pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Regorafenib (Stivarga)

Submitted Funding Request:
For treatment of patients with unresectable hepatocellular carcinoma (HCC) who have been previously treated with sorafenib

Submitted by:
Bayer Inc.

Manufactured by:
Bayer Inc.

NOC Date:
September 29, 2017

Submission Date:
October 12, 2017

Initial Recommendation Issued:
March 29, 2018

Approximate drug costs per patient per month (28 Days)	Regorafenib (Stivarga): $72.60 per 40 mg tablet At the recommended dose, regorafenib costs $217.86 per day and $6,100.08 per 28-day cycle.

pERC RECOMMENDATION	pERC conditionally recommends the reimbursement of regorafenib (Stivarga) for patients with unresectable HCC who have been previously treated with sorafenib only if the following condition is met: • cost-effectiveness being improved to an acceptable level. If the aforementioned condition cannot be met, pERC does not recommend reimbursement of regorafenib. Eligible patients should have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1, a Child-Pugh class status of A, and otherwise meet the RESORCE trial criteria. pERC made this recommendation because it was satisfied that there is a net clinical benefit of regorafenib based on a clinically meaningful improvement in overall survival (OS) and an acceptable toxicity profile. pERC also concluded that the therapy aligns with patient values in that it offers an improvement in OS and no detriment in quality of life (QoL) in a disease where there is considerable unmet need. However, pERC noted that, at the submitted price, regorafenib could not be considered cost-effective compared with best supportive care (BSC).
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there was a net clinical benefit with regorafenib plus BSC compared with placebo plus BSC in patients

with unresectable HCC who have been previously treated with sorafenib, jurisdictions may want to consider alternate pricing arrangements and/or cost structures to improve cost-effectiveness to an acceptable level.

RESORCE Trial Criteria for Treatment Eligibility
pERC agreed that the reimbursement population should follow the trial inclusion criteria, which were restricted to patients with Child-Pugh class A and have an ECOG PS of 0 to 1. Additionally, patients who were unable to tolerate sorafenib (i.e., unable to tolerate sorafenib at ≥ 400 mg/day for ≥ 20 days of the last 28 days of treatment) were excluded.

pERC agreed that a broader patient population with impaired liver function (Child-Pugh class B), lower PS (≥ 2), and intolerance to sorafenib is unlikely to tolerate treatment with regorafenib.

Implementation of First Assessment of Six-Week Computed Tomography Scan for First Assessment
pERC noted differences in the interval for radiographic assessment for disease progression between the trial (every six weeks) and Canadian clinical practice (every three months). pERC agreed that if patients are not assessed for progression more frequently in the clinical setting, it is possible that the drug acquisition cost will be higher, as progression will take longer to confirm. Based on this, pERC agreed that during implementation, jurisdictions should consider introducing a six-week radiographic assessment, at least for the first scan, to ensure that patients who progress early are detected sooner and stop treatment.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

In 2017, approximately 2,500 new cases of HCC were diagnosed in Canada. The treatment approach and prognosis of patients with HCC depends upon the extent of disease, hepatic functional reserve, and PS. Child-Pugh class (A, B, or C) is the most commonly employed metric to assess hepatic reserve. As per the Barcelona Clinic Liver Cancer (BCLC) algorithm, the prognosis for patients with advanced, unresectable HCC even with preserved hepatic reserve is poor, with a median OS of less than one year. Sorafenib is currently approved and funded across Canada for the first-line systemic treatment of Child-Pugh class A patients with advanced HCC. For patients who experience progression while being treated with sorafenib, prognosis is poor, as there are currently no available treatments outside of clinical trials. Therefore, pERC concluded that there is an unmet need in this setting.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one phase III multinational, multi-centre, double-blind, placebo-controlled randomized controlled trial (RCT), RESORCE. The trial assessed the efficacy and safety of regorafenib plus BSC versus placebo plus BSC (hereafter called BSC alone) in patients with unresectable HCC who had previously been treated with sorafenib. pERC concluded that there is a net clinical benefit of regorafenib in this population based on a statistically significant and clinically meaningful improvement in OS. pERC agreed that an absolute improvement of 2.8 months in OS is meaningful in this patient population with an extremely poor prognosis otherwise. The RESORCE trial also demonstrated improvements in progression free survival (PFS) and objective response rate (ORR). QoL was measured using a number of scales, all of which reported that treatment with regorafenib did not cause detriment to patients' QoL. pERC agreed that since quality of life did not worsen (there was no detriment to quality of life), , this is meaningful for patients in this setting. pERC noted that patients receiving regorafenib experienced more toxicities compared with BSC alone; however, the toxicities were expected and manageable. pERC noted input from registered clinicians indicating that patients with HCC appear to better tolerate regorafenib compared with other indications for which regorafenib has been used. pERC noted that a variety of factors, such as the number of prior treatments or possibly due to more stringent eligibility criteria for HCC patients, may contribute to why patients with HCC appear to better tolerate regorafenib. However, pERC agreed that making such cross-trial and cross-indication comparisons are subject to a very high risk of bias. Overall, pERC agreed that there is a net clinical benefit of regorafenib in this setting.

pERC considered the generalizability of the RESORCE trial results and noted that the trial was restricted to patients with Child-Pugh class A with an ECOG PS of 0 to 1. Additionally, patients who were unable to tolerate sorafenib (i.e., unable to tolerate sorafenib at ≥ 400 mg/day for ≥ 20 days of the last 28 days of treatment) were excluded. pERC agreed that the reimbursement population should follow these criteria, as a broader patient population with impaired liver function (Child-Pugh class B), lower PS (≥ 2) or intolerance to sorafenib is unlikely to tolerate treatment with regorafenib. pERC noted that input from registered clinicians and the Clinical Guidance Panel (CGP) supported the use of the RESORCE trial criteria to determine eligibility for treatment. Although the trial allowed patients to continue treatment beyond progression, pERC concluded that treatment with regorafenib should be continued until disease progression or unacceptable toxicity. pERC also agreed that there is no evidence to support the use of regorafenib in the first-line setting.

pERC deliberated upon input from one patient advocacy group and noted that patients with unresectable HCC have a high disease burden and experience a variety of disease-related side effects that affect their QoL. Among these, fatigue had the largest impact, followed by abdominal pain and nausea. pERC agreed that there is an unmet need in this setting. Patients also understood that new treatment options will not be curative, but expressed that there was value in having access to therapies that could extend their lives and give them additional time with their families. In discussing the submission from the patient advocacy group, pERC noted that the descriptions of patients' experiences powerfully conveyed their feelings of despair due to the disease. pERC noted that the patients included in the RESORCE trial were a select

group (e.g., they had an ECOG PS of 0 to 1, adequate hepatic function, and were able to tolerate sorafenib treatment) and may not fully reflect patients who contributed to the patient group submission or patients typically seen in clinical practice (i.e., those with a high disease burden and QoL impact). Despite this difference, pERC agreed that prolonged survival, an absence of detriment to QoL and a manageable toxicity profile would be meaningful to patients with unresectable HCC. Therefore, pERC concluded that regorafenib aligned with patient values. pERC also noted that patient input was solicited in multiple languages and commended the Canadian Liver Foundation for its efforts to collect experience from a broader patient population.

pERC deliberated on the cost-effectiveness of regorafenib compared with BSC alone and concluded that, at the submitted price, regorafenib is not cost-effective. pERC noted that the incremental cost-effectiveness ratio (ICER) was most sensitive to the cost of radiographic assessment and whether patients took the full protocol dose of regorafenib, as per the RESORCE trial. pERC acknowledged that patients may not receive the full protocol dose of regorafenib due to dose reductions, such as those reported in the RESORCE trial. However, pERC considered that each patient would be dispensed a given number of capsules each month, and some wastage would occur if the patient's dose is reduced. Therefore, the pCODR Economic Guidance Panel (EGP) modelled the cost associated with 100% of the dose as opposed to 85%. pERC further accepted the EGP's reanalysis, which increased the cost for radiographic assessment to better reflect the cost of a computed tomography (CT) scan of the abdomen in Canada. Lastly, the EGP modelled alternative utility values. The CGP considered the values used in the base case to be high and not reflective of the HCC clinical population. Based on the described changes, pERC agreed that regorafenib is not cost-effective and that the true ICER is likely closer to the higher end of the EGP's reanalysis estimate. pERC further noted differences in the interval for radiographic assessment for disease progression between the trial (every six weeks) and Canadian clinical practice (every three months). pERC agreed that if patients are not assessed for progression more frequently, the cost for drug acquisition will be higher since patients will be taking regorafenib even though the disease has progressed. Based on this, pERC agreed that during implementation, jurisdictions should consider introducing a six-week radiographic assessment, at least for the first scan, to ensure that patients who progress early are detected sooner and stop treatment.

pERC also considered factors affecting the feasibility of implementing a conditional reimbursement recommendation for regorafenib for patients with unresectable HCC. pERC noted that the eligible reimbursement population should align with the trial inclusion criteria, and agreed that the exclusion of patients with Child-Pugh class B liver function, ECOG PS >1, and those who are intolerant to sorafenib (i.e., unable to tolerate ≥ 400 mg/day for the past 20 of 28 days of treatment) does not reduce the clinical importance of regorafenib. pERC noted that this aligned with the CGP's conclusions and input from registered clinicians. pERC also agreed that there is no evidence for the use of regorafenib in the first-line setting. pERC agreed that the 40 mg tablets will reduce the potential for wastage; however, pERC considered that there is a potential for wastage if a full monthly dose is dispensed and patients subsequently need a dose reduction. pERC discussed the budget impact of regorafenib and noted that it is sensitive to the market share. pERC also noted that if more frequent intervals for radiographic assessment are not available, it is likely patients will continue treatment beyond disease progression, increasing the drug acquisition costs. It is unclear how large an impact this may have on the budget impact. Furthermore, pERC agreed that the funding mechanism of oral therapies is not uniform across Canada and may result in barriers to accessible, affordable medications for some patients.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis (BIA)
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group (the Canadian Liver Foundation [CLF])
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of regorafenib in patients with unresectable hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Studies included: Randomized phase III trial

The pCODR systematic review included one multi-centre, double-blind, placebo-controlled, phase III randomized controlled trial (RCT), RESORCE, comparing regorafenib plus best supportive are (BSC) with placebo plus BSC (referred to hereafter as BSC alone) in patients with unresectable HCC who were previously treated with sorafenib. Key inclusion criteria required that patients be 18 years or older; have Child-Pugh class A liver function; have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1; have tolerability of sorafenib during prior treatment (defined as not less than 20 days at a minimum daily dose of 400 mg once daily within the last 28 days prior to treatment discontinuation); and have a life expectancy of at least three months. Patients were randomized (2:1) to receive treatment with regorafenib (N = 379) or placebo (N = 194). Randomization was stratified by geological region (Asia versus all other locations). Treatment continued until disease progression using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria, clinical progression (i.e., ECOG performance score ≥ 3 or symptomatic deterioration, including increased liver function tests), death, unacceptable toxicities, withdrawal of consent, or investigator decision. Patients were permitted treatment beyond progression if the investigator judged that the patient would experience a clinical benefit. After the primary analysis, patients who were receiving placebo could cross over and receive regorafenib. Therefore, the primary analysis results are not impacted by the cross-over.

Patient populations: Child-Pugh Class A, intolerant to sorafenib

Baseline characteristics were well-balanced across treatment groups. Although the trial inclusion criteria limited patients to Child-Pugh class A status, there were 11 patients who progressed to Child-Pugh class B after screening and who were included in the intention-to-treat population. Patients enrolled in the trial had an ECOG PS of 0 (65% and 67%) or 1(35% and 33%) and a median age of 64 and 62 in the regorafenib and placebo groups, respectively. The majority of patients were classified as white (36% and 35%) or Asian (41% and 40%) and were male (88% in both groups) in the two groups respectively.

At the primary cut-off date (February 29, 2016), most patients had discontinued their assigned therapies (83% and 95% in the regorafenib and placebo groups, respectively). The most common reason for discontinuing treatment was radiological progression in both treatment groups respectively (48.2% and 65.0%). Patients also discontinued treatment due to adverse events (AEs) associated with disease progression (18.1% and 15.3%), AEs not associated with disease progression (15.2% and 6.6%), and withdrawal by patient (8.4% and 2.7%).

Key efficacy results: Statistically significant and clinically meaningful improvement in overall survival

The key efficacy outcome deliberated on by pERC was overall survival (OS), which was the primary outcome of the trial. Key secondary outcomes included progression free survival (PFS), objective response rate (ORR), quality of life (QoL), and safety. At the February 29, 2016 data cut-off, regorafenib was associated with a statistically significant improvement in OS relative to placebo (hazard ratio 0.63; 95%

confidence interval [CI], 0.50 to 0.79; $P \leq 0.0001$). The median OS was 10.6 months compared with 7.8 months, with an absolute improvement of 2.8 months. Regorafenib was also associated with longer PFS compared with placebo according to mRECIST criteria (hazard ratio 0.46; 95% CI, 0.37 to 0.56; $P \leq 0.0001$) and RECIST 1.1 criteria (hazard ratio 0.43; 95% CI, 0.35 to 0.52; $P < 0{\cdot}0001$). ORR was significantly higher with regorafenib compared with placebo (11% and 4%, respectively). Notably, the trial did not implement hierarchical testing or other multiplicity analyses to control for type I error.

pERC deliberated upon the results of the RESORCE trial and agreed that an absolute improvement of 2.8 months in OS is meaningful in a population with a poor prognosis (median OS of less than one year at presentation). pERC also agreed that regorafenib improved PFS and ORR.

pERC agreed that the eligible reimbursement population should follow the trial inclusion criteria. Namely, patients with impaired liver function (Child-Pugh class B), lower PS (≥ 2), and intolerance to sorafenib are unlikely to tolerate treatment with regorafenib and should not be eligible. pERC noted that input from registered clinicians and the Clinical Guidance Panel (CGP) supported the use of the RESORCE trial criteria to determine eligibility for treatment. Although the trial allowed patients to continue treatment beyond progression, pERC concluded that treatment with regorafenib should be continued until disease progression or unacceptable toxicity.

Patient-reported outcomes: No detriment to quality of life

Patient-reported outcomes were measured using four instruments: Functional Assessment of Cancer Therapy–General (FACT-G); FACT–Hepatobiliary (FACT-Hep); and the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L and EQ-5D visual analogue scale (EQ VAS) instruments. There were no statistical differences between regorafenib and placebo for the FACT-G, EQ-5D-3L, or EQ VAS scales ($P > 0.05$ for all), and no clinically meaningful differences for these scales, as the minimally important difference (MID) was not met. The least-squared, mean time-adjusted area-under-the curve analysis favoured placebo for the FACT-Hep total score ($P = 0.0006$); however, the difference is not clinically meaningful, since the MID threshold was not met. The results from the four QoL instruments used in the trial demonstrate that treatment with regorafenib did not cause detriment to patients' QoL. pERC agreed that an absence of worsening of QoL is meaningful for patients.

Safety: Greater number of adverse events with regorafenib, but expected and manageable

Almost all patients had at least one treatment-emergent adverse event (TEAE) (100% and 93% in the regorafenib and placebo groups, respectively). There were fewer grade 3 to grade 4 TEAEs among the placebo group (39%) versus the regorafenib group (67%). Patients in the regorafenib group had more grade 3 or higher drug-related TEAEs (50% versus 17%) compared with the control group. There were more drug-related serious adverse events (SAEs) (10% versus 3%) and dose modifications (68% versus 31%) in the regorafenib group compared with placebo, respectively. More patients treated with regorafenib (25%) had to discontinue treatment due to AEs compared with patients taking placebo (19%). Aspartate aminotransferase (AST) levels, hand-foot skin reaction, and alanine aminotransferase (ALT) increase were the most common reasons for discontinuation due to AEs. There were more deaths among patients taking regorafenib (n = 7) compared with placebo (n = 2).

pERC agreed that patients receiving regorafenib experienced more toxicities compared with BSC alone; however, the toxicities were expected and considered manageable. pERC noted input from registered clinicians indicating that HCC patients appear to better tolerate regorafenib compared with other indications where regorafenib has been investigated. pERC noted that a variety of factors may contribute to why patients appear to better tolerate regorafenib, including how far along patients are in their lines of treatment and strict eligibility criteria for RESORCE. However, pERC agreed that it is difficult to make cross-trial and cross-indication comparisons.

Need and burden of illness: High unmet need after progression on sorafenib

In 2017, approximately 2,500 new cases of HCC were diagnosed in Canada. In the last two decades, the incidence of HCC has increased by 3.1% per year in men, and 2.1% per year in women. This is attributed in part to rising immigration from countries where risk factors for HCC (such as hepatitis B and C) are more common. The treatment approach and prognosis of patients with HCC depends upon the extent of disease, hepatic functional reserve, and PS. Child-Pugh class (A: 5 to 6; B: 7 to 9; and C: 10 to 15) is the most commonly employed score to assess hepatic reserve. HCC is considered to be a chemo-refractory tumour. Sorafenib is currently approved and funded across Canada for the first-line systemic treatment of Child-Pugh class A patients with advanced HCC. As per the Barcelona Clinic Liver Cancer (BCLC)

algorithm, the prognosis for patients with advanced, unresectable HCC even with preserved hepatic reserve is poor, with a median OS of less than one year. For patients who experience progression while being treated with sorafenib, there are currently no available treatments outside of clinical trials. Patients with HCC face a poor prognosis and are usually offered BSC after progression on sorafenib. Therefore, pERC agreed there is an unmet need in this setting.

Registered clinician input: Unmet need after progression on sorafenib

The registered clinician input acknowledged a significant unmet need as survival of patients with HCC is poor, and there is a lack of treatment other than palliative care after disease progression on sorafenib. Clinicians identified that the proportion of patients eligible for first-line sorafenib is small, and the subsequent proportion of patients who would be eligible for second-line sorafenib is even smaller. The clinicians highlighted that patients who discontinue sorafenib treatment due to toxicity, and who progress on sorafenib with hepatic dysfunction, would not be candidates for regorafenib.

Based on the RESORCE trial, the clinician input noted a prolonged survival of approximately three months for patients taking regorafenib. Clinicians agreed that patients eligible for treatment should have preserved liver function (i.e., Child-Pugh class A) and good PS (ECOG 0 to 1), while patients who discontinued treatment with sorafenib due to sorafenib-related toxicity and patients who progress on sorafenib with hepatic dysfunction would not be candidates for regorafenib. Due to the toxicities related to regorafenib, clinicians noted that patients will need to be closely monitored, but that toxicities can be managed by dose reductions as needed. However, one group of clinicians reported that toxicity in patients with HCC from the RESORCE trial is not as severe as what was observed with regorafenib in the CORRECT trial comparing regorafenib with placebo for colorectal cancer. pERC noted that a variety of factors may contribute to why patients appear to better tolerate regorafenib, including how far along patients may be in their lines of treatment and strict eligibility criteria for RESORCE. However, pERC agreed on the difficulty of making cross-trial and cross-indication comparisons.

PATIENT-BASED VALUES

Values of patients with hepatocellular carcinoma: Substantial impact on quality of life

The CLF provided input on regorafenib (Stivarga) for the treatment of patients with unresectable HCC who have previously been treated with sorafenib. The input is summarized below. Input from patients was collected through a variety of methods. pERC noted that an online survey was available in English, French, and Chinese, and commended the group's effort to solicit experiences from a broader patient population through the use of multiple languages.

pERC discussed input that noted that HCC has a significant impact on patients' QoL, with fatigue having the biggest impact, followed by abdominal pain and nausea. Patients also indicated that appetite loss, weight loss, diarrhea, skin disorders and alopecia affected their QoL. Quotes provided by CLF indicate that patients have difficulty with symptoms and feel they are a burden to family members. Patients described their experiences with HCC as fearful, worrisome, shocking, frightening, and saddening. pERC noted that the descriptions of patients' experiences powerfully conveyed their feelings of despair. However, pERC noted that the patients included in the RESORCE trial were a select group (e.g., had a good PS and adequate renal function, and were able to tolerate treatment) and may not fully reflect patients with such a high disease burden and QoL impact.

Patient values on treatment: Difficult treatments, management of side effects, quality of life, unmet need

According to survey data reported by CLF, transarterial chemoembolization (TACE) followed by liver ablation, surgery, and liver transplant are the most common forms of treatment for patients with HCC. Based on the patient input, TACE was the most challenging treatment to undergo, followed by treatment with sorafenib. Patients were also more likely to rate their current QoL as poor if their most recent treatment was sorafenib. CLF reported pain, low energy, pruritus (itching), vomiting, light-headedness, and abdominal pain as the most common side effects of current treatments.

Treatment expectations for patients, as reported by CLF, include an improvement of physical symptoms that allow for greater independence. Also, patients reported that the addition of new treatment options may help reduce feelings of anxiety and offer hope to patients who may not have any other options. Given the poor prognosis of patients with HCC and the lack of treatment options for patients who have

progressed while taking sorafenib, CLF acknowledged that regorafenib fulfills an unmet need in the second-line setting. Overall, pERC agreed that prolonged survival, an absence of detriment to QoL and the manageable toxicity profile reported in the RESORCE trial would be meaningful to patients with unresectable HCC. Therefore, pERC concluded that regorafenib aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and utility analysis

The pCODR Economic and Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis comparing regorafenib with BSC alone in patients with unresectable HCC following treatment with sorafenib (Nexavar).

Basis of the economic model: Reasonable clinical and cost inputs

Costs considered in the analysis were those related to drug acquisition, disease managements, AEs, and monitoring. Key clinical effect estimates considered in the analysis include OS, PFS, utilities and disutilities associated with AEs. The survival benefit observed in the RESORCE trial was extrapolated over a three-year time horizon. Efficacy and safety parameters as well as utilities were based on the RESORCE trial. Inputs for costs and resource use were taken from the RESORCE trial as well as an Ontario population-based database analysis of health care utilization in HCC from 2002 to 2010.

The submitted base-case analysis assumed that all background costs were considered equivalent between regorafenib and BSC alone, and common parameters were used across treatment arms. Since Canadian clinical practice specifies longer frequency between assessments for radiographic progression (three months) compared to what was reported in the trial (six weeks), it is likely that patients in clinical practice may be on regorafenib longer if more frequent assessment is not implemented. It is unclear how much this may impact the incremental cost-effectiveness ratio (ICER). Notably, the model did not allow the EGP to assess the impact of this factor on the cost effectiveness.

Drug costs: Full protocol dose not modelled in base case

Regorafenib costs $72.60 per 40 mg tablet. At the recommended dose of 160 mg orally once daily for the first three weeks of each four-week cycle, regorafenib costs $217.86 per day and $6,100.08 per 28-day cycle. The economic model included an adjusted daily dose and cost of regorafenib that was 85% of the protocol specified dose.

Cost-effectiveness estimates: Unknown impact of infrequent assessment for radiographic progression

pERC deliberated on the cost-effectiveness of regorafenib compared with BSC alone and concluded that, at the submitted price, regorafenib is not cost-effective. pERC noted that the ICER was most sensitive to whether patients take the full protocol dose of regorafenib. The submitted model did not model the cost of the full protocol dose of regorafenib, but instead used the observed dose from the RESORCE trial. pERC acknowledged that patients may not receive the full protocol dose of regorafenib due to dose reductions, such as those reported in the RESORCE trial. However, pERC considered that each patient would be dispensed a given number of capsules each month and some wastage would occur since it is unlikely that capsules not taken due to dose reductions would be taken into consideration when the patient's next dispensation of medication occurs. The ICER was also sensitive to the cost of radiographic assessment. pERC accepted the EGP's reanalysis, which increased the cost for radiographic assessment to better reflect the cost of a computed tomography (CT) scan of the abdomen in Canada. Lastly, the EGP also used alternative utility values, as the CGP agreed the utilities derived from the trial were high and did not reflect the HCC clinical population. Based on the described changes, pERC agreed that regorafenib is not cost-effective and that the true ICER is likely closer to the higher end of the EGP's reanalysis estimate.

pERC further noted differences in the interval for radiographic assessment for disease progression between the trial (every six weeks) and Canadian clinical practice (every three months). pERC agreed that if patients are not assessed for progression more frequently in the clinical setting, it is possible that the costs for drug acquisition will be higher since disease progression will take longer to confirm. Based on this, pERC agreed that during implementation, jurisdictions should consider introducing a six-week radiographic assessment, at least for the first scan, to ensure that patients who progress early are detected sooner and stop treatment.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Eligibility based on trial inclusion criteria

pERC also discussed factors that would affect the feasibility of implementing a conditional reimbursement recommendation and which PAG considered important. pERC noted that while the oral route of administration is an enabler to implementation, in some provinces the reimbursement mechanism for oral therapies can result in barriers to accessible, affordable medications for patients. PAG also noted that there are specific fat and caloric diet considerations required for patients taking regorafenib and they queried whether this may be challenging for some patients. The dosing schedule of regorafenib (three weeks on and one week off) may be challenging for some patients. In addition, the toxicities and AEs may require additional resources to monitor and manage patients.

pERC discussed the eligible reimbursement population, and concluded that eligibility for treatment should follow the trial inclusion criteria and agreed that the exclusion of patients with Child-Pugh class B liver function, ECOG PS >1, and those who are intolerant to sorafenib (e.g., unable to tolerate ≥ 400 mg/day sorafenib for the past 20 days of 28 days) does not reduce the clinical importance of regorafenib. pERC noted that this recommendation aligned with the CGP's conclusions and the input from registered clinicians. pERC also agreed that there is no evidence for the use of regorafenib in the first-line setting. pERC agreed that the 40 mg tablets will reduce the potential for wastage; however, pERC agreed that there will be wastage if a full monthly dose is dispensed and patients subsequently need a dose reduction. pERC discussed the budget impact of regorafenib and noted that it is sensitive to the market share. pERC also noted that if more frequent radiographic assessments are not available, it is likely patients will continue treatment past disease progression, thus increasing the cost of drug acquisition. It is unclear how large an impact this may have on the BIA.

DRUG AND CONDITION INFORMATION

Drug Information	• Multi-kinase inhibitor • 40 mg film-coated tablet • 160 mg (4 tablets, orally) daily for 3 weeks, followed by 1 week off treatment
Cancer Treated	• Unresectable hepatocellular carcinoma.
Burden of Illness	• Approximately 2,500 new cases of hepatocellular carcinoma were diagnosed in Canada in 2017. • Patients with this condition face a poor survival prognosis, and currently have no available treatment options after progression on sorafenib (outside of clinical trials).
Current Standard Treatment	• Best supportive care.
Limitations of Current Therapy	• Select fit population that can be treated.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Christopher Longo, Economist
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Kelvin Chan and Dr. Craig Earle who were not present for the meeting
- Valerie McDonald who was excluded from voting due to a conflict of interest

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of regorafenib for hepatocellular carcinoma, through their declarations, one member had a real, potential or perceived conflict. Based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

To inform its deliberations, pERC was provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which included input from a patient advocacy group and the Provincial

Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking data on the use of regorafenib in hepatocellular cancer patients with Child-Pugh class B.	• pERC noted that eligibility for treatment should follow the trial inclusion criteria, and agreed that patients with Child-Pugh class B liver function should not be treated with regorafenib.
• PAG indicated that there may be requests for regorafenib for first-line treatment, particularly in patients who did not tolerate sorafenib. • The trial excluded patients who did not tolerate sorafenib. However, in clinical practice, there are patients who cannot tolerate sorafenib and have no other treatment options.	• pERC agreed that there is no evidence for the use of regorafenib in the first-line setting. • pERC noted that the eligibility for treatment should follow the trial inclusion criteria, and agreed that patients who are intolerant to sorafenib (e.g., unable to tolerate ≥ 400 mg per day sorafenib for the past 20 days of 28 days) should not be included in the reimbursement population. Furthermore, sorafenib and regorafenib have a similar mechanism of action; patients unable to tolerate sorafenib would not tolerate treatment with regorafenib.

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.