PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Regorafenib (Stivarga) for Gastrointestinal Stromal Tumors

May 2, 2014

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1 GUIDANCE IN BRIEF

1.1 Background

Regorafenib is a novel, oral multikinase inhibitor that blocks the activity of several protein kinases, including those involved in the regulation of tumor angiogenesis, oncogenesis and the tumor microenvironment.

Regorafenib has a Health Canada approved indication for use in patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) who have had disease progression on or intolerance to imatinib mesylate and sunitinib malate treatment.[8] The approval of regorafenib is based on progression-free survival from one phase III randomized controlled trial. The recommended dose of regorafenib is 160 mg daily for 3 weeks on therapy and 1 week off therapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one international multicentre double-blind randomized controlled trial, GRID, which evaluated the efficacy and safety of regorafenib (n=133) compared to placebo (n=66).[1]

This study recruited patients with histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib (either through disease progression or from intolerance) and previous sunitinib (through disease progression only). Baseline characteristics were similar between the two groups, though there appeared to be a difference between the two groups in the duration of previous imatinib therapy. Patients received either oral regorafenib 160 mg once daily or matching placebo for the first 3 weeks of each 4 week cycle, along with best supportive care.

Analysis was done according to intention-to-treat and included 199 patients who were randomized. At the time of analysis, 56 patients from the placebo group had crossed-over to receive open-label regorafenib.

Efficacy

The primary outcome of the trial was progression free survival (PFS) with overall survival (OS) as a secondary outcome.

There was a statistically significant difference between groups for progression-free survival with a median PFS of 4.8 months vs 0.9 months for the regorafenib vs placebo arms, respectively (HR 0.268, 95% CI 0.185-0.388, P <0.0001). Prespecified subgroup analysis demonstrated HR mostly consistent with that of the primary analysis in favour of regorafenib. Specifically, the HR for those with exon 11 and exon 9 mutations were 0.21 (0.10-0.46) and 0.24 (0.07-0.88) respectively. Only the group that were on imatinib less than 6 months had a HR that crossed unity (HR 0.50, 95% CI 0.17-1.73).

There was no difference between groups for overall survival with a hazard ratio (HR) of 0.772 (95% confidence interval [CI]: 0.423, 1.408, p-value 0.199). The overall survival data presented was considered an interim analysis, and was done at the time of final PFS analysis (January 26, 2012). Given the high level of cross over in the trial, the overall survival data should be interpreted with caution.

Health related quality of life was measured using the EORTC QLQ-C30 questionnaire. While there was no actual improvement in quality of life, both the time to deterioration for global health and for physical functioning statistically favoured the regorafenib group.

Harms

Although statistically significant difference were not reported, there were greater overall grade 3-4 serious adverse events (AEs) in the regorafenib vs placebo groups (59.8% vs 9.1%, respectively). The most common regorafenib-related AE's of any grade were hand-foot skin reaction (56% vs 14%), hypertension (49% vs 17%) and diarrhea (40% vs 5%). The most common regorafenib-rated Grade 3-4 AE's were hypertension (24% vs 3%), hand-foot skin reaction (20% vs 0%), diarrhea (5% vs 0%).

From both the double-blind and open label periods in which 188 patients received regorafenib, 16 patients experienced grade 5 adverse events of which 6 were deemed to be related to study drug; consisting one each of : cardiac arrest, colonic perforation, hepatic failure, acute renal injury, adult respiratory distress syndrome and thromboembolic event).

The majority of patients in the regorafenib arm (72%), compared with 26% in the placebo arm, required dose modifications during the double-blind period with no patients requiring reductions beyond dose level -2 (pre-specified at 80 mg from 160 mg, once daily); while 6% vs 8% of patients in the regorafenib vs placebo arms discontinued treatment due to adverse events, respectively. No further detail was provided on which adverse events led to discontinuation of therapy.

1.2.2 Additional Evidence

pCODR received input on regorafenib for GIST from one patient advocacy group, Sarcoma Cancer Foundation of Canada, SCFC. Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

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

1.2.3 Interpretation and Guidance

Burden of Illness and Need:

Despite being the most common sarcoma of the gastrointestinal tract, the incidence of GIST is approximately 500 per year in Canada. Over the past 15 years, the treatment of recurrent or metastatic GIST with imatinib mesylate has significantly improved the overall survival of this patient population to over 24 months. The majority of patients have clinical benefit with primary resistance to imatinib seen in only a minority of patients. However, despite a long progression free survival experienced by most patients on imatinib, the majority of patients eventually develop imatinib-resistant disease. A modest benefit has been demonstrated for those re-challenged with imatinib however most provincial authorities do not fund 3rd line imatinib for GIST. Sunitinib has also been demonstrated to significantly increase the median time to progression and has approval by Health Canada[1] for use in imatinib-resistant or intolerant patients.

Although the majority of patients with advanced GIST benefit from imatinib, currently, there is no standard of care for patients whose disease has progressed despite treatment with imatinib and sunitinib.

Effectiveness:

The GRID study demonstrated a meaningful improvement in median progression free survival when compared to placebo in patients previously treated with both imatinib and sunitinib. Prespecified subgroup analysis demonstrated HR mostly consistent with that of the primary analysis in favour of those on regorafenib. For the secondary outcome of OS, there was no significant difference between the two study groups. PFS is however recognized as an acceptable primary endpoint, particularly in a setting where OS is expected to be compromised due to post-progression crossover or contamination, which was the case in GRID.

While there was no actual improvement in quality of life, both the time to deterioration for global health and for physical functioning statistically favoured the regorafenib group.

Safety:

Despite the higher rate of grade 3 or higher adverse events, the rate of treatment discontinuation due to adverse events was similar in both groups. Importantly, the majority of patients required at least one dose reduction.

1.3 Conclusions

The pCODR Clinical Guidance Panel concluded that there is a net overall clinical benefit to regorafenib based on one randomized clinical trial, the GRID study, which demonstrated a meaningful improvement in median progression free survival by nearly 4 months when compared to placebo in patients previously treated with both imatinib and sunitinib.

The Clinical Guidance Panel also considered that:

- There remains an unmet clinical need in GIST patients whose disease has progressed on imatinib and sunitinib given the modest benefit observed with imatinib re-introduction in this setting.
- Clinical benefit was observed in patients with either exon 11 or 9 mutations in c-kit.
- Secondary endpoints included health related quality of life which also favoured the treatment arm.
- An overall survival benefit was not observed in this pivotal study but the results may have been affected by the high crossover rate of patients on placebo to regorafenib.
- Despite the higher rate of grade 3 or higher adverse events, the rate of treatment discontinuation due to adverse events was similar in both groups. Importantly, the majority of patients required at least one dose reduction.
- Currently, there are no data that supports the use of regorafenib in metastatic GIST patients who are treatment naïve or who have only been treated with imatinib. Similarly, no data support the use of regorafenib in the adjuvant setting.

2 CLINICAL GUIDANCE

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Regorafenib has a Health Canada approved indication for use in patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) who have had disease progression on or intolerance to imatinib mesylate and sunitinib malate treatment.[8] The approval of regorafenib is based on progression-free survival from one phase III randomized controlled trial. The recommended dose of regorafenib is 160 mg daily for 3 weeks on therapy and 1 week off therapy.

Regorafenib is a novel, oral multikinase inhibitor that blocks the activity of several protein kinases, including those involved in the regulation of tumor angiogenesis, oncogenesis and the tumor microenvironment.

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 progression free survival, overall survival, quality of life and harms compared to standard treatment in patients with metastatic and / or unresectable GIST.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

The efficacy and safety of regorafenib 160 mg administered daily (n=133) was compared to placebo (n=66) in an international multicentre double-blind randomized controlled trial (GRID).[1]

This study recruited patients with histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib (either through disease progression or from intolerance) and previous sunitinib (through disease progression only). Baseline characteristics were similar between the two groups, though there appeared to be a difference between the two groups in the duration of previous imatinib therapy.

Patients received either oral regorafenib 160 mg once daily or matching placebo for the first 3 weeks of each 4 week cycle, along with best supportive care. In the event of centrally assessed tumour progression, treatment assessment could be unmasked. Patients originally in the placebo group were offered the option to crossover to receive open-label regorafenib. During the double-blind period, patients in the regorafenib group had a median treatment duration of 22.9 weeks (IQR 9.3 – 28.6) and patients in the placebo group had a median treatment duration of 7.0 weeks (IQR 5.1 – 11.3). At the data cut-off, 53 of the 133 (40%) patients in the regorafenib group and 3 of the 66 (5%) patients in the placebo group were still receiving double-blind treatment. In the placebo group, 56 patients had crossed-over to receive open-label regorafenib at time of analysis.

Analysis was done according to intention-to-treat and included 199 patients who were randomized, regardless of whether or not they received the study drug or a different drug from the original assignment. There was no difference between groups for overall survival

with a hazard ratio (HR) of 0.772 (95% confidence interval [CI]: 0.423, 1.408, p-value 0.199). There was a difference, however, between groups for progression-free survival with a HR of 0.268 (95% CI: 0.19, 0.39, p-value <0.000001). Given the high level of cross over in the trial, the overall survival data should be interpreted with caution.

Patient reported outcomes were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 instrument (EORTC QLQ-C30), version 3.0. There were no significant differences between groups in global health or physical functioning throughout the trial. There were decreases in global health within both groups through the trial. There were quite a few missing data points, though the submitter did a pattern-mixture model to account for this.

Compared to the placebo group, the regorafenib group had greater overall grade 3-4 serious adverse events (AEs) (59.8% vs 9.1%), though the paper does not report statistical significance between these two groups. The regorafenib group also had a greater proportion of hand-foot skin reaction (56% vs 14%), hypertension (49% vs 17%) and diarrhea (40% vs 5%), of any grade.

Dose modifications during the double-blind phase occurred in a total of 112 patients: 95 patients in the regorafenib group (72%) and 17 patients in the placebo group (26%). Dose interruptions during the double-blind phase occurred in 58.3% of the regorafenib group, compared to 16.7% of the placebo group; dose reductions occurred in 50% of the regorafenib group compared to 3.0% of the placebo group.

2.1.4 Comparison with Other Literature

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

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

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

Patient Advocacy Group Input

From a patient perspective, it is important to have different treatment options in the event that existing treatments are not effective or prove to have untenable side effects. SCFC indicated that patients who have used regorafenib have reported positive results to date. The patients' experience has shown it to be an easy to use drug as a result of its oral format, and has minimal side effects.

PAG Input

Input on regorafenib (Stivarga) for gastrointestinal stromal tumour was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, the key enablers are the small number of patients who would be eligible for third-line treatment, there is no current standard treatment in the third-line setting and regorafenib is an oral treatment that can be provided in the community.

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. 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. There is also the potential for use in other lines of therapy.

There is a particular Black Box warning advising of regorafenib associated 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

The important identified risks are severe drug-induced liver injury (DILI), hemorrhage, myocardial ischemia and infarction, arterial hypertension and hypertensive crisis, palmar-plantar erythrodysesthesia syndrome/hand-foot skin reaction (HFSR), gastrointestinal perforation and fistula, reversible posterior leukoencephalopathy syndrome (RPLS), and Stevens-Johnson syndrome (SJS). These are considered identified risks due to pharmacological plausibility and clinical safety data suggesting a causal link to regorafenib. Severe DILI, hemorrhage, myocardial infarction/ischemia, SJS and RPLSare considered important because of their potential to result in severe or fatal outcomes. Hypertension and HFSR are important in that they are very common and may adversely impact effective therapy delivery and quality of life. A Serious Warnings and Precautions box in the Stivarga Product Monograph contains warnings regarding hepatotoxicity, hemorrhage involving the respiratory and gastrointestinal tracts, cardiac ischemia and infarction, RPLS, gastrointestinal perforation and fistula, arterial hypertension, and HFSR. The cardiovascular section of the Stivarga Product Monograph contains explicit warnings regarding the increased incidence of cardiac adverse events (8.4 vs. 5.5%) including cardiac arrhythmia (3% vs. 0.8%), cardiac ischemia and infarction (1.2% vs. 0.4%) and severe (Grade 3/4) congestive heart failure (1.2% vs.0.4%) in Stivarga-treated patients compared to placebo-treated patients.

2.2 Interpretation and Guidance

Despite being the most common sarcoma of the gastrointestinal tract, the incidence of GIST is approximately 500 per year in Canada. Over the past 15 years, the treatment of recurrent or metastatic GIST with imatinib mesylate has significantly improved the overall survival of this patient population to over 24 months. However, despite a long progression free survival experienced by most patients on imatinib, the majority of patients eventually develop imatinib-resistant disease. A small proportion of patients treated with imatinib are either intolerant of the medication or have primary imatinib-resistant disease. Sunitinib, another tyrosine kinase inhibitor, has been shown to be of clinical benefit in those with imatinib resistant GIST with an acceptable toxicity profile. The duration of

clinical benefit with sunitinib in this 2nd line setting is significantly shorter with a median progression free survival of 7 months in the pivotal phase III study. Although a small phase III study demonstrated a modest benefit for those re-challenged with imatinib, most provincial authorities do not fund 3rd line imatinib for GIST. Although the majority of patients with advanced GIST benefit from imatinib, currently, there is no standard of care for patients whose disease has progressed despite treatment with imatinib and sunitinib. Regorafenib is a novel, multikinase inhibitor that blocks the activity of several key protein kinases has been tested in both advanced colorectal cancer as well as in GIST.

GRID Trial

The pCODR systematic review identified only one randomized clinical trial of regorafenib versus placebo in previously treated GIST patients. In the study reported by Demetri et al, 199 patients previously treated with both imatinib and sunitinib were randomized in a 2:1 ratio, to regorafenib 160 mg once daily or matching placebo for the first 3 weeks of each 4 weeks. The primary endpoint was progression free survival as per modified RECIST criteria conducted by central review. A total of 133 patients were randomized to regorafenib and 66 to matching placebo. Only 6 patients had been intolerant of imatinib and 43% of patients had received three or more lines of therapy. The study was well balanced in terms of age, performance status although more patients on the placebo arm were on imatinib longer than 18 months. Both efficacy and safety analysis was conducted at the data cut-off date of January 26, 2012 when a predetermined criteria of 144 progression-free survival events had been reached.

Effectiveness of Regorafenib

At data cut-off, 53 of the 133 (40%) patients in the regorafenib group and 3 of the 66 (5%) patients in the placebo group were still receiving double-blind treatment. In the placebo group, 56 of the 66 patients had crossed over to open-label regorafenib.

The median progression-free survival was 147 days (4.8 months) for those on the regorafenib arm and 28 days on the placebo arm (HR 0.268, 95% CI 0.185-0.388, P <0.0001). Prespecified subgroup analysis demonstrated HR mostly consistent with that of the primary analysis in favour of those on regorafenib. Specifically, the HR for those with exon 11 and exon 9 mutations were 0.21 (0.10-0.46) and 0.24 (0.07-0.88) respectively. Only the group that were on imatinib less than 6 months had a HR that crossed unity (HR 0.50, 95% CI 0.17-1.73).

This study used PFS as the primary efficacy endpoint which is consistent with the FDA guidelines on clinical trial endpoints for cancer drugs. Both imatinib and sunitinib were approved by Health Canada on response rate and time to progression respectively. PFS is recognized as an acceptable primary endpoint, particularly in a setting where OS is expected to be compromised due to post-progression crossover or contamination, which was the case in GRID.

Overall survival was a secondary endpoint, and was presented as an interim analysis with the results being confounded by the high crossover rate. The HR for death was 0.772 (95% CI, 0.423-1.408) and there was no significant difference between the two study groups. No complete tumour responses were observed and 6 of the 133 patients on the regorafenib group and 1 of the 66 patients in the placebo group had a partial response.

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 instrument (EORTC QLQ-C30), version 3.0 which was administered at baseline and at beginning of the each cycle for the first 3 months and every other cycle thereafter. While there was no actual

improvement in quality of life, both the time to deterioration for global health and for physical functioning statistically favoured the regorafenib group.

Although the majority of patients in both groups experienced treatment-related toxicity, only 6% of regorafenib patients and 8% of placebo patients discontinued treatment due to adverse events. From both the double-blind and open label periods in which 188 patients received regorafenib, 16 patients experienced grade 5 adverse events of which 6 were deemed to be related to study drug, consisting one each of: cardiac arrest, colonic perforation, hepatic failure, acute renal injury, adult respiratory distress syndrome and thromboembolic event). The most common regorafenib-related grade 3 or higher events were hypertension, hand-foot reaction, and diarrhea. The majority of patients (72%) required dose modifications during the double-blind period with no patients required reductions beyond dose level -2 (pre-specified at 80 mg from 160 mg, once daily).

2.3 Conclusions

The pCODR Clinical Guidance Panel concluded that there is a net overall clinical benefit to regorafenib based on one randomized clinical trial, the GRID study, which demonstrated a meaningful improvement in median progression free survival by nearly 4 months when compared to placebo in patients previously treated with both imatinib and sunitinib.

The Clinical Guidance Panel also considered that:

- There remains an unmet clinical need in GIST patients whose disease has progressed on imatinib and sunitinib given the modest benefit observed with imatinib re-introduction in this setting.
- Clinical benefit was observed in patients with either exon 11 or 9 mutations in c-kit.
- Secondary endpoints included health related quality of life which also favoured the treatment arm.
- An overall survival benefit was not observed in this pivotal study but the results may have been affected by the high crossover rate of patients on placebo to regorafenib.
- Despite the higher rate of grade 3 or higher adverse events, the rate of treatment discontinuation due to adverse events was similar in both groups. Importantly, the majority of patients required at least one dose reduction.
- Currently, there are no data that supports the use of regorafenib in metastatic GIST patients who are treatment naïve or who have only been treated with imatinib. Similarly, no data support the use of regorafenib in the adjuvant setting.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Gastrointestinal Stromal Tumors (GISTs) are the most common sarcoma of the gastrointestinal (GI) tract but are considered rare with approximately 500 new cases diagnosed in Canada each year. The putative cells of origin are the interstitial cells of Cajal, which are considered to be the pacemaker cells of the GI tract. GISTs can occur anywhere in the GI tract but most commonly occur in the stomach and less commonly in the small and large intestine. The majority of GISTs have a mutation in the proto-oncogene, KIT which results in the constitutive activation of the tyrosine kinase receptor.[14] Until imatinib mesylate became available[15], there was no known systemic treatment of advanced GIST as both cytotoxic chemotherapy and radiation therapy were ineffective. Mutational testing on tumour samples is available in certain jurisdictions and may guide treatment strategies especially in patients whose tumours may possess exon 9 mutations in whom the dose of imatinib is often increased. Currently, there is no consensus on whether mutational testing should be performed at time of diagnosis or at time of disease progression.

3.2 Accepted Clinical Practice

Treatment of resectable GIST

Surgery remains the mainstay of therapy for those with resectable tumors. For patients with a significant risk of recurrence following resection, adjuvant therapy with imatinib has been shown to improve both recurrence free survival and overall survival. Risk factors for recurrence including tumour size, mitotic count and location of the primary tumour.[16] Intermediate or high risk patients have tumours larger 10 cm, tumours with mitotic counts higher than 10 in 50 high-power field (HPF), tumours exceeding 5 cm and mitotic count higher than 5 per 50 HPF or tumours that have ruptured. To date, two randomized studies have demonstrated the efficacy of imatinib in the adjuvant setting.[17, 18] The first study randomized patients with resected tumours larger than 3 cm to 1 year of imatinib or placebo and demonstrated a significant reduction in relapse free survival for all subgroups. The Scandinavian study randomized patients with higher risk tumours to 1 or 3 years of adjuvant imatinib and demonstrated a reduction in both relapse free as well as overall survival.[18] As the clinical practice of prolonged adjuvant therapy is relatively recent, the impact of adjuvant therapy on the proportion of patients presenting with advanced or imatinib resistant disease has yet to be determined.

Treatment of unresectable or advanced GIST

The treatment for patients with unresectable, recurrent or metastatic disease is imatinib. The majority of patients have clinical benefit with primary resistance seen in only a minority of patients with tumors that possess imatinib resistant mutations such as in platelet derived growth factor receptor alpha (PDGFR-A) or those with wild-type tumours. Although the median progression free survival is over 24 months[19], the majority of patients eventually experience disease progression and in some patients who tolerate the drug well, it may be possible to increase the dose to 800 mg with a delay of progression in about a quarter of patients lasting a few months. A randomized placebo-controlled phase III study demonstrated that sunitinib significantly increased the median time to progression from 6.4 weeks to 27.3 weeks (HR=0.33 $p<0.0001$) which led to the approval of sunitinib for imatinib-resistant or intolerant patients by

Health Canada in 2006.[20] The study was unblinded and those who were on placebo were crossed over to sunitinib on the recommendation of the Data Safety Monitoring Board. The most common side effects were hypertension, gastrointestinal disturbances, skin and hair abnormalities, altered sense of taste, fatigues and anorexia.

For patients who progress or are intolerant of both imatinib and sunitinib, there is currently no standard of therapy. A large randomized phase III study of nilotinib, a novel tyrosine kinase inhibitor, versus best supportive care failed to improve progression free survival based on central radiology review.[21] Although a post-hoc analysis of nilotinib in the third line population demonstrated that overall survival was significantly better in those treated with the drug, the drug was no longer pursued for this indication.

A recent small randomized phase III study examined the role of re-introducing imatinib to control patients with GISTs after failure of imatinib and sunitinib.[22] The double-blind placebo controlled trial of 41 patients demonstrated that median PFS was 1.8 months versus 0.9 months for those who received placebo suggesting that a there is modest clinical benefit for re-introducing imatinib in this patient population. However, in most Canadian jurisdictions, no funding exists for the re-introduction of imatinib.

Surrogate Endpoints

In clinical practice, progression-free survival (PFS) as well as relapse free survival (RFS) has been accepted as a surrogate endpoint for overall survival in both adjuvant and metastatic GIST settings. Both of the published phase III adjuvant studies used RFS as the primary endpoint although the SSG study did also demonstrate a statistically higher OS in the 3 year imatinib group. The pivotal study of 2nd line sunitinib also used PFS rather than OS as its primary endpoint. An analysis of 9 different GIST studies, demonstrated a moderately strong linear relationship between median PFS and median OS in patients with advanced GIST with the relationship being stronger in the 2nd and 3rd line setting than in the 1st line treatment settings.[23]

3.3 Evidence-Based Considerations for a Funding Population

A minority of patients are intolerant of one or both of these tyrosine kinase inhibitors. For those with unresectable or metastatic GIST with imatinib, discontinuation of imatinib is not recommended as long as patients are tolerating well as a randomized trial demonstrated that discontinuation of imatinib after 3 years of therapy was associated with inferior clinical outcomes.[24] Higher plasma imatinib trough levels have been correlated with better clinical outcomes.[25] This drug monitoring is currently available for toxicity related dose adjustments and to optimize clinical outcomes. Although no large scale studies have been conducted to assess drug compliance, smaller short-term studies have suggested a compliance rate of nearly in 80% in the adjuvant setting.[26]

Although the majority of patients with advanced GIST benefit from imatinib, currently, there is no standard of care for patients whose disease has progressed despite treatment with imatinib and sunitinib. Neither cytotoxic chemotherapy nor radiation therapy is beneficial and patients are offered best supportive care in order to palliate their symptoms. The survival for this group of patients is less than 8 months.

The likelihood of indication creep is low as there have been no studies of regorafenib in the adjuvant or first line settings. Furthermore, the clinical efficacy of imatinib in the first line setting is high with acceptable toxicity. Although both sunitinib and regorafenib are associated with significant toxicities, until there is a head to head study in the second line setting, it is unlikely, that clinicians or patients will use regorafenib prior to sunitinib.

Several novel agents are currently being tested in metatastic GIST including masitinib which is currently in phase III studies in both the 1st and 2nd line setting compared to imatinib and sunitinib respectively.[27]

3.4 Other Patient Populations in Whom the Drug May Be Used

Regorafenib has been approved by Health Canada for the treatment of advanced colorectal cancer refractory to other therapies. To date, no studies have demonstrated efficacy in earlier stages of GIST (i.e. either in first line or second line setting).

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

A patient advocacy group, the Sarcoma Cancer Foundation of Canada ("SCFC"), provided input on regorafenib (Stivarga) for the treatment of patients with metastatic and/or unresectable gastrointestinal stromal tumours ("GIST"), which is summarized below.

SCFC conducted a one-on-one interview with patients, caregivers and medical professionals. Specifically, SCFC interviewed four (4) patients, three (3) caregivers and three (3) medical professionals who had direct experience with regorafenib.

From a patient perspective, it is important to have different treatment options in the event that existing treatments are not effective or prove to have untenable side effects. SCFC indicated that patients who have used regorafenib have reported positive results to date. The patients' experience has shown it to be an easy to use drug as a result of its oral format, and has minimal side effects.

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 GIST

SCFC noted that gastrointestinal stromal tumours ("GIST") can affect up to approximately 700 new Canadians each year. According to the SCFC, patients diagnosed with GIST experience many day to day side effects, such as loss of appetite, mouth sores, depression, muscle and joint pain, fatigue and/or heartburn/indigestion. Moreover, patients who have to undergo a gastrectomy or partial gastrectomy often suffer additional issues and daily effects, such as bloating and severe abdominal pain, additional dietary restrictions, and bleeding, to name a few.

SCFC reported that a GIST diagnosis requires treatment that may take a patient away from their family or their place of employment, to the point that some patients have reported an inability to work due to surgery, recovery time, treatments administered in hospital and side effects experienced from various treatments.

From a patient perspective, a GIST diagnosis is very difficult on a patient emotionally and can put undue stress on personal relationships and marriages.

4.1.2 Patients' Experiences with Current Therapy for GIST

SCFC submitted that a patient might be eligible for surgery depending on the type of GIST diagnosis. However, if surgery is not possible and if neoadjuvant therapy is not an option, then the patient may consider using an ongoing drug therapy such as imatinib mesylate, sunitinib or regorafenib, now that it is available.

As with many cancer treatments, SCFC indicated that the concern for patients is not only the efficacy of the drug, but also its side effect profile and the quality of life that a patient can expect while on treatment. Prior to the approval of regorafenib for third-line GIST treatment, SCFC identified that there has not been any new treatment approved for GIST in some time.

SCFC suggested that there are not many specialists with experience treating GIST in Canada; therefore, depending on where a patient lives, they may need to travel long distances or re-

locate entirely, which can cost a significant amount of money not only in expenses but in lost wages from their place of employment, among other costs.

SCFC reported receiving increasing number of calls from patients across Canada who do not have private drug coverage, or who, even with some coverage through a private plan, are not able to afford the cost of their treatment if it is not covered by the province that they live in.

4.1.3 Impact of GIST and Current Therapy on Caregivers

SCFC reported that the challenges facing caregivers differs depending on where the patient lives. Because some patients are required to travel a long distance to access their specialist and their treatment, this can present a challenge to caregivers as they often have to spend time driving or coordinating travel for the patient or investing money for the patient to travel and/or relocate.

Other challenges for caregivers may arise if a patient is the parent of young children. In these cases, the side effects such as abdominal pain and joint pain, depression, fatigue and other symptoms often make it difficult for the patient to carry out regular parenting duties. This puts more strain on caregivers as they have to be caregiver not only to the patient, but to the children as well.

Depending on the stage and severity of the GIST diagnosis, some patients have reported having to stop work for an extended period of time, or having to relocate for surgery and recovery time, or to receive treatment. According to SCFC, patients report different levels of accessing their support network and support from their primary caregivers (e.g., spouse, adult child, others).

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Regorafenib

According to SCFC, the approval of a new drug for GIST with promising clinical results and demonstrating a positive toxicity/tolerability profile is positive news for GIST patients in Canada who have been waiting a long time for a new treatment.

SCFC noted the importance for patients to have different treatment options in the event that existing treatments are not effective or prove to have untenable side effects.

SCFC reported that patients who have had access to regorafenib have had positive results to date. These patients stated that had they not been able to receive regorafenib, there was nothing else that would have had an impact on their cancer. These patients reported that they have responded well to the drug and appreciate its oral form as it is an accessible and time-saving treatment that has proven to have minimal side effects. The patients' experiences have shown it to be an easy to use drug, and that it is a welcome option for those who would have had no other treatment available to them.

4.3 Additional Information

None were provided.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for regorafenib (Stivarga) for gastrointestinal stromal tumour (GIST). 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 regorafenib (Stivarga) for gastrointestinal stromal tumour was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, the key enablers are the small number of patients who would be eligible for third-line treatment, there is no current standard treatment in the third-line setting and regorafenib is an oral treatment that can be provided in the community.

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. 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. There is also the potential for use in other lines of therapy.

There is a particular Black Box warning advising of regorafenib associated 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 details.

5.1 Factors Related to Comparators

The current standard treatment for GIST after failure of two prior treatments is best supportive care. PAG noted that the availability of a third-line treatment option in this patient population as an enabler to implementation.

5.2 Factors Related to Patient Population

PAG noted that a small patient population who would be eligible for third-line treatment would be an enabler. PAG identified the potential for use in the first-line or adjuvant treatment setting would be a barrier.

5.3 Factors Related to Accessibility

PAG noted that regorafenib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration, in which patients could easily use in the community, as an enabler.

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, which is a potential barrier due to pill burden. However, PAG noted that dose adjustments will be easier, if needed by patients.

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

5.5 Factors Related to Implementation Costs

As a potential barrier to implementation, PAG noted that the availability of a new treatment where previously patients would have received best supportive care 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 for regorafenib 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.

PAG also noted that a generic version of Imatinib has recently been approved for sale in Canada. Imatinib is the standard of care in the first-line treatment of GIST and a generic version may impact the costs of the entire category of treatments. However, the implementation of generic imatinib for the treatment of GIST is variable across Canada at this time; this may be a near future implementation issue.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness of regorafenib, as a single agent, in the third line setting, on patient outcomes compared with appropriate comparators or best supportive care in the treatment of patients and associated subgroups with: metastatic and/or unresectable gastrointestinal stromal tumours (GIST) who have had disease progression on or intolerance to imatinib mesylate, and sunitinib malate treatment.

No supplemental questions were identified.

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 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized controlled trials	Patients with histologically confirmed, metastatic and/or unresectable GIST, with failure of at least previous imatinib mesylate (disease progression and previous sunitinib malate (failure only, not intolerance) treatment.	Regorafenib	• Re-treatment with imatinib; or • Best supportive care, through symptom control.	• **OS** • **PFS** • **TTP** • **ORR** • **QOL** AE's • Overall grade 3-4 serious AEs • Overall AEs • Withdrawal due to AEs • Liver toxicity • Hepatic failure • Hand-foot-skin reaction • Hypertension • Diarrhea • Dose reduction
[Abbreviations]: GIST, gastrointestinal stromal tumors; OS, overall survival; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; QOL, quality of life; AE, 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 (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Ovid; 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 Stivarga (regorafenib) and gastrointestinal stromal tumors (GIST).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search was completed October 3, 2013 and was updated periodically during the review. The search is considered up to date as of February 7, 2014.

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, clinicatrials.gov, and Ontario Institute for Cancer Research – Ontario Cancer Trials) along with relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and 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 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 other than p-values for select harms outcomes.

6.2.6 Writing of the Review Report

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

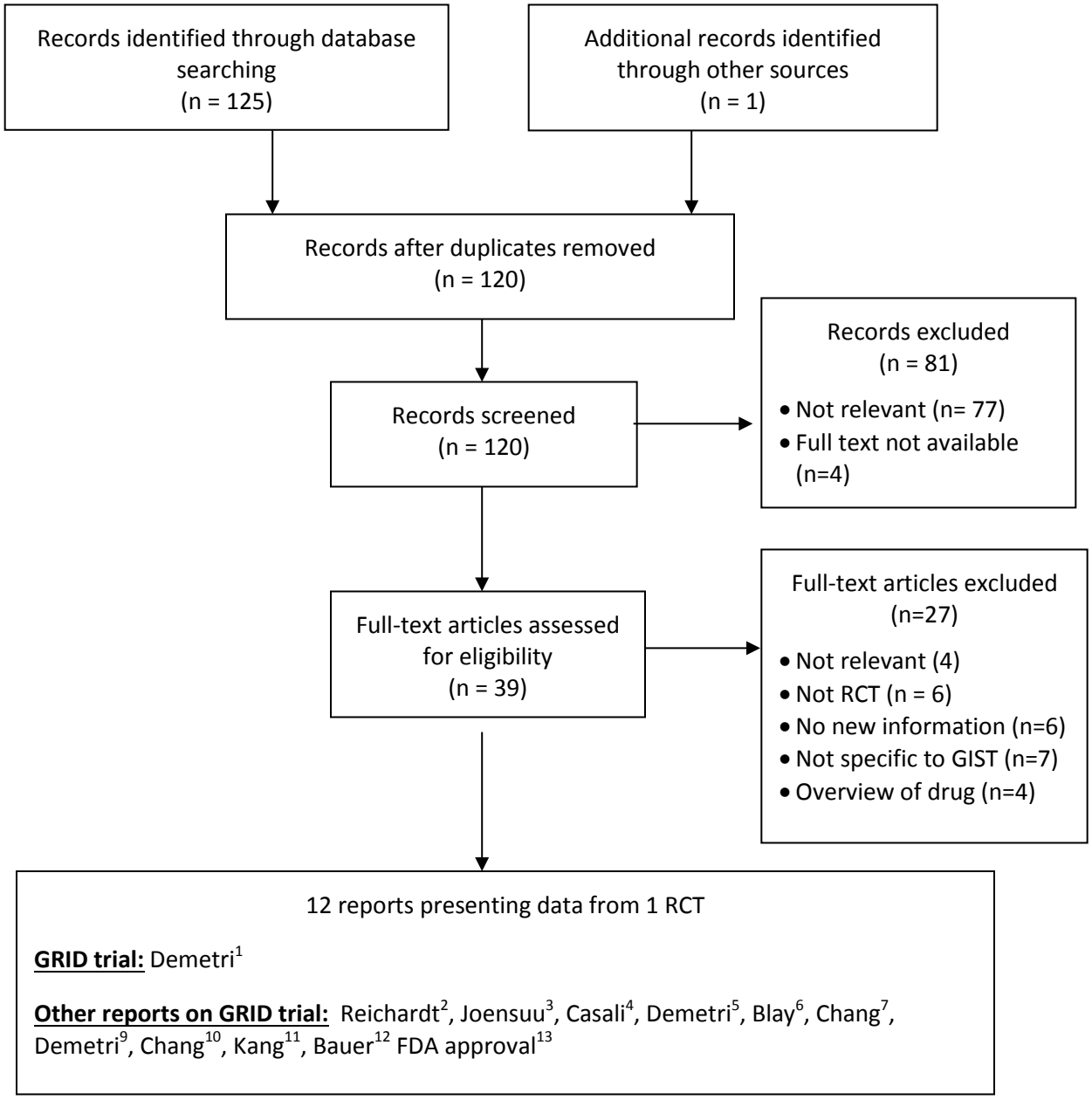
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions 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 120 potentially relevant reports identified, 12 studies were included in the pCODR systematic review[1-7, 9-13] and 108 studies were excluded. Studies were excluded after full text review because they were not relevant[28-31], not the appropriate study design[32-37], contained no new information[38-43], were not specific to GIST[44-50] or provided only an overview of the drug.[51 52-54] There were an additional 4 reports that were excluded as the full text was not available.[55-58] However, the methods team did not identify these 4 reports as crucial to the review.

PRISMA flow diagram for the inclusion and exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of Trial characteristics of the included Study

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
GRID[1] 57 sites in 17 countries* January - August, 2011 DB, PC, RCT n=199 randomised; all included in primary analysis Funded by: Bayer HealthCare Pharmaceuticals	- Histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib (either disease progression or intolerance) and previous sunitinib (disease progression only) -Other systemic therapies allowed, except any VEGFR inhibitors (other than sunitinib) -At least 1 measurable lesion with CT or MIR - Resolution of all toxic effects of previous therapy to grade 1 or lower - Adequate haematological, hepatic, cardiac and renal function - ECOG performance status of 0 or 1	- Either oral regorafenib 160 mg once daily OR matching placebo for the first 3 weeks of each 4 week cycle	<u>Primary</u> -Progression-free survival+ (RECIST) <u>Secondary</u> -Overall survival - Time to progression - Objective response rate - Disease control rate - Safety - Tolerability - Quality of life - Physical functioning - Time to deterioration of global health or physical functioning <u>Endpoints not reported</u> - Pharmaco-kinetics - Secondary PFS - Biomarker asessment

CR= complete response; DB= double-blind; ECOG = Eastern Cooperative Oncology Group; PC= placebo controlled; PR= partial response; RECIST= Response Evaluation Criteria in Solid Tumours; RCT= randomized controlled trial; QOL = quality of life; PFS = progression free survival

+ assessed by central radiology reviewers who were masked to assignment and data from patients

a) Trials

One randomized double-blind placebo controlled trial was included in this review (Table 1).[1] The study was conducted at 57 sites across 17 countries, including Canada.

The study included patients with histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib (either through disease progression or from intolerance) and previous sunitinib (through disease progression only). Additional inclusion criteria included the allowance of other systemic therapies, other than vascual endothelial growth factor receptor (VEGFR inhibitors) (other than sunitinib); at least 1 measurable lesion with CT or MIR; the resolution of all toxic effects of previous therapies to grade 1 or lower; adequate haematological, hepatic, cardiac and renal function; and ECOG performance status of 0 or 1. Exclusion criteria included prior treatment with regorafenib or VEGFR inhibitors or cancer other than GIST within 5 years before randomisation except for curatively treated cervical cancer *in situ*, non-melanoma skin cancer, and superficial bladder tumors.

Trial commenced enrolment on January 4, 2011. A total of 199 patients were randomised, which was the previously calculated sample size. Assuming a target treatment effect of 100% improvement in PFS, a randomisation of 2:1 (regorafenib: placebo), a one-sided alpha of 0.01, and a power of 0.94, 144 events were needed for the final PFS analysis. No interim analyses were planned for the primary endpoint. Enrolment ended August 18, 2011 after 240 patients were screened, and 199 patients were randomised.

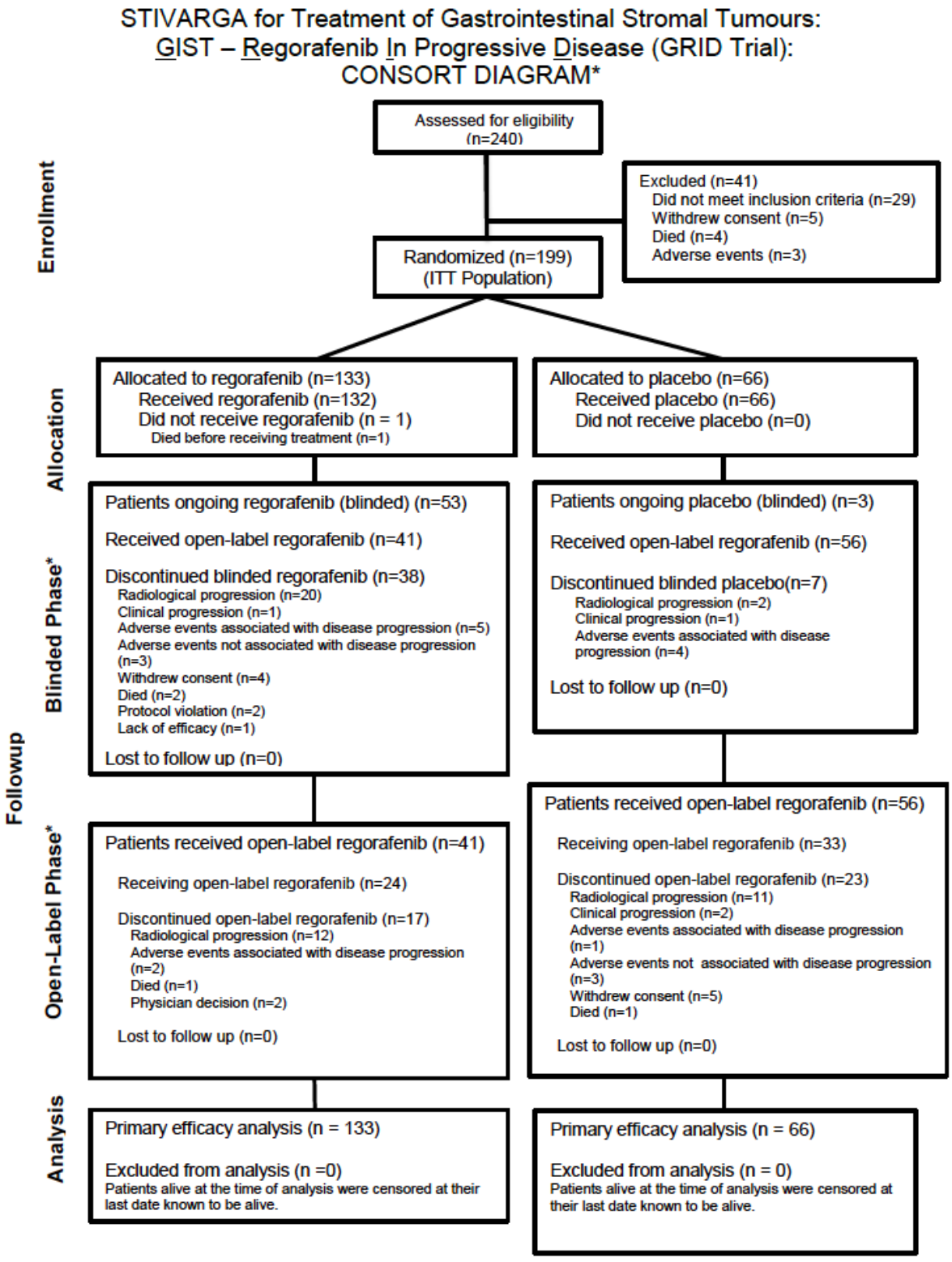
Trial procedures for randomisation and allocation concealment were considered adequate. Patients were randomly assigned in a 2:1 ration to regorafenib or placebo. Allocation to treatment was done randomly with a computer-generated randomisation list prepared by the study sponsor (pre-allocated block design, block size 12). Randomisation was masked to the patient, the investigator and the sponsor. Randomisation was stratified by treatment line (true third-line vs failure of previous imatinib, sunitinib, and other GIST therapies) and geographical region (Asia vs rest of world). Randomisation was not stratified based on mutational analysis, which would have been ideal, but not feasible. Masked study drug administration continued until disease progression, occurrence of unacceptable toxic effects, or withdrawal of the patient from the study.

b) Populations

A total of 199 patients from one randomized trial are included in this review. Figure 1 outlines the flow of patients in this trial.

A total of 133 patients were randomised to regorafenib and 66 to the placebo group. No detail was provided on the randomisation by geographic area. Median age was 60 and 61 for regorafenib and placebo, respectively. Patients ranged in age from 18-87. Groups were balanced for gender (64% male), ethnic group (68% White) and ECOG performance status (55%/56% = 0). There appeared to be a difference between the two groups in the duration of previous imatinib therapy: 67% patients in the regorafenib group vs 83% of patients in the placebo group were on imatinib therapy for longer than 18 months. A total of 6 patients (3%) entered with a history of intolerance to imatinib, though the study did not detail which group they were randomised to. Further, 86 patients (43%) had received three or more previous lines of treatment for GIST. Though this was not detailed by group assignment, baseline characteristics for >2 previous systemic anticancer therapies were similar between the groups.

Figure 1. CONSORT diagram as taken from pCODR submission



c) Interventions

Patients received either oral regorafenib 160 mg once daily or matching placebo, for the first 3 weeks of each 4 week cycle, along with best supportive care. In the event of centrally assessed tumour progression, treatment assignment could be unmasked. Patients originally in the placebo group were offered the option to crossover to receive open-label regorafenib, and patient's original in the regorafenib group could continue to receive open-label regorafenib. Throughout the trial, dosing could be delayed or reduced according to a prespecified schedule.

During the double-blind period, patients in the regorafenib group had a median treatment duration of 22.9 weeks (IQR 9.3-28.6), with a mean of 20.2 weeks (SD 11.6), and patients in the placebo group had a median treatment duration of 7.0 weeks (IQR 5.1 – 11.3), with a mean of 9.1 weeks (SD 5.9). The median daily dose during the double-blind treatment was 146.8 mg for regorafenib-treated patients (mean 139.8 mg, SD 22.9) and 160 mg for placebo recipients (mean 159.5 mg, SD 3.0).

d) Patient Disposition

The intention to treat population included 199 patients who were randomized to either regorafenib or placebo, regardless of whether or not they had received the study drug, or a different drug from the original assignment. No as-treated analysis is presented.

At the data cut-off (January 26, 2012), 53 of the 133 (40%) patients in the regorafenib group and 3 of the 66 (5%) patients in the placebo group were still receiving double-blind treatment. In the regorafenib group, 41 patients continued to receive open-label regorafenib after disease progression and 24 of the 41 patients were still receiving regorafenib at time of analysis. In the placebo group, 56 patients had crossed over to receive open-label regorafenib after disease progression, and 33 of the 56 were still receiving open-label regorafenib at data cut-off (Figure 1). During the double-blind period, 38 patients (29%) in the regorafenib group and 7 patients (11%) in the placebo group discontinued treatment; the most common reason for termination was radiologically confirmed disease progression. Other reasons for discontinuation of study treatment are outlined in Figure 1. No patients were lost to follow-up.

e) Limitations/Sources of Bias

Overall survival was difficult to assess in this study given the high occurrence of crossover: 56 patients (85%) in the placebo group received regorafenib after progression. However, progression-free survival may be an appropriate surrogate outcome for overall survival in patients with GIST.

There was a significant difference in the number of adverse events between the two groups: all 132 assessable patients in the regorafenib and 61 (92%) of the 66 patients in the placebo group had an adverse event (p-value calculated by Methods team to be 0.001). Drug-related adverse events were reported in 130 (98%) patients in the regorafenib group and 45 (68%) patients in the placebo group (p-value calculated by Methods team to be 0.0001) (Table 3 in detailed results section). This may have introduced bias if the investigator became aware to which treatment the patient is assigned, however, tumour response was centrally assessed by radiologists unaware of patient characteristics and therefore this bias is minimized. Further, the occurrence of adverse events that led to permanent discontinuation of treatment was almost the same between the groups (8 patients in regorafenib vs 5 patients in placebo group), which suggests that adverse events were manageable by dose modification.

Tumor assessment was done by a modified RECIST protocol, which were the following criteria: no lymph nodes were chosen as target lesions, no bone lesions were chosen as

target lesions, and PET was not acceptable for radiological assessment. Further, the lesion had to be at least 2 cm in size and definitely a new active GIST lesion or the lesion had to be expanding on at least two sequential imaging studies. Although the pCODR CGP considered that these modifications to the original RECIST guidelines seemed reasonable, these modifications are not clearly outlined in the primary publication.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The efficacy analysis was based on intention to treat and included all patients that were randomized (n=199). The safety analysis included all patients who had received at least one dose of study treatment (n=198). Tumour assessments were made at baseline, then every 4 weeks for the first 3 months, every 6 weeks for the next 3 months, and subsequently every 8 weeks until the end of the study drug administration. Tumor assessments were made by central review and investigator assessment during the double-blind period and by investigator assessment only during the open-label period. Safety and tolerability were assessed by analysis of adverse events, physical examinations, vital signs, ECOG performance status, and laboratory assessments on days 1 and 15 of each treatment cycle for the first six cycles.

Analysis was done when the predetermined criteria of 144 progression-free survival events were reached (January 26, 2012). Progression-free survival and overall survival estimates were with the Kaplan-Meier method. Hazard ratios and 95% confidence intervals were derived using Cox proportional hazard models and p values with the stratified log-rank test. Overall response rate were analyzed with the Cochran-Mantel-Haenszel test.

Data for health-related quality of life (HRQoL) was provided at the checkpoint meeting upon request by the Methods team; however, this data is non-disclosable as per the submitter's request. Analysis of HRQoL data was done with a linear mixed-effects model (LMM) and pattern-mixture model. The analysis also included a time to health-related quality of life to attempt to account for dropouts who often have worse HRQoL, using Kaplan-Meier estimates and a Cox regression model to obtain the hazard ratios.

Table 3. Summary of key outcomes in the ITT population[1, 59]

EFFICACY (ITT)				
Outcome	**Study group**	**Events (%)**	**HR (95% CI)**	**p value**
Overall survival[a]	Regorafenib Placebo	29 (22) 17 (26)	0.772 (0.423, 1.408)	0.199
Outcome	**Study group**	**Median days (95% CI)**	**HR (95% CI)**	**p value**
Progression free survival[b]	Regorafenib Placebo	147 (122, 173) 28 (28, 32)	0.268[c] (0.185, 0.388)	<0.0001
Outcome	**Study group**	**Events (%)**	**% (95% CI)**	**p value**
Response rate[d]	Regorafenib Placebo	6/133 (4.5) 1/66 (1.5)	NR	NR
Outcome	**Study group**	**Median days (95% CI)**	**HR (95% CI)**	**p value**
Time to progression	Regorafenib Placebo	165 (125, 174) 28 (28, 34)	0.248 (0.170, 0.364)	<0.000001

QUALITY OF LIFE				
Outcome	**Study group**	**n[e]**	**Difference (95% CI)**	**p value**
Global health-between groups[f]	Regorafenib minus Placebo	123 62	-1.0 (-8.5, 6.5)	0.788
Global health-within group[e]	Regorafenib	123	-5.9 (-9.5, -2.2)	NR
Global health - within group	Placebo	62	-4.9 (-11.8, 2.1)	NR
Physical functioning - between groups	Regorafenib minus Placebo	123 62	2.5 (-3.4, 8.3)	0.405
Physical functioning-within group	Regorafenib	123	-5.9 (-8.9, -3.0)	NR
Physical functioning - within group	Placebo	62	-8.4 (-13.8, -3.0)	NR
Outcome	**Study group**	**N**	**Median weeks (95% CI)**	**p-value**
Time to deterioration- global health status	Regorafenib Placebo	122 57	6.5 (4.1, 8.0) 4.0 (4.0, 4.6)	<0.01
Time to deterioration - physical functioning	Regorafenib Placebo	122 57	8.0 (4.6, 8.6) 4.0 (4.0, 4.1)	<0.01
HARMS				
Outcome	**Study group**	**n/N**	**%**	**p value**
Drug-related Grade 5 events (death)	Regorafenib Placebo	2/132 1/66	1.5% 1.5%	NR
Overall grade 3-4 serious AEs	Regorafenib Placebo	79/132 6/66	59.8% 9.1%	NR
Overall AEs	Regorafenib Placebo	130/132 45/66	98% 68%	NR
Withdrawal due to AEs	Regorafenib Placebo	8/132 5/66	6% 8%	NR
Liver toxicity	NR			
Hepatic failure	NR			
Hand-foot skin reaction- any grade	Regorafenib Placebo	74/132 9/66	56% 14%	NR
Hand-foot skin reaction- grade ≥3	Regorafenib Placebo	26/132 0	20% 0	NR
Hypertension-any grade	Regorafenib Placebo	64/132 11/66	49% 17%	NR
Hypertension - Grade ≥3	Regorafenib Placebo	31/132 2/66	23.5% 3%	NR
Diarrhea-any grade	Regorafenib Placebo	53/132 3/66	40% 5%	NR
Diarrhea-Grade ≥3	Regorafenib Placebo	7/132 0	5% 0%	NR
Permanent discontinuation[g]	Regorafenib Placebo	8/132 5/66	6.1% 7.6%	NR
Dose interruption[g]	Regorafenib	77/132	58.3%	NR

	Placebo	11/66	16.7%	
Dose reduction[g]	Regorafenib Placebo	66/132 2/66	50.0% 3.0%	NR
ITT = intention to treat; HR = hazard ratio; CI = confidence interval; AE = adverse event;				

[a]interim OS analysis, denominator not provided; [b]assessed by central review; [c]for progression or death; [d]no complete responses observed; [e] number who completed at least one questionnaire; [f] adusted analysis; [g] information disclosed at checkpoint meeting, only reported for double-blind period

Efficacy Outcomes

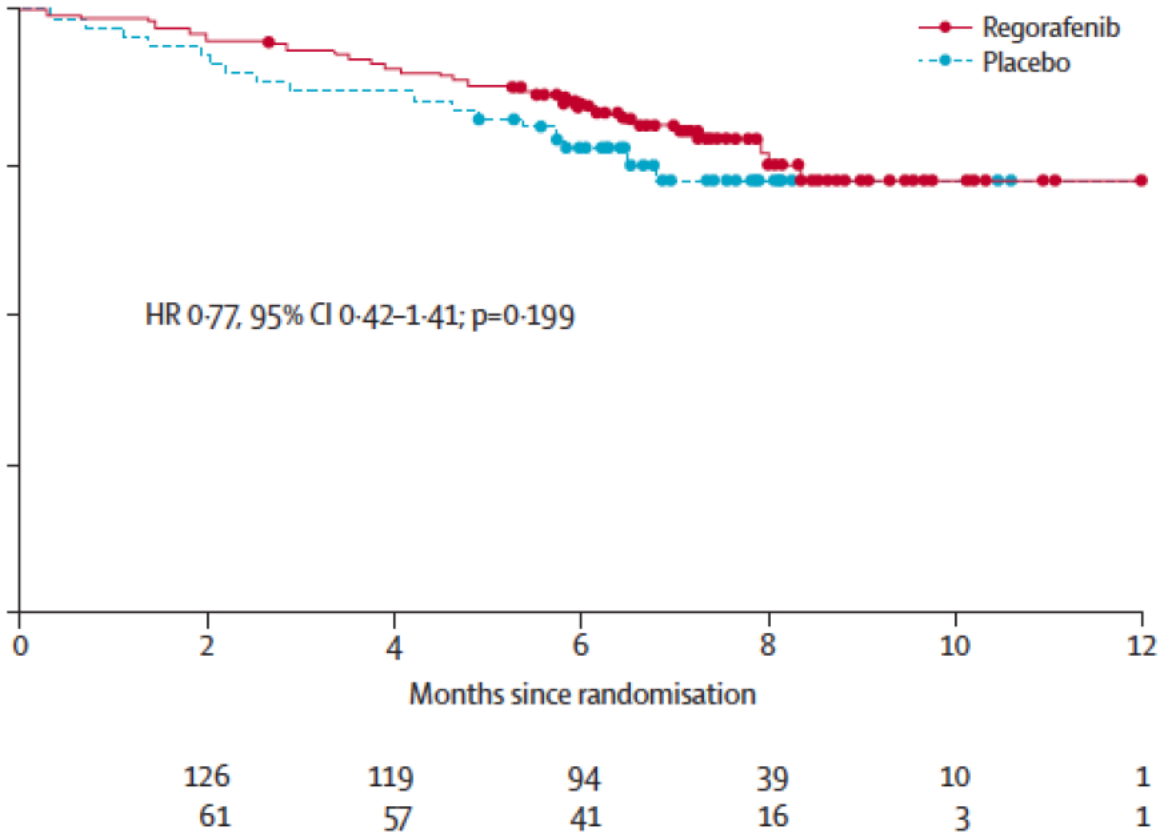
a) Overall survival

Overall survival was a secondary end-point. It was not defined in the study. The overall survival data presented was considered an interim analysis, and was done at the time of final PFS analysis (January 26, 2012).

There were 29 events (deaths) in the regorafenib group and 17 events (deaths) in the placebo group. The hazard ratio for death was 0.772 (95% CI: 0.423-1.408) and there no was significant difference between the two study groups.

The following figure taken from Demetri et al. shows that there was no difference in overall survival between the two groups, which could be due in part to cross-over in the trial.

Figure 2. Kaplan-Meier overall survival analysis, per central review, after treatment with regorafenib or placebo[1]



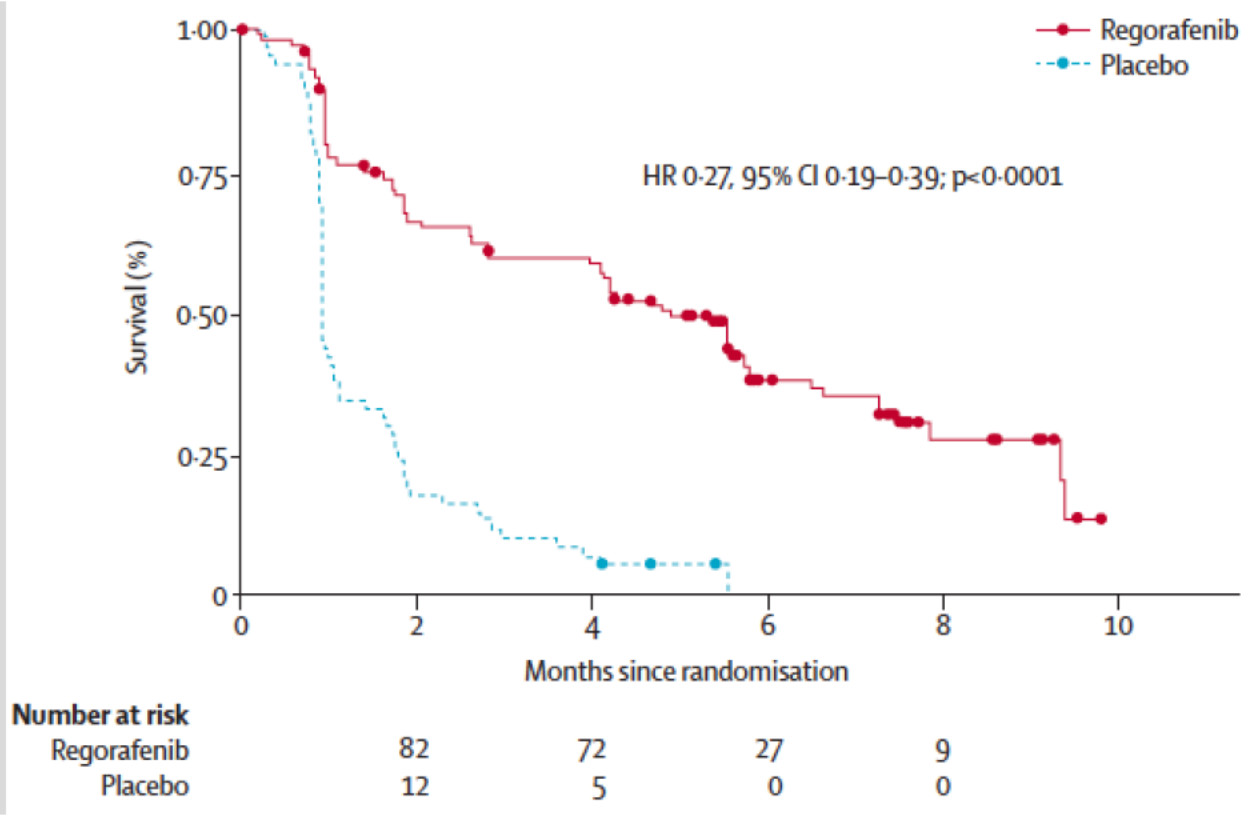
b) Progression-free survival

Progression-free survival was the primary end point as per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. For the PFS analysis patients without tumor progression or death at the time of analysis were censored at their last date of radiological tumor assessment. Determination of disease progress was done centrally by radiology reviewers masked to assignment and data from patients.

At trial termination, patients in the regorafenib group had 147 median days (4.8 months) of PFS, vs 28 days (0.9 months) for patients in the placebo group. Patients treated with regorafenib had an improvement in PFS compared to placebo (HR 0.268, 95% CI 0.185-0.388, P <0.0001).

The follow figure taken from Demetri et al. shows the early treatment effect in the study.

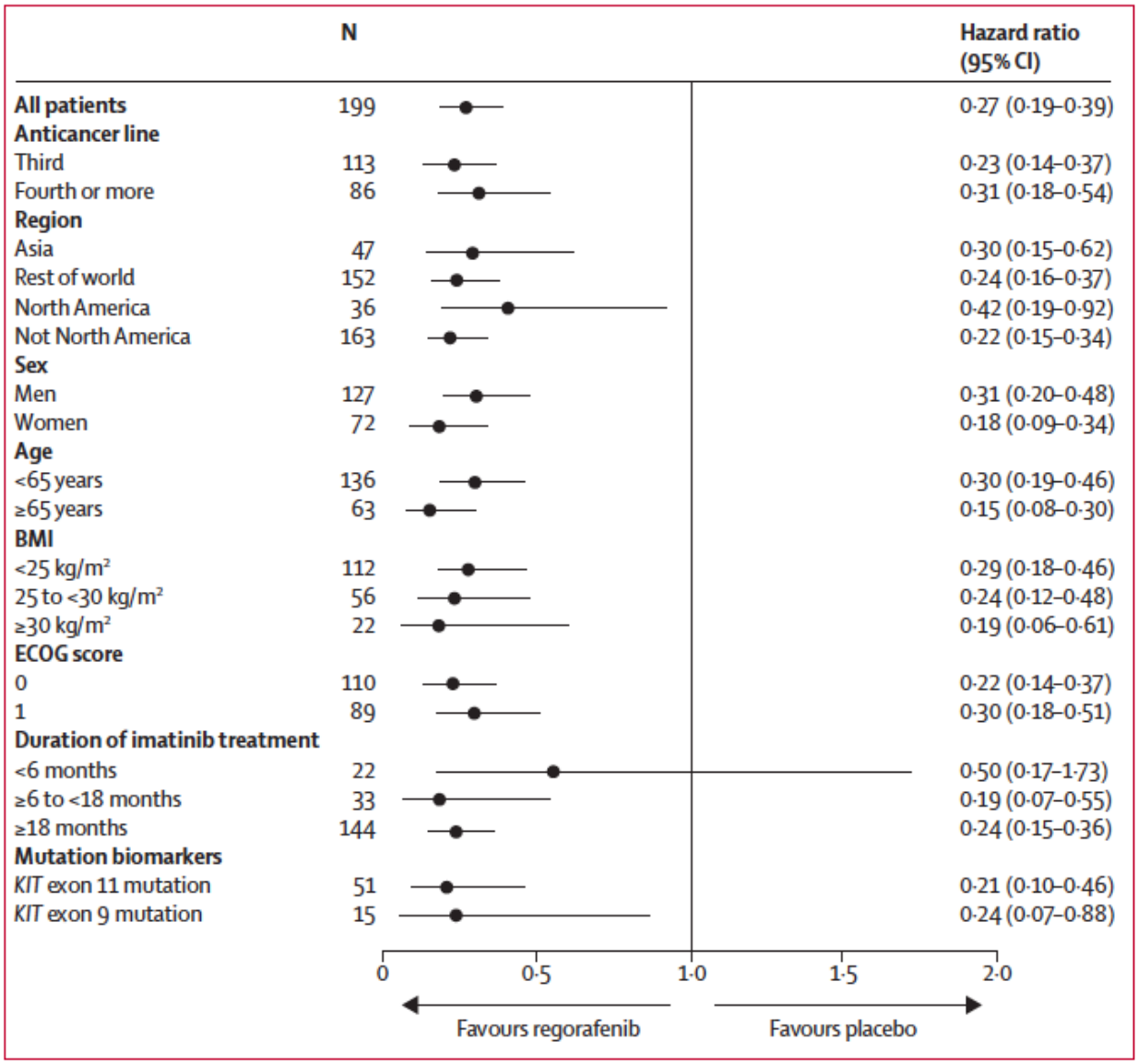
Figure 3. Kaplan-Meier progression-free survival analysis, per central review, after treatment with regorafenib or placebo[1]



<u>Sub-group analyses for progression-free survival</u>

The relative efficacy of regorafenib for PFS was explored in a number of pre-specific sub-group analyses (Figure 4). The hazard ratios were fairly consistent with that of the primary analysis; however, median PFS times were not calculated.

Figure 4. Progression-free survival by subgroup[1]



c) Response rate

Objective response rate was a secondary end-point, and upon clarification from the checkpoint meeting was defined as the proportion of randomized patients with a best overall tumor response of either complete response or patient response according to central assessment. No patients, in either group, had a complete response, whereas 6 of the 133 patients in the regorafenib group and 1 of the patients in the placebo group had a partial response (at least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions and no appearance of new lesions). No test of significance was reported.

d) Time to progression

Time to progression was a secondary end-point, measured from the date of randomization until the date of radiological progression. Median time to progression was significantly longer (p<0.000001) for patients randomized to the regorafenib group (165 days (5.5 months); 95% CI: 125, 174 days) than those randomized to placebo group (28 days (0.9 months); 95% CI: 28, 34 days).

Quality of life Outcomes

a) Health-related quality of life

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 instrument (EORTC QLQ-C30), version 3.0. Questionnaires were administered at baseline (day 1 of cycle 1), the first day of each cycle (every 4 weeks) during the next 3 months, the first day of every other cycle (every 8 weeks) thereafter during the double0blind and open-label phases. The questionnaire was also administered at the end-of-treatment visit. Higher scores represent better HRQoL and a change in 10 points was estimated to be a minimal clinically important difference. 40% of patients were classified as early dropout (last measurement <4 cycles) and the remaining 60% were grouped as late dropout (≥4 cycles). In the linear mixed model, missing data was assumed to be missing at random.

Using a linear mixed models, there were no significant differences between regorafenib and placebo groups in global health status. Global health status declined through the trial period: -5.9 points for regorafenib and -4.9 points for placebo with an overall difference between groups (regorafenib – placebo) of -1.0 points (95% CI: -8.5, 6.5, p value 0.788). There were no significant differences between groups in physical functioning through the trial period: -5.9 points for regorafenib and -8.4 points for placebo with an overall difference between groups (regorafenib – placebo) of 2.5 points (95% CI: -3.4, 8.3, p-value 0.405).

Using a pattern-mixture model to account for missing data, global health declined -6.3 points (95% CI: -13.6, 0.9) and -6.4 points (95%CI: -10.3, -2.6) in the early and late dropouts respectively for the regorafenib treatment arm. In the placebo treatment arm, global health declined -12.0 points (95% CI: -18.7, -5.2) and increased 3.1 points (95% CI: -5.6, 11.9) in the early and late dropouts respectively. When considering dropouts, physical functioning declined -7.2 points (95% CI: -13.0, -1.3) and -5.8 points (95% CI: -8.9, -2.6) in the early and late dropouts respective for the regorafenib treatment arm. In the placebo treatment arm, physical functioning declined -8.7 points (95% CI: -14.1, -3.3) and -3.5 points (95% CI: -10.6, 3.7) in the early and late dropouts respectively.

There was a significant difference between regorafenib and the placebo treatment arms for time to deterioration for both global health and physical functioning. Time to deterioration for global health was a median of 6.5 weeks (95% CI: 4.1, 8.0) for the regorafenib group and 4.0 weeks (95%CI: 4.0,4.6) for the placebo group (p-value <0.01). Time to deterioration for physical functioning was a median of 8.0 weeks (95% CI: 4.6, 8.6) for the regorafenib group and 4.0 weeks (95% CI: 4.0, 4.1) for the placebo group.

A comparable percentage of patients in the two treatment groups achieved the minimal important difference (MID) of 10 points. For global health status, 26.2% and 25.4% of patients in the regorafenib and placebo group, respective, achieved the MID (p-value >0.99). For physical functioning, 18.0% and 15.3% of patients in the regorafenib and placebo group, respectively, achieved MID (p-value = 0.83).

Harms Outcomes

a) Drug-related grade 5 events

From the checkpoint meeting, the submitter clarified that during both the double-blind and open label treatment period of the study, there were 188 patients that actually received regorafenib. From this population, there were 16 patients with grade 5 adverse events that were reported. Of these 16, 6 were considered related to regorafenib. These six deaths were detailed as cardiac arrest, colonic perforation, fatigue, hepatic failure, acute kidney injury, adult respiratory distress syndrome and thromboembolic event. The submitter noted in the checkpoint materials that the incidence of hepatobiliary disorders was very low and no notable differences were observed in different subgroups.

b) Overall grade 3-4 serious adverse events

Data on adverse events was collected from study start until study end date. In the study by Demetri et al. only those drug-related adverse events in greater than 10% of patients during the double-blind treatment period are reported. Drug-related adverse events of grade 3 or higher occurred more frequently in regorafenib patients and were reported in 81 (61%) of patients assigned to the regorafenib group and 9 (14%) patients assigned to the placebo group. The most common regorafenib-related adverse events of grade 3 or higher were hypertension (31/132 patients, 23%), hand-foot skin reaction (26/132, 20%), and diarrhea (7/132, 5%). These grade 3/4 adverse events occurred more frequently in regorafenib patients (59.8%) compared to placebo patients (9.1%), including a greater incidence of hand-foot skin reaction (20% vs. 0), hypertension (23.5% vs 3%), diarrhea (5% vs. 0).

Table 4. Drug-related adverse events in ≥10% of patients during double-blind treatment period[1]

	Regorafenib (N=132*)			Placebo (N=66)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any event	130 (98%)	77 (58%)	2 (2%)	45 (68%)	5 (8%)	1 (2%)
Hand-foot skin reaction	74 (56%)	26 (20%)	0	9 (14%)	0	0
Hypertension	64 (49%)	30 (23%)	1 (1%)	11 (17%)	2 (3%)	0
Diarrhoea	53 (40%)	7 (5%)	0	3 (5%)	0	0
Fatigue	51 (39%)	3 (2%)	0	18 (27%)	0	0
Oral mucositis	50 (38%)	2 (2%)	0	5 (8%)	1 (2%)	0
Alopecia	31 (24%)	2 (2%)	0	1 (2%)	0	0
Hoarseness	29 (22%)	0	0	3 (5%)	0	0
Anorexia	27 (21%)	0	0	5 (8%)	0	0
Rash, maculopapular	24 (18%)	3 (2%)	0	2 (3%)	0	0
Nausea	21 (16%)	1 (1%)	0	6 (9%)	1 (2%)	0
Constipation	20 (15%)	1 (1%)	0	4 (6%)	0	0
Myalgia	18 (14%)	1 (1%)	0	6 (9%)	0	0
Voice alteration	14 (11%)	0	0	2 (3%)	0	0

Data are n (%). *Excluding one patient who did not receive study treatment.

c) Overall adverse events

The majority of patients in both groups experienced treatment-related adverse events: 130/132 (98%) patients in the regorafenib group and 45/66 (68%) in the placebo group. Patients in the regorafenib group experience a greater incidence of hand-foot skin reaction, hypertension, diarrhea, fatigue, oral mucositis, alopecia, hoarseness, anorexia, rash, nausea, constipation, myalgia and voice alteration (see Table 4 above).

d) Withdrawal due to adverse events

A total of 6% (8/132) of regorafenib patients and 8% (5/66) of placebo patients discontinued treatment due to adverse events. No further detail was provided on which adverse events led to discontinuation of therapy.

e) Liver toxicity

No information on liver toxicity was reported in the randomized controlled trial.

f) Hepatic failure

One patient died from hepatic failure, which was deemed to be a drug-related adverse event in the regorafenib group.

g) Hand-foot skin reaction

The most common adverse event of any grade was hand-foot skin reaction, which occurred in 56% (74/132) of patients in the regorafenib group and 14% (9/66) patients in the placebo group. In the regorafenib group, 20% (26/132) experienced a grade 3 hand-foot skin reaction.

h) Hypertension

Hypertension was the second most common adverse event of any grade, and occurred in 49% (64/132) of patients in the regorafenib group and 17% (11/66) of patients in the placebo group. There were also 30 (23%) grade 3 hypertension adverse events in the regorafenib group and 2 (3%) grade 3 hypertension adverse events in the placebo group. Only 1 (1%) grade 4 hypertension adverse event occurred.

i) Diarrhea

Diarrhea was the third most common adverse event of any grade, and occurred in 40% (64/132) of patients in regorafenib group and 5% (3/66) of patients in the placebo group. There were also 7 (5%) grade 3 diarrhea adverse events in the regorafenib group, and none in the placebo group. No grade 4 adverse events occurred for diarrhea.

j) Dose modifications

Dose modifications included both dose interruptions (time off drug) as well as dose reductions. Dose modifications during the double-blind phase occurred in a total of 112 patients: 95 patients in the regorafenib group (72%) and 17 patients in the placebo group (26%). Dose reductions occurred in 50% of the regorafenib group compared to 3.0% of the placebo group. The submitter clarified at the checkpoint meeting that there were no dose reductions that needed to be reduced by more than two levels (dose level -2; pre-specified at 80 mg from 160 mg, once daily). Dose interruptions during the double-blind phase occurred in 58.3% of the regorafenib group, compared to 16.7% of the placebo group.

6.4 Ongoing Trials

No additional on-going trials were identified that would have been included had they been completed.

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 GIST. 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. There was no information redacted from this publicly available Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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

1. Literature search via OVID platform

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations AND Ovid MEDLINE(R) 1946 to Present, Ovid MEDLINE(R) Daily Update October 01, 2013
Date: October 3, 2013

#	Search	Results
1	(Stivarga$ or regorafenib$ or "BAY 73 4506" or "BAY73 4506").ti,ot,ab,sh,rn,hw,nm.	79
2	(755037-03-7 or 24T2A1DOYB).rn,nm.	27
3	or/1-2	79
4	limit 3 to english language	75
5	exp animals/	17681780
6	exp animal experimentation/	6409
7	exp models animal/	434051
8	exp animal experiment/	6409
9	nonhuman/	0
10	exp vertebrate/	17157950
11	or/5-10	17689764
12	exp humans/	13631693
13	exp human experimentation/ or exp human experiment/	12312
14	or/12-13	13632340
15	11 not 14	4058041
16	4 not 15	73

Database: Embase 1974 to 2013 October 04 via Ovid
Date: October 3, 2013

#	Search	Results
1	*regorafenib/	82
2	(Stivarga$ or regorafenib$ or "BAY 73 4506" or "BAY73 4506").ti,ab.	123
3	1 or 2	129
4	limit 3 to english language	120
5	exp animals/	19343936
6	exp animal experimentation/ or exp animal experiment/	1722730
7	exp models animal/	718649
8	nonhuman/	4143032
9	exp vertebrate/ or exp vertebrates/	18903480
10	or/5-9	20539331
11	exp humans/	15000350
12	exp human experimentation/ or exp human experiment/	317026
13	or/11-12	15001791
14	10 not 13	5538519
15	4 not 14	117

2. Literature search via PubMed

Database: PubMed
Date searched: October 3, 2013

1	stivarga[All Fields] OR regorafenib[All Fields]OR"BAY 73 4506"[All FIelds] OR "BAY73 4506"[All Fields] OR 24T2A1DOYB[rn]	32

3. Cochrane Library

Database: EBM Reviews - Cochrane Central Register of Controlled Trials September 2013, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 2013
Date: October 3, 2013

Searches	Results	Search Type
1	*regorafenib/	0
2	(Stivarga$ or regorafenib$ or "BAY 73 4506" or "BAY73 4506").ti,ab.	2
3	1 or 2	2
4	limit 3 to english language [Limit not valid in CCTR,CDSR; records were retained]	2
5	exp animals/	400798
6	exp animal experimentation/ or exp animal experiment/	2
7	exp models animal/	286
8	nonhuman/	0
9	exp vertebrate/ or exp vertebrates/	400795
10	or/5-9	400798
11	exp humans/	400794
12	exp human experimentation/ or exp human experiment/	134
13	or/11-12	400794
14	10 not 13	4
15	4 not 14	2

4. Grey Literature Search via

a) www.clinicaltrials.gov
(Stivarga or regorafenib) AND (GIST)
No ongoing trials or unreported trials.

b) www.canadiancancertrials.ca
(Stivarga or regorafenib)
Nothing found

c) www.fda.gov
(Stivarga or regorafenib) AND (GIST)
Approval recommendation found

d) http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp
(Stivarga or regorafenib) AND (GIST)
Nothing found

Conference abstracts (last 5 years) via Web of Science:

a) American Society of Clinical Oncology (ASCO)—3 identified; 2 unique
http://www.asco.org/
Topic=(Stivarga or regorafenib) AND Language=(English) AND Conference=(ASCO)

b) European Society for Medical Oncology (ESMO)—4 identified
http://www.esmo.org/
Topic=(Stivarga or regorafenib) AND Language=(English) AND Conference=(ESMO)

REFERENCES

1. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**(9863): 295-302.

2. Reichardt P, Demetri G, Kang YK, et al. Randomized phase 3 trial of regorafenib in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU)-GRID trial. *Onkologie* 2012; **35**: 168.

3. Joensuu H, Casali PG, Reichardt P, et al. Results from a phase III trial (GRID) evaluating regorafenib (REG) in metastatic gastrointestinal stromal tumour (GIST): Subgroup analysis of outcomes based on pretreatment characteristics. *Journal of Clinical Oncology* 2013; **1)**.

4. Casali PG, Reichardt P, Kang Y, et al. Clinical Benefit with Regorafenib across Subgroups and Post-Progression in Patients with Advanced Gastrointestinal Stromal Tumor (Gist) after Progression on Imatinib (Im) and Sunitinib (Su): Phase 3 Grid Trial Update. *Annals of Oncology* 2012; **23**: 478-9.

5. Demetri GD, Reichardt P, Kang YK, et al. Randomized phase III trial of regorafenib in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU): GRID trial. *Journal of Clinical Oncology* 2012; **30**(18).

6. Blay J, Casali P, Reichardt P, et al. Time course of adverse events in the phase III GRID study of regorafenib in patients with metastatic gastrointestinal stromal tumors (GIST). *European journal of cancer (Oxford, England : 1990)* 2013; **49**: S884.

7. Chang J, Casali P, Reichardt P, et al. Health-related quality of life (HRQoL) of patients with advanced gastrointestinal stromal tumors (GIST) treated with regorafenib (REG) vs placebo in the phase III GRID trial *European journal of cancer (Oxford, England : 1990)* 2013; **49**: S886.

8. Stivarga® (regorafenib tablets): 40 mg [product monograph]. Toronto (ON): Bayer, Oct 2, 2013.

9. Demetri G, Smeets J, Casali P, et al. Exposure-efficacy of regorafenib and its metabolites M-2 and M-5 in the phase III GRID study in patients with metastatic gastrointestinal stromal tumors (GIST). *European journal of cancer (Oxford, England : 1990)* 2013; **49**: S886.

10. Chang J, Casali P, Reichardt P, et al. Health-related quality of life (HRQoL) of patients with advanced gastrointestinal stromal tumors (GIST) treated with regorafenib (reg) vs placebo (P) in the phase III grid trial. European Cancer Congress 2013. Amsterdam; 2013. p. S886.

11. Kang Y, Xu J, Komatsu Y, et al. Subgroup analysis of Asian patients in the phase III trial (GRID) of regorafenib in pretreated metastatic gst. *Annals of Oncology* 2013; **24**: ix6.

12. Bauer S, Joensuu H, Casali P, et al. Results from a phase III trial (GRID) evaluating regorafenib in metastatic gastrointestinal stromal tumour (GIST): Subgroup analysis of outcomes based on pretreatment characteristics. *Onkologie* 2013; **36**: 180-1.

13. FDA approves regorafenib (Stivarga) for GIST. *Oncology (Williston Park, NY)* 2013; **27**(3): 164.

14. Hirota S, Isozaki K, Moriyama Y, al. e. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; **279**: 577-80.

15. Demetri G, von Mehren M, Blanke C, al. e. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; **347**: 474-80.

16. Miettinen M, Makhlouf H, sobin L, Lasot J. Gastrointestinal stromal tumors of the jejunum and ileum. *Am J Surg Path* 2006; **30**: 477-80.

17. Dematteo R, Ballman K, Antonescu C, al. e, on behalf of the American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumor: a randomized, double-blind, placebo-controlled trial. *Lancet* 2009; **373**: 1097-104.

18. Joensuu H, Eriksson M, Sundby Hall K, al. e. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA* 2012; **307**: 1265-72.

19. Blanke C, Demetri G, von Mehren M, al. e. Long-term results from a randomized phase II trial of standard versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol* 2008; **26**: 620-5.

20. Demetri G, van Oosterom A, Garrett C, al. e. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368**: 1329-38.

21. Reichardt P, Blay J, Gelderblom H, al. e. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. *Ann Oncol* 2012; **23**: 1680-7.

22. Kang Y, Ryu M, Changhoon Y, al. e. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomized, placebo-controlled, phase 3 trial. *Lancet Oncology* 2013; **14**: 1175-82.

23. Keyser R, Tranbarger F, Hoaglin S, al. e. Exploring the relation between overall survival (OS) and progression-free survival (PFS) in gastrointestinal stromal tumor (GIST) via meta-analysis. *J Clin Oncol* 2011; **29**: S100058.

24. Le Cesne A, Ray-Coquard I, Bui B, al. e. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. *Lancet Oncology* 2010; **11**: 942-9.

25. Demetri G, Wang Y, Wehrle E, al. e. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. *J Clin Oncol* 2009; **27**: 3141-7.

26. Mazzeo F, Duck L, Joosens E, al. e. Nonadherence to imatinib treatment in patients with gastrointestinal stromal tumors: the ADAGIO study. *Anticancer Research* 2011; **31**: 1407-9.

27. Le Cesne A, Blay J, Bui B, al. e. Phase II study of oral masitinib mesilate in imatinib-naive patients with locally advanced or metastatic gastro-intestinal stromal tumour (GIST). *European journal of cancer (Oxford, England : 1990)* 2010; **46**: 1344-51.

28. Heinrich MC, Fletcher JA, Anjum R, et al. Use of ponatinib to inhibit kinase mutations associated with drug-resistant gastrointestinal stromal tumors (GIST). *Journal of Clinical Oncology* 2013; **1)**.

29. Demetri GD, Jeffers M, Reichardt P, et al. Mutational analysis of plasma DNA from patients (pts) in the phase III GRID study of regorafenib (REG) versus placebo (PL) in tyrosine kinase inhibitor (TKI)-refractory GIST: Correlating genotype with clinical outcomes. *Journal of Clinical Oncology* 2013; **1)**.

30. Sunakawa Y, Furuse J, Okusaka T, et al. Erratum to: Regorafenib in Japanese patients with solid tumors: phase I study of safety, efficacy, and pharmacokinetics. *Invest New Drugs* 2013.

31. Sunakawa Y, Furuse J, Okusaka T, et al. Regorafenib in Japanese patients with solid tumors: phase I study of safety, efficacy, and pharmacokinetics. *Invest New Drugs* 2013.

32. George S, Wang Q, Heinrich MC, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. *Journal of Clinical Oncology* 2012; **30**(19): 2401-7.

33. George S, Feng Y, Von Mehren M, et al. Prolonged survival and disease control in the academic phase II trial of regorafenib in GIST: Response based on genotype. *Journal of Clinical Oncology* 2013; **1)**.

34. George S, von Mehren M, Heinrich MC, et al. A multicenter phase II study of regorafenib in patients (pts) with advanced gastrointestinal stromal tumor (GIST), after therapy with imatinib (IM) and sunitinib (SU). *ASCO Meeting Abstracts* 2011; **29**(15_suppl): 10007.

35. Van Den Abbeele AD, Tanaka Y, Locascio T, et al. Assessment of regorafenib activity with FDG-PET/CT in a multicenter phase II study in patients (pts) with advanced gastrointestinal stromal tumor (GIST) following failure of standard therapy (Rx). *ASCO Meeting Abstracts* 2011; **29**(15_suppl): 10050.

36. Mross K, Frost A, Steinbild S, et al. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. *Clinical Cancer Research* 2012; **18**(9): 2658-67.

37. Serrano-Garcia C, Heinrich MC, Zhu M, et al. In vitro and in vivo activity of regorafenib (REGO) in drug-resistant gastrointestinal stromal tumors (GIST). *Journal of Clinical Oncology* 2013; **1)**.

38. Lyseng-Williamson KA. Regorafenib: A Guide to Its Use in Advanced Gastrointestinal Stromal Tumor (GIST) After Failure of Imatinib and Sunitinib. *Biodrugs* 2013; **27**(5): 525-31.

39. Villanueva MT. Gastrointestinal cancer: regorafenib, the CORRECT way forward or just another GRIDlock? *Nature Reviews Gastroenterology & Hepatology* 2013; **10**(1): 1.

40. Villanueva MT. Regorafenib, the CORRECT way forward or just another GRIDlock? *Nature Reviews Clinical Oncology* 2013; **10**(1): 1.

41. Waddell T, Cunningham D. Evaluation of regorafenib in colorectal cancer and GIST. *Lancet* 2013; **381**(9863): 273-5.

42. Anonymous. ESMO: regorafenib improved PFS for GIST in post-imatinib/sunitinib setting. *Oncology (Williston Park)* 2012; **26**(11): 1072.

43. Mechcatie E. Third drug approved for metastatic, treatment-resistant GIST. *Oncology Report* 2013; (MAR): 15.

44. Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. *Investigational New Drugs* 2013; **31**(4): 1078-86.

45. Belum VR, Wu S, Lacouture ME. Incidence and risk of hand foot skin reaction (HFSR) in patients receiving regorafenib for cancer: A meta-analysis. *Journal of Clinical Oncology* 2013; **1)**.

46. de Jesus-Gonzalez N, Robinson E, Penchev R, et al. Regorafenib induces rapid and reversible changes in plasma nitric oxide and endothelin-1. *American Journal of Hypertension* 2012; **25**(10): 1118-23.

47. Adenis A, Kotecki N, Decanter G, Clisant S, Penel N. Regorafenib use as a possible cause of intestinal perforation. *Acta oncologica (Stockholm, Sweden)* 2013.

48. Sajithlal GB, Hamed HA, Cruickshanks N, et al. Sorafenib/Regorafenib and phosphatidyl inositol 3 kinase/thymoma viral proto-oncogene inhibition interact to kill tumor cells. *Molecular Pharmacology* 2013; **84**(4): 562-71.

49. Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. *Drug Safety* 2013; **36**(7): 491-503.

50. Davis SL, Eckhardt SG, Messersmith WA, Jimeno A. The development of regorafenib and its current and potential future role in cancer therapy. *Drugs of Today* 2013; **49**(2): 105-15.

51. Aprile G, Macerelli M, Giuliani F. Regorafenib for gastrointestinal malignancies : from preclinical data to clinical results of a novel multi-target inhibitor. *Biodrugs* 2013; **27**(3): 213-24.

52. Hussar DA, Koval JM. Apixaban, sodium picosulfate, and regorafenib. *Journal of the American Pharmacists Association: JAPhA* 2013; **53**(2): 217-22.

53. Strumberg D, Schultheis B. Regorafenib for cancer. *Expert Opinion on Investigational Drugs* 2012; **21**(6): 879-89.

54. Demetri GD. Differential properties of current tyrosine kinase inhibitors in gastrointestinal stromal tumors. *Seminars in Oncology* 2011; **38 Suppl 1**: S10-9.

55. Rajendra R, Pollack SM, Jones RL. Management of gastrointestinal stromal tumors. *Future Oncology* 2013; **9**(2): 193-206.

56. Sirohi B, Philip DS, Shrikhande SV. Regorafenib: carving a niche in the crowded therapeutic landscape. *Expert Review of Anticancer Therapy* 2013; **13**(4): 385-93.

57. Anonymous. Regorafenib (Stivarga) for metastatic colorectal cancer and GIST. *Medical Letter on Drugs & Therapeutics* 2013; **55**(1415): e36.

58. Small S. Hem/Onc. *Clinical Advances in Hematology and Oncology* 2013; **11**(3): 225-6.

59. pan-Canadian Oncology Drug Review manufacturer submission: Stivarga® (regorafenib) 40 mg oral tablets; Company: Bayer. Toronto (ON); 2013 October 11.