.58) P< 0.0001
	Placebo	1.7 (1.7, 1.7)	
Outcome - HRQoL	**Intervention**	**Baseline score† (mean± SD)**	**End of treatment score† (mean± SD)**
EORTC QLQ-30C	Regorafenib	62.6± 21.7	48.9± 21.6
	Placebo	64.7± 22.4	51.9± 23.9
EQ 5D Index	Regorafenib	0.73± 0.25	0.59± 0.31
	Placebo	0.74± 0.27	0.59± 0.34
EQ 5D VAS	Regorafenib	65.4± 19.6	55.5± 20.4
	Placebo	65.8± 20.5	57.3± 21.6
Harm			
Outcome	**Intervention**	**Proportion of patients (n/N)**	**Percentage of patients**
SAE	Regorafenib	219/500	44%
	Placebo	100/253	40%
AE (any grade)	Regorafenib	465/500	93%

Table 7: Summary of Key Outcomes from the CORRECT study[1-3,13]			
	Placebo	154/253	61%
AE (leading to any dose modification)	Regorafenib	378/500	75.6%
	Placebo	97/253	38.3%
WDAE	Regorafenib	88/500	17.6%
	Placebo	32/253	12.6%
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, **PFS**= progression free survival, **SAE**= serious adverse event, **SD**= standard deviation, **VAS**= visual analog scale, **WDAE**= withdrawal due to adverse event *HR < 1 favours regorafenib † Higher scores indicate better HRQoL and better health status.			
**The results are from the second interim analysis (database cut-off of July21, 2011) unless otherwise stated. At the second interim analysis, the prespecified efficacy boundary was crossed as p≤ 0.0093, approximately corresponding to HR of 0.7864 for overall survival in the regorafenib group compared to the placebo group.			

Efficacy Outcomes

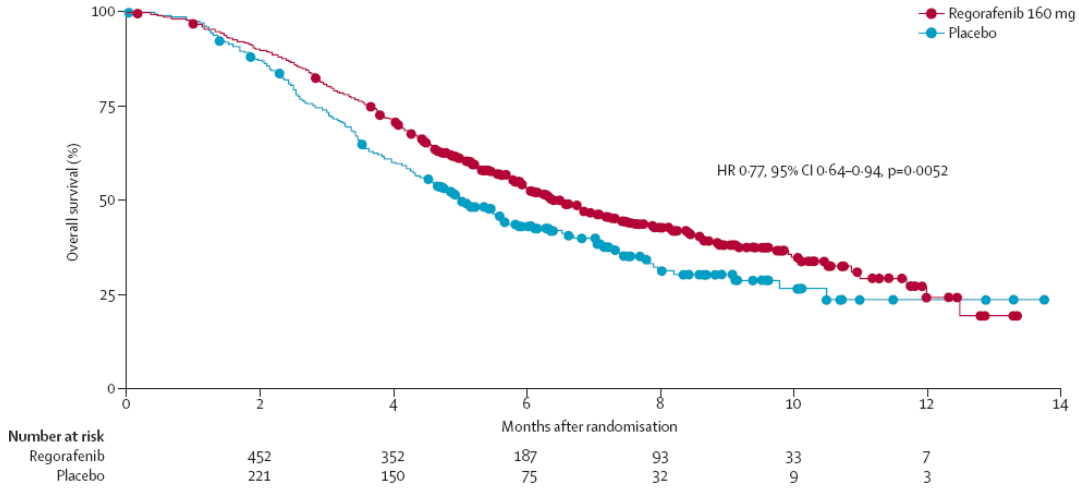
Overall Survival

Overall survival was the primary end-point. It was defined as the time from randomization to death due to any cause.[32] Median overall survival 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. The hazard ratio (95% confidence interval) for regorafenib versus placebo was 0.77 (0.64, 0.94) and p= 0.0052 indicating a 23% reduction in the risk of death in the regorafenib group. After the study was unblinded and at database cut-off of November 13, 2011 an additional analysis showed similar results as the second interim analysis, with a median overall survival of 6.4 months in the regorafenib group and 5.0 months in the placebo group and the hazard ratio (95% confidence interval) for overall survival was 0.79 (0.66, 0.94) and p= 0.0038 for regorafenib versus placebo.[14] In the predefined subgroups (patients previously treated with VEGF-targeting drugs, patients with diagnosis of metastatic disease ≥18 months, and patients from North America, Western Europe, Israel and Australia) the risks of death were statistically significantly reduced with regorafenib compared with placebo. Numerical values indicated that overall survival rates were higher in the regorafenib group compared to the placebo group up to 9 months and was similar in both groups at 12 months. Details of overall survival from the second interim analysis are provided in Table 8 and Figure 2. After the second interim analysis and at database cut-off of November 13, 2011, an additional analysis showed that at 6 and 12 months the overall survival rates were 52.2% and 24.1% in regorafenib group and 43.1% and 17% in the placebo groups. [14]

Table 8: Overall survival (second interim analysis with database cut-off of July 21, 2011)[2]		
Outcome	**Regorafenib**	**Placebo**
Overall survival (months) [median (IQR)]	6.4 (6, 11.8)	5.0 (2.8, 10.4)
Overall survival rate at:		
3 months	80.3%	72.7%
6 months	52.5%	43.5%
9 months	38.2%	30.8%
12 months	24.3%	24.0%
IQR= interquartile range		

Source: Grothey et al. Lancet 2013, 381; p.307[2]

Figure 2 : Kaplan-Meier curves for overall survival in intent-to-treat population (**second interim analysis with database cut-off of July 21, 2011**)[2]

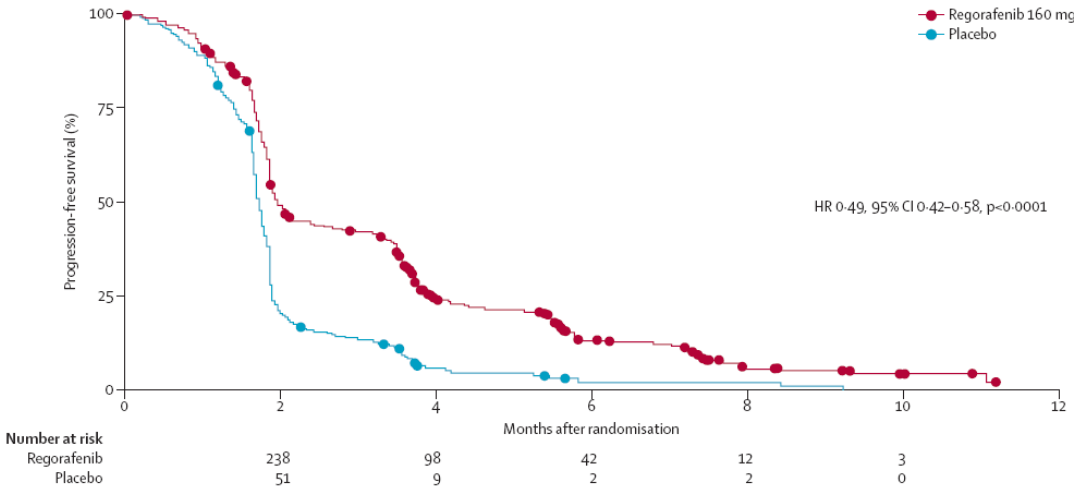


Source: Grothey et al.[2]

Progression free survival (PFS)

Progression free survival (PFS) was 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 documented.[32] The median PFS and interquartile ranges in months were 1.9 (1.6, 3.9) in the regorafenib group and 1.7 (1.4, 1.9) for the placebo group indicating a difference of 0.2 months. The hazard ratio (95% confidence interval; p-value) for regorafenib versus placebo was 0.49 (0.42, 0.58; p< 0.0001) indicating a 51% reduction of risk of disease progression or death in the regorafenib group compared to the placebo group. In the predefined subgroups (by previous treatment with VEGF-targeting drug, by time from diagnosis of metastatic disease and by geographical region) the risks of disease progression were statistically significantly reduced with regorafenib compared with placebo. Kaplan-Meier curves for PFS are shown in Figure 3.

Figure 3: Kaplan-Meier curves for progression free survival in intent-to-treat population[2]



Source: Grothey et al.[2]

Health related quality of life (HRQoL)

Health related quality of life 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). Overall results at end of treatment indicated a decline in patients' HRQoL in both the regorafenib and placebo groups (Table 9). Results at various times of treatment are shown in Table 10 and 11. Results for the EORTC QLQ-C30 global health status and five functional dimensions indicated similar deteriorations in HRQoL of patients in the regorafenib and placebo groups (Table 10). Results for EQ 5D index and EQ 5D VAS also indicated similar deteriorations in HRQoL of patients in the regorafenib and placebo groups (Table 11). Variation in the change from baseline was considerable [high standard deviation (SD) values]. At the end of treatment in both groups, the magnitude of deterioration was greater than the minimal important difference (MID). MIDs were reported as at least 10 points for the EORTC QLQ-C30,[2,36,37] 0.06 to 0.12 points for EQ-5D index and 7 to 12 points for EQ-5D VAS.[2,38] In the placebo group, in cycles 3 and 4 for two of the functional dimensions (emotional function and social function) the mean changes from baseline were positive suggesting an improvement however, with the large standard deviations no definite conclusions are possible. The proportion of patients with data for EORTC QLQ-C30, EQ 5D index and EQ 5D VAS appeared to be similar in the regorafenib and placebo groups for cycle 2 and end of treatment (EOT). The proportion of patients with data for EORTC QLQ-C30, EQ 5D index and EQ 5D VAS was lower in the placebo group compared to the regorafenib group for treatment cycles 3 and 4. The number of patients completing the HRQoL questionnaires decreased with time.

The analyses of time-adjusted area under the curve (AUC) for EORTC QLQ-C30, EQ 5D index and EQ 5D VAS demonstrated that treatment effects were similar (overlapping confidence intervals) in both the regorafenib and placebo groups. Differences were not clinically significant.[32] Data are not present here.

Table 9: Health-related quality of life and health utilities values[2]				
Measure	**Intervention**	**Score (mean± SD)***		
		Baseline	**End of treatment**	**Change from baseline†**
EORTC QLQ-C30	Regorafenib	62.6± 21.7	48.9± 21.6	-13.7
	Placebo	64.7± 22.4	51.9± 23.9	-12.8
EQ-5D index	Regorafenib	0.73± 0.25	0.59± 0.31	-0.14
	Placebo	0.74± 0.27	0.59± 0.34	-0.15
EQ-5D VAS	Regorafenib	65.4± 19.6	55.5± 20.4	-9.9
	Placebo	65.8± 20.5	57.3± 21.6	-8.5

EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, **EQ-5D**= European Quality of Life Scale, **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;[2,36,37] 0.06 to 0.12 points for EQ-5D index; and 7 to 12 points for EQ-5D VAS.[2,38]
†Calculated by Methods Team

Table 10: Changes in HRQoL at various times evaluated using EORTC QLQ-C30 (ITT analyses)[31]				
Treatment phase*	**Change from baseline**			
	Regorafenib (N=505)		**Placebo (N= 255)**	
	n (%)†	**Mean ± SD**	**n (%)†**	**Mean ± SD**
Physical function				
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
Role function				
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
Emotional function				
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
Social function				
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]

Table 10: Changes in HRQoL at various times evaluated using EORTC QLQ-C30 (ITT analyses)[31]

Treatment phase*	Change from baseline			
	Regorafenib (N=505)		Placebo (N= 255)	
	n (%)†	Mean ± SD	n (%)†	Mean ± SD
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive function				
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
Global health status (QoL)				
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]

EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, **EOT**= end of treatment, **HRQoL**= health related quality of life, **ITT**= intent-to-treat, **SD**= standard deviation

*Each cycle comprises of 3 weeks on regorafenib or placebo and 1 week off

†Percentages calculated by systematic review author

(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.)

Table 11: Changes in HRQoL at various times evaluated using EQ 5D index and EQ 5D VAS (ITT analyses)

Treatment phase	Change from baseline			
	Regorafenib (N=505)		Placebo (N= 255)	
	n (%)*	Mean ± SD	n (%)*	Mean ± SD
EQ 5D index				
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]
EQ 5D VAS				
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
EOT	[redacted]	[redacted]	[redacted]	[redacted]

EQ 5D= European Quality of life 5 dimensions, **EOT**= end of treatment, **HRQoL**= health related quality of life, **ITT**= intent-to-treat, **SD**= standard deviation

*Percentages calculated by systematic review author

(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.)

Disease control rate (DCR)

The disease control rate (DCR) was defined as the proportion of patients with complete or partial response or stable disease for greater than or equal to six months after randomization.[32] None of the patients had complete response; five patients in the regorafenib group and two in the placebo group had partial responses. The DCR was 41% (207/505) in the regorafenib group and 15% (38/255) in the placebo group ($p< 0.0001$).[2]

Harms Outcomes

Serious Adverse Events (SAE)

A serious adverse event was defined as any untoward 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.[32] Fatal hepatic adverse events were 8 (2.1%) and 1 (0.6%) 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 SMQ of Hepatic failure, fibrosis, and cirrhosis and other liver damages related to conditions.[13] Serious hepatobiliary adverse

events (by MedDRA system organ class and preferred term) were 27 (5.4%) and 9 (3.6%) in the regorafenib and placebo groups respectively.[32]

Occurrence of non-fatal serious adverse events appeared to be similar in both groups (Table 12).

Table 12: Serious adverse events[13]

Category	Regorafenib (N= 500)	Placebo (N= 253)
Any SAE	219 (44%)	100 (40%)
General health deterioration	36 (7%)	24 (10%)
Pyrexia	14 (3%)	1 (0.4%)
Abdominal pain	12 (2.4%)	2 (1%)
Pneumonia	10 (2%)	4 (2%)
Dyspnea	10 (2%)	3 (1%)
Diarrhea	8 (2%)	0
Intestinal Obstruction	7 (1%)	2 (1%)
Hepatic Failure	7 (1%)	2 (1%)
Multi-organ failure	6 (1%)	4 (2%)

Data expressed as number and percentage of patients

Adverse events

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

Adverse events (≥1%) leading to dose reductions, occurred in 188 (37.6%) and 8 (3.2 %) patients in the regorafenib and placebo groups respectively (Table 14). Adverse events (≥1%) leading to dose interruptions, occurred in 304 (60.8%) and 55 (21.7 %) patients in the regorafenib and placebo groups, respectively (Table 15). Adverse events leading to any dose modifications, occurred in 378 (75.6%) and 97 (38.3%) patients in the regorafenib and placebo groups respectively (Table 16).

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[2]

Category	Regorafenib (N= 500)			Placebo (N= 253)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any event	465 (93%)	253 (51%)	17 (3%)	154 (61%)	31 (12%)	4 (2%)
Fatigue	237 (47%)	46 (9%)	2 (<1%)	71 (28%)	12 (5%)	1 (<1%)
Hand-foot skin reaction	233 (47%)	**83 (17%)**	0	19 (8%)	**1 (<1%)**	0

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[2]

Category	Regorafenib (N= 500)			Placebo (N= 253)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Diarrhoea	169 (34%)	35 (7%)	1 (<1%)	21 (8%)	2 (1%)	0
Anorexia	152 (30%)	16 (3%)	0	39 (15%)	7 (3%)	0
Voice changes	147 (29%)	1 (<1%)	0	14 (6%)	0	0
Hypertension	139 (28%)	36 (7%)	0	15 (6%)	2 (1%)	0
Oral mucositis	136 (27%)	15 (3%)	0	9 (4%)	0	0
Rash or desquamation	130 (26%)	29 (6%)	0	10 (4%)	0	0
Nausea	72 (14%)	2 (<1%)	0	28 (11%)	0	0
Weight loss	69 (14%)	0	0	6 (2%)	0	0
Fever	52 (10%)	4 (1%)	0	7 (3%)	0	0
Constipation	42 (8%)	0	0	12 (5%)	0	0
Dry skin	39 (8%)	0	0	7 (3%)	0	0
Alopecia	36 (7%)	0	0	1 (<1%)	0	0
Taste alteration	35 (7%)	0	0	5 (2%)	0	0
Vomiting	38 (8%)	3 (1%)	0	13 (5%)	0	0
Sensory neuropathy	34 (7%)	2 (<1%)	0	9 (4%)	0	0
Nose bleed	36 (7%)	0	0	5 (2%)	0	0
Dyspnoea	28 (6%)	1 (<1%)	0	4 (2%)	0	0
Muscle pain	28 (6%)	2 (<1%)	0	7 (3%)	1 (<1%)	0
Headache	26 (5%)	3 (1%)	0	0	0	
Pain abdomen	25 (5%)	1 (<1%)	0	10 (4%)	0	0

Data expressed as number and percentage of patients

Table 14: Adverse events (≥1%) leading to dose reduction[13]

Category	Regorafenib (N= 500)	Placebo (N= 253)
Any Event	188 (37.6%)	8 (3.2 %)
Palmar-Plantar Erythrodysaesthesia	91 (18.2%)	1 (0.4 %)
Diarrhea	19 (3.8%)	0
Hypertension	16 (3.2%)	1 (0.4 %)
Fatigue	10 (2%)	5 (2 %)
Rash	10 (2%)	0
Mucositis	6 (1.2%)	0
Abdominal pain	5 (1%)	0
Asthenia	5 (1%)	0

Data expressed as number and percentage of patients

Table 15: Adverse events (≥1%) leading to dose interruption[13]		
Category	**Regorafenib (N= 500)**	**Placebo (N= 253)**
Any Event	304 (60.8%)	55 (21.7 %)
Palmar-Plantar Erythrodysaesthesia	94 (18.8%)	0
Diarrhea	31 (6.2%)	2 (0.8%)
Pyrexia	23 (4.6%)	3 (1.2 %)
Fatigue	20 (4.0%)	4 (1.6%)
Rash	18 (3.6%)	0
Hyperbilirubinemia	18 (3.6%)	5 (2 %)
Decreased appetite	15 (3%)	5 (2 %)
Asthenia	14 (2.8%)	0
Hypertension	13 (2.6%)	1 (0.4%)
Abdominal pain	12 (2.4%)	0
Stomatitis	11 (2.2%)	0
Dyspnea	10 (2%)	3 (1.2 %)
AST increased	9 (1.8%)	1 (0.4%)
Vomiting	9 (1.8%)	1 (0.4%)
Thrombocytopenia	8 (1.6%)	0
ALT increased	7 (1.4%)	1 (0.4%)
Proteinuria	6 (1.2%)	2 (0.8%)

Table 16: Dose modifications or interruptions due to adverse events is presented as number (%) of patients[2]			
Category		**Regorafenib (N= 500)**	**Placebo (N= 253)**
Patients with any dose modification		378 (75.6%)	97 (38.3%)
Patients with dose reductions	Total	100 (20·0%)	8 (3·2%)
Dose reductions per patient	1	82 (16·4%)	8 (3·2%)
	2	14 (2·8%)	0
	3	4 (0·8%)	0
Duration of dose reduction	<3 days	9 (1·8%)	3 (1·2%)
	3–5 days	9 (1·8%)	0
	>5 days	82 (16·4%)	4 (1·6%)
	Missing	0	1 (0·4%)
Patients with dose interruptions	Total	352 (70·4%)	95 (37·5%)
Dose interruptions per patient	1	178 (35·6%)	70 (27·7%)
	2	94 (18·8%)	19 (7·5%)
	≥3	80 (16·0%)	6 (2·4%)
Duration of dose interruptions	<3 days	41 (8·2%)	25 (9·9%)
	3–5 days	47 (9·4%)	26 (10·3%)
	>5 days	263 (52·6%)	43 (17·0%)
	Missing	1 (0·2%)	1 (0·4%)

Withdrawals due to Adverse Events

Withdrawals due to adverse event occurred in 88 (17.6%) and 32 (12.6%) patients in the regorafenib and placebo groups respectively. Details are provided in (Table 17).

Table 17: Withdrawals due to adverse events[13]

Category	Regorafenib (N= 500)	Placebo (N= 253)
Any Event	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
Data expressed as number and percentage of patients		

6.4 Ongoing Trials

An ongoing trial that would have met the inclusion criteria for this review had it been completed is shown in Table 18

Table 18: Ongoing RCT on Regorafenib in patients with mCRC who have failed standard therapies

Trial	Design	Population	Intervention	Comparator	Outcomes
A randomized, double-blind, placebo-controlled phase III study of Regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy[15]					
NCT01584830 CONCUR[15] Study start date: April 2012 Estimated study completion date: May 2014	Randomized, double-blind, phase III study	Patients with metastatic colorectal cancer (Stage IV) who have failed at least two lines of prior treatment	Regorafenib (3 weeks on/ 1 week off (160 mg, oral dose, QD) +BSC	Placebo +BSC	Primary: OS Secondary: PFS DCR (CR+PR) AE

AE=adverse events; **BSC**= best supportive care, **CR**= complete response**; DB**= double blind; **DCR=**disease control rate; **mCRC**= metastatic colorectal cancer; **OS=**overall survival; **PFS=**progression-free survival; **PR**= partial response**; QD=**once daily; **RCT**= randomized controlled trial

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Gastrointestinal 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.pcodr.ca).

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 Final Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report

The Gastrointestinal Clinical Guidance Panel is comprised of three medical 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.pcodr.ca). 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

Embase 1980-present (emez) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE (R) (pmez)

#	Searches	Results
1	(Stivarga$ or regorafenib$ or "BAY 73 4506" or "BAY73 4506").ti,ot,ab,sh,rn,hw,nm.	238
2	(755037-03-7 or 24T2A1DOYB).rn,nm.	176
3	or/1-2	238
4	3 use pmez	49
5	*regorafenib/	40
6	(Stivarga$ or regorafenib$ or "BAY 73 4506" or "BAY73 4506").ti,ab.	105
7	5 or 6	107
8	7 use oemezd	62
9	4 or 8	111
10	remove duplicates from 9	74
11	limit 10 to english language	66
12	exp animals/	35225675
13	exp animal experimentation/ or exp animal experiment/	1691955
14	exp models animal/	1080707
15	nonhuman/	4041076

#	Searches	Results
16	exp vertebrate/ or exp vertebrates/	34314814
17	animal.po.	0
18	or/12-17	36404114
19	exp humans/	27176006
20	exp human experimentation/ or exp human experiment/	323074
21	human.po.	0
22	or/19-21	27178079
23	18 not 22	9227619
24	11 not 23	65

2. Literature search via PubMed

8.2.1 History

Search	Add to builder	Query	Items found
#2	Add	Search ((Stivarga*[tiab] OR regorafenib*[tiab] OR "BAY 73 4506"[tiab] OR "BAY73 4506"[tiab] OR Regorafenibum*[tiab] OR 24T2A1DOYB[rn] OR "regorafenib"[Supplementary Concept]) AND publisher[sb] Filters: English Sort by: PublicationDate	3
#1	Add	Search ((Stivarga*[tiab] OR regorafenib*[tiab] OR "BAY 73 4506"[tiab] OR "BAY73 4506"[tiab] OR Regorafenibum*[tiab] OR 24T2A1DOYB[rn] OR "regorafenib"[Supplementary Concept]) AND publisher[sb]	3

3. Cochrane Central Register of Controlled Trials (Central)

Cochrane Central Register of Controlled Trials : Issue 6 of 12, 2013

There are 2 results from 687344 records for your search on #1 - Stivarga* or regorafenib* or "BAY 73 4506" or "BAY73 4506" in title abstract keywords in Trials in the strategy currently being edited

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Canadian Cancer Trials registry
http://www.canadiancancertrials.ca/

Search terms: (Stivarga or regorafenib) AND (colorectal cancer)

Select international agencies including:

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

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Search terms: (Stivarga or regorafenib) AND (colorectal cancer)

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search terms: (Stivarga or regorafenib) AND (colorectal cancer) / last 5 years

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