pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Regorafenib (Stivarga) for Hepatocellular Carcinoma

April 18, 2018

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LIST OF ABBREVATIONS

AASLD American Association for the Study of Liver Disease
AE Adverse events
AFP alpha-fetoprotein
AUC Area under the curve
BCLC Barcelona Clinic Liver Cancer
BSC Best supportive care
CGP Clinical Guidance Panel
CI Confidence intervals
CMH Cochran-Mantel-Haenszel
CR Complete response
CT Computed tomography
DCR disease control rate
DMC Data monitoring committee
DOR Duration of response
ECOG Eastern Cooperative Oncology Group
EOT End of treatment EQ-5D VAS EuroQol five dimension scale visual analog scale
EQ-5D-3L EuroQol five dimension scale
FACT-G Functional Assessment of Cancer Therapy-General
FACT-Hep Functional Assessment of Cancer Therapy Hepatobiliary
GFR Glomerular filtration rate
HCC Hepatocellular carcinoma
HR Hazard ratio
HRQoL health-related quality of life
ILD Interstitial lung disease
IQR Interquartile range
ITT Intention-to-treat
LSM least-squares mean
MID Minimally important difference
mRECIST modified Response Evaluation Criteria in Solid Tumors
MRI Magnetic resonance imaging
NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events
ORR objective response rate
OS overall survival
pERC pCODR Expert Review Committee
PFS Progression-free survival
PR Partial response
RECIST Response Evaluation Criteria in Solid Tumors
SAE Serious adverse event
SD Stable disease
SD Standard deviation
TACE Transarterial Chemoembolization
TEAE treatment-emergent adverse events
TTP time to progression

1 GUIDANCE IN BRIEF

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

This Clinical Guidance is based on: a systematic review of the literature regarding regorafenib (Stivarga) for HCC conducted by the Genitourinary Clinical Guidance Panel and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review is fully reported in Sections 6. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on regorafenib (Stivarga) for HCC, a summary of submitted Provincial Advisory Group Input on regorafenib (Stivarga) for HCC, and a summary of submitted Registered Clinician Input on regorafenib (Stivarga) for HCC, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of regorafenib (Stivarga) for the treatment of patients with unresectable HCC who have been previously treated with sorafenib. This is similar to the Health Canada regulatory approval.

Regorafenib is an inhibitor of multiple protein kinases, including kinases involved in tumor angiogenesis, oncogenesis, metastasis, and tumor immunity. The recommended dose of regorafenib is 160mg once-daily for 21 days of each 28 day cycle.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one global, multi-centre, double-blind, placebo-controlled, randomized phase 3 trial (RESORCE) comparing regorafenib to placebo in patients with HCC who have been previously treated with sorafenib.[1] Patients were eligible to enroll into RESORCE if they met the following criteria: 18 years of age; pathological confirmation or non-invasive diagnosis of HCC according to AASLD criteria in those with confirmed cirrhosis; at least one measurable lesion using RECIST 1.1 or mRECIST; BCLC stage Category B or C that cannot benefit from resection, local ablation or chemoembolization; documented radiological progression during sorafenib treatment; tolerated sorafenib (≥400 mg daily for at least 20 of the 28 days before discontinuation); received their last sorafenib dose within 10 weeks of randomisation; Child-Pugh Class A liver function; ECOG performance status of 0 or 1; adequate bone marrow, liver and renal function.[1] Patients were excluded if received any other previous systemic treatment for HCCC or if they discontinued sorafenib for toxicity.[1]

A total of 843 patients were randomly assigned on a 2:1 ratio to receive regorafenib at 160 mg/d every 3 weeks of a 4 week cycle (n = 379) or to a matching placebo (n = 194).[1] Patients were assessed for tumour progression every 6 weeks for 8 cycles and then every 12 weeks thereafter.[2] Treatment continued until disease progression using the mRECIST and RECIST 1.1 criteria, clinical progression (i.e. ECOG performance score of ≥ 3 or symptomatic deterioration, including increased

liver function tests), death, unacceptable toxicities, withdraw consent or investigator decision.[2] Treatment beyond progression was permitted if investigator judged that the patient would experience a clinical benefit.[2] Clinical benefit was defined as the absence of deterioration of ECOG status (e.g. ECOG should not deteriorate from baseline status: 0 to 2 or higher, from 1 to 3 or higher) and/or absence of deterioration of liver function.[2] Patients receiving placebo could cross-over and received regorafenib after the primary analysis.[2]

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.[1]

Efficacy

The primary outcome in RESORCE was OS. Secondary endpoints were PFS, TTP, ORR and DCR while tertiary endpoints included: DOR, duration of stable disease, HRQoL and safety. The trial required a sample size of 560 patients, representing 370 deaths, to have 90% power to detect a HR of 0.70 using a one-sided level of 0.025.[2] As a result of a protocol amendment, the trial increased the sample size from 530 to 560 patients.[2] This was done to allow 150 patients from China to be recruited in the study and adhere to the 40% cap for Asian patients.

The cut-off for the final analysis occurred on 29-Feb-2016, which represents a median follow-up of 7.0 months (IQR: 3.7 to 12.6).[1]

At the 29-Feb-2016 data cut-off, there were 373 deaths.[1] Sixty-one percent of patients in the regorafenib group died (N=233) while 72% (N=140) of patients in the placebo group died.[1]Median OS was longer in the regorafenib arm (10.6 months [95% CI: 9.1 to 12.1]) as compared to the control arm (7.8 months [95% CI: 6.3 to 8.8]). Regorafenib was associated with a significantly prolonged OS relative to placebo in patients with HCC (HR: 0.63, 95% CI: 0.50 to 0.79; p ≤ 0.0001) (Table 1).[1]

An unplanned interim analysis occurred on 23-Feb-2017.[3] Seventy-seven percent of patients in the regorafenib group died (N=290) and 87% (N=169) of patients in the placebo group died.[3] Median OS was longer in the regorafenib arm (10.7 months [95% CI: 9.1 to 12.2]) as compared to the control arm (7.9 months [95% CI: 6.4 to 9.0]). Regorafenib was associated with a significantly prolonged OS relative to placebo in patients with HCC (HR: 0.61, 95% CI: 0.50 to 0.75; p ≤ 0.0001) (Table 1).[1]

More patients in the placebo group (93.3%) had disease progression or died as compared to those in the regorafenib group (77.3%).[4]The median PFS for the regorafenib group was 3.1 months (95% CI: 2.8 to 4.2) and 1.5 months (95% CI: 1.4 to 1.6) in the placebo group.[1] The authors reported that regorafenib was associated with prolonged PFS as compared to placebo using mRECIST criteria (HR: 0.46, 95% CI: 0.37 to 0.56; p-value ≤ 0.0001) (Table 1).[1] Similar PFS estimates were reported using the RECIST 1.1 criteria (HR: 0.43, 95% CI: 0.35 to 0.52; p<0·0001).[5]

ORR was significantly higher for patients treated with regorafenib versus those treated with placebo using mRECIST criteria (11% [N = 40/379] vs. 4% [N = 8/194]; p-value: 0.0047) (Table 1).[1] Similar ORR estimates were reported using the RECIST 1.1 criteria (p-value: 0.02).[5]

HRQoL

HRQoL was measured using four different patient-reported outcome measures from two questionnaires, which includes the FACT-G, the FACT-Hep, the EQ-5D-3L (i.e. EQ-5D) and the EQ-5D VAS questionnaires.[6]

Bruix et al (2016) reported that there were no statistical differences between regorafenib or placebo for the FACT-G, EQ-5D or EQ-5D VAS scales ($p > 0.05$ for all).[6] Furthermore, there was no clinically meaningful differences for these scales because the MID was not met. For the FACT-Hep Total scale, the LSM time-adjusted AUC analysis favoured placebo (p=0.0006); however, the difference is not clinically meaningful since the MID threshold was not met.[1]

Harms

A large proportion of patients from the RESORCE trial were included in the safety analysis, with 98.7% of patients from the regorafenib arm (N=374/379) and 99.5% from the control arm (N=193/194).[4] Bruix et al (2017) stated that the median duration of regorafenib treatment was 3.6 months (IQR: 1.6 to 7.6) and the median duration of treatment was 1.9 months (range: 1.4 to 3.9) for placebo.[1]

The majority of patients enrolled in RESORCE had at least one TEAE (regorafenib: 100% and placebo: 93%).[1] Similar patterns were also reported for grade 3 to 4 TEAEs (regorafenib: 66% and placebo: 39%).[1] More patients in the regorafenib arm had a drug-related TEAE (93%) versus those treated with placebo (52%).[1] Likewise, more patients in the regorafenib group (50%) had at least one grade 3 or higher drug-related TEAE as compared to the control group (17%).[1]

Treatment-emergent SAEs were reported equally for the regorafenib group (44%) and the placebo group (47%).[1] However, more drug-related SAEs occurred in the regorafenib arm (10%) than in the placebo group (3%).[1]

Patients in the regorafenib group were twice as likely to have a dose modification (i.e. dose interruption or dose reduction) than those in the placebo group (68% vs. 31%).[1] A quarter of patients treated with regorafenib discontinued due to an AE (25%) while 19% treated with placebo discontinued (N=37).[1]

Bruix et al (2017) reported that nine drug-related deaths occurred in the trial.[1] Seven deaths occurred in the regorafenib group [myocardial infarction (n=1), gastric perforation (n=1), upper gastrointestinal haemorrhage (n=1), death not otherwise specified (n=1), other general disorders and administrative site conditions (n=1), hepatic failure (n=1), intracranial haemorrhage (n=1) and encephalopathy (n=1)] and two occurred in the placebo [hepatic failure (n=2)].[5]

Limitations

Overall, RESORCE was a well-designed double-blind, placebo-controlled RCT. There was minimal risk of selection, performance, detection, attrition and reporting bias. However, there are few limitations that should be considered when interpreting the results of the trial, more specifically:

- After the primary analysis (29-Feb-2016), patients originally randomized to the placebo arm could cross over and receive regorafenib. The results in Bruix et al (2017) will not be impacted because patient crossover was implemented after the primary analysis was performed.[1] However, an unplanned interim analysis of the trial was conducted on 23-Jan-2017.[3] Thus, the updated OS estimates from this unplanned analysis may be confounded because patients were permitted to cross over from the placebo arm to the regorafenib arm.
- The trial implemented strict eligibility criteria, such that patients who were intolerant to sorafenib (i.e. unable to tolerate sorafenib at ≥400 mg/day for ≥20 of the last 28 days of treatment), who had Child-Pugh class B or patients who had an ECOG performance status ≥ 2 were excluded. The authors indicated that only patients with Child-Pugh A liver function were included in the trial to avoid the potential confounding effect of impaired liver function on survival.
- It was stated in the eunetHTA report that the trial did not implement hierarchical testing or other multiplicity analyses to control for type 1 error.[7] A type 1 error leads to false-

positives, such that a study may report a treatment difference between two groups (p-value ≤ 0.05), when in fact, there is no true difference.[8]

Table 1. Highlights of the Key Outcomes from RESORCE

	Regorafenib Arm N= 379	Placebo Arm N=194
February 29, 2016 Data Cut		
Median OS	61 (233)	72 (140)
	10.6 months (95% CI: 9.1 to 12.1)	7.8 months (95% CI: 6.3 to 8.8)
	HR 0.63; (95% CI: 0.50 to 0.79) p≤0.0001	
Median PFS[1]	77.3 (293)	93.3 (181)
	3.1 months (95% CI: 2.8 to 4.2)	1.5 months (95% CI: 1.4 to 1.6)
	HR 0.46; (95% CI: 0.37 to 0.56) p≤0.0001	
ORR[1], n (%)	11 (40)	4 (8)
Median Follow-up	7.0 months (IQR: 3.7 to 12.6)	
January 23, 2017 Data Cut		
Median OS	77 (290)	87 (169)
	10.7 months (95% CI: 9.1 to 12.2)	7.9 months (95% CI: 6.4 to 9.0)
	HR 0.61; (95% CI: 0.50 to 0.75) p≤0.0001	
Median Follow-up	NR	NR

CI = confidence interval, HR = hazard ratio, OS = Overall survival; PFS = Progression-free survival; ORR = Objective response rate

1. Assessed using the mRECIST criteria

Data sources: Bruix et al (2017)[1] and Bruix et al (2017)[3]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, fatigue has the largest impact on quality of life, followed by abdominal pain and nausea. Other factors that impact quality of life include loss of appetite, weight loss, diarrhea, skin disorders and alopecia. CLF notes that HCC is a difficult disease to treat as it is usually a result of a pre-existing and progressive underlying liver disease which means that the patient may already be experiencing the effect of living function impairment, including cirrhosis, jaundice, abdominal pain and ascites. Current treatments for intermediate and advanced stages of HCC include TACE, systemic therapy such as sorafenib, and best supportive care.

Please see Section 3 below for a summary of specific input received from the patient advocacy group.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Provides an option for patients who have failed sorafenib

Economic factors:

- Additional resources to monitor and treat serious adverse events.

Please see Section 4 below for a summary of specific input received from PAG.

Registered Clinician Input

The clinicians providing input identified that there is a need for second line treatment for HCC patients who have been treated with sorafenib in the first line as there are currently no treatment options available.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

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.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for regorafenib (Stivarga) in the treatment of patients with unresectable HCC who have been previously treated with sorafenib.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(RESORCE trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Performance Status</td><td>Patients were enrolled in the trial if they had an ECOG performance status of 0 to 1.

Baseline Characteristics<table><tr><th>ECOG</th><th>Reg</th><th>Plac</th></tr><tr><td>0</td><td>247 (65%)</td><td>121 (67%)</td></tr><tr><td>1</td><td>132 (35%)</td><td>64 (33%)</td></tr></table>
Subgroup Analyses<table><tr><th>ECOG</th><th>Reg/Plac</th><th>HR (OS)</th><th>Reg/Plac</th><th>PFS HR</th></tr><tr><td>0</td><td>377/231</td><td>0.61 (0.47-0.80)</td><td>377/310</td><td>0.43 (0.34-0.54)</td></tr><tr><td>1</td><td>196/142</td><td>0.78 (0.55-1.11)</td><td>196/164</td><td>0.62 (0.45-0.86)</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The CGP noted that only patients with an ECOG performance status of 0 to 1 should be eligible to receive regorafenib. Based on clinical experience with this drug in other disease sites, the CGP stated that patients with an ECOG performance status of 2 or worse will not be able to tolerate the drug.</td></tr>
<tr><td>Metastatic Sites</td><td>Patients were excluded from the trial if they had a known history or symptomatic metastatic brain or meningeal tumours.</td><td>Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The CGP noted that patients with symptomatic brain metastatic are rarely encountered in this clinical setting. Therefore, the CGP agree that the reimbursement population does not need to be expanded to include those with asymptomatic brain metastasis.</td></tr>
<tr><td>Intervention</td><td>Line of therapy</td><td>Second-line therapy</td><td>Are the results of the trial generalizable to other lines of therapy</td><td>The CGP agree that only patients who have previously been treated with sorafenib and who did not develop intolerance should be eligible for treatment with regorafenib.</td></tr>
</table>

1.2.4 Interpretation

Burden of illness & Need

An estimated 2,500 new cases of HCC were diagnosed in Canada in 2017. Sorafenib, an oral-multi-tyrosine kinase agent that inhibits RAF-kinase and VEGFR intracellular kinases, is currently approved and funded across Canada for the first-line systemic treatment of patients with advanced HCC no longer amenable to locoregional therapy and/or with M1 disease, who have Child-Pugh Class A hepatic reserve.

There are currently no standard treatment options for patients beyond sorafenib therapy outside of a clinical trial. Patient group input from the Canadian Liver Foundation affirms that patients with HCC face a poor prognosis, and that there are currently no other approved treatment options for patients following sorafenib progression. Input from registered clinician's supports that there is a significant unmet need for these patients. While regorafenib is not curative, the CGP agree that it should be available to patients because it satisfies a current unmet need.

The Provincial Advisory Group also acknowledges that Canadian patients currently have no other options after failing treatment with sorafenib. Regorafenib's oral route of administration will favourably enable implementation. Concerns raised by PAG included the dosing schedule of three weeks on and one week off which may be confusing for some patients.

Effectiveness

Regorafenib is an orally active inhibitor (structurally similar to sorafenib), targeting multiple kinases including VEGFR, stromal and oncogenic receptor tyrosine kinases. A benefit for regorafenib in patients with advanced HCC previously treated with sorafenib was demonstrated in a single, multinational, multicentre double-blind, placebo-controlled randomized phase 3 trial (RESORCE). Patients were eligible if they previously tolerated treatment with and progressed on sorafenib (at a dose of ≥400mg daily for at least 20/28 days). Patients also had advanced HCC (per AASLD criteria) no longer amenable to locoregional therapy with measurable disease, Child-Pugh Class A liver function and ECOG performance status of 0 or 1 and were randomized in a 2:1 fashion to receive regorafenib at 160mg/day every 21 of 28 days (n=379) or matching placebo (n=194). The primary endpoint of OS was met with an improved median OS of 10.6 months (95% CI: 9.1 to 12.1) versus 7.8 months (95% CI: 6.3 to 8.8), HR 0.63, p<0.00001). The CGP agreed this absolute improvement in OS of 2.8 months was statistically significant and clinically meaningful. In a pre-specified subgroup analysis, a consistent beneficial effect of regorafenib relative to placebo was observed. Improvement was also seen in PFS (median 3.1 versus 1.5 months, HR 0.46, p<=0.0001) and ORR (11% versus 4%, p=0.0047).

No significant differences were observed between regorafenib and placebo in health-related QoL.

There are no known clinically-defined patient subgroups or validated predictive biomarkers which would assist in determining which patients with advanced HCC are most likely to benefit from regorafenib.

Safety

The median duration of regorafenib therapy was 3.6 months. The most common treatment related adverse events for patients on regorafenib vs placebo were hand-foot skin reaction

(52% vs 7%), diarrhea (33% vs 9%), fatigue (29% vs 19%), hypertension (23% vs 5%), anorexia (24% vs 6%), hyperbilirubinemia (19% vs 4%), nausea (11% vs 7%) and mucositis (11% vs 3%). Patients on regorafenib were twice as likely to have a dose modification (67% vs 31%). Treatment discontinuation rate due to an AE was 25% on regorafenib and 19% on placebo. The CGP agreed that the toxicities observed with regorafenib in this patient population were expected and manageable.

It is noted that patients with Child-Pugh Class B (score of 7 or greater) and patients unable to tolerate sorafenib or who discontinued sorafenib due to toxicity were not eligible to participate in RESORCE. The CGP agreed that the exclusion of these patients from the trial does not reduce the clinical importance of regorafenib. The CGP do support that the trial inclusion criteria be used to determine eligibility for treatment in this instance. Furthermore, given that sorafenib and regorafenib target a similar molecular pathway, it is reasonable that patients intolerant to sorafenib not be treated with regorafenib. The CGP also noted that first-line sorafenib use is limited to patients with Child Pugh Class A (score of less than 7) because of greater liver toxicity. The Child Pugh score is a measure of hepatic functional reserve and it is very important in the population of patients with HCC because many of these patients have underlying liver disease and cirrhosis.

The CGP recognizes that there is emerging data for immune checkpoint inhibitors in pre-treated advanced HCC, however, such therapy is neither approved nor clinically available in Canada. Hence, it was not deemed to be presently relevant to this guidance.

In summary, regorafenib is an oral therapy that offers a clinically meaningful and statistically significant improvement in OS, PFS and ORR with no demonstrated detriment to HRQoL in patients who have progressed on sorafenib therapy and currently have no alternative therapeutic options.

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit with the use of regorafenib in patients with sorafenib-refractory advanced HCC, with Child-Pugh Class A hepatic reserve and an ECOG performance status of 0-1.

In reaching this conclusion, the CGP considered:

- Effectiveness: The survival benefit of regorafenib has been demonstrated in a single, well-designed, global, multi-centre randomized controlled trial, RESORCE, demonstrated a statistically significant 2.8 month improvement in median OS with a meaningful HR of 0.63.
- Safety: The toxicities observed with regorafenib in this patient population were expected and manageable. The rate of treatment discontinuation due to toxicity was modestly higher in the regorafenib arm when compared to placebo (25% vs 19%).
- It is noted that the eligible patient population should be limited to patients with Child-Pugh Class A hepatic reserve and ECOG PS of 0-1. Regorafenib is not recommended in patient with Child-Pugh B7 or in patients with an ECOG performance status greater than or equal to 2.
- Need: Regorafenib fulfills an unmet need for the treatment of patients with advanced HCC who have progressed on sorafenib therapy and currently have no available effective treatment options, yet are still well enough to receive further therapy with preserved hepatic reserve and good performance status.

- The CGP does not support the use of regorafenib in the front line setting as this population is out of scope for the current review. The CGP is also unable to comment on the future impact of checkpoint inhibitors in post-sorafenib progression. While there is emerging data to support their use, these agents are neither currently approved nor funded for use in Canada outside the context of a clinical trial.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

In the last two decades the incidence of HCC (liver cancer) has increased by 3.1% per year in men, and 2.1% per year in women attributed in part to rising immigration from countries where risk factors for HCC such as hepatitis B and C, are more common. An estimated 2,500 new cases of HCC will be diagnosed in Canada in 2017 [9]. HCC is a challenging disease to treat as it typically appears in the setting of underlying hepatic cirrhosis which can lead to underlying hepatic impairment. Thus the treatment approach and consequent prognosis of patients with HCC depends upon the extent of disease, hepatic functional reserve and performance status. Child-Pugh class is the most commonly employed metric to assess hepatic reserve, and includes the parameters of serum levels of INR, albumin and bilirubin as well as clinical evidence of ascites or encephalopathy. (Table 1)

Table 1: Child-Pugh Classification

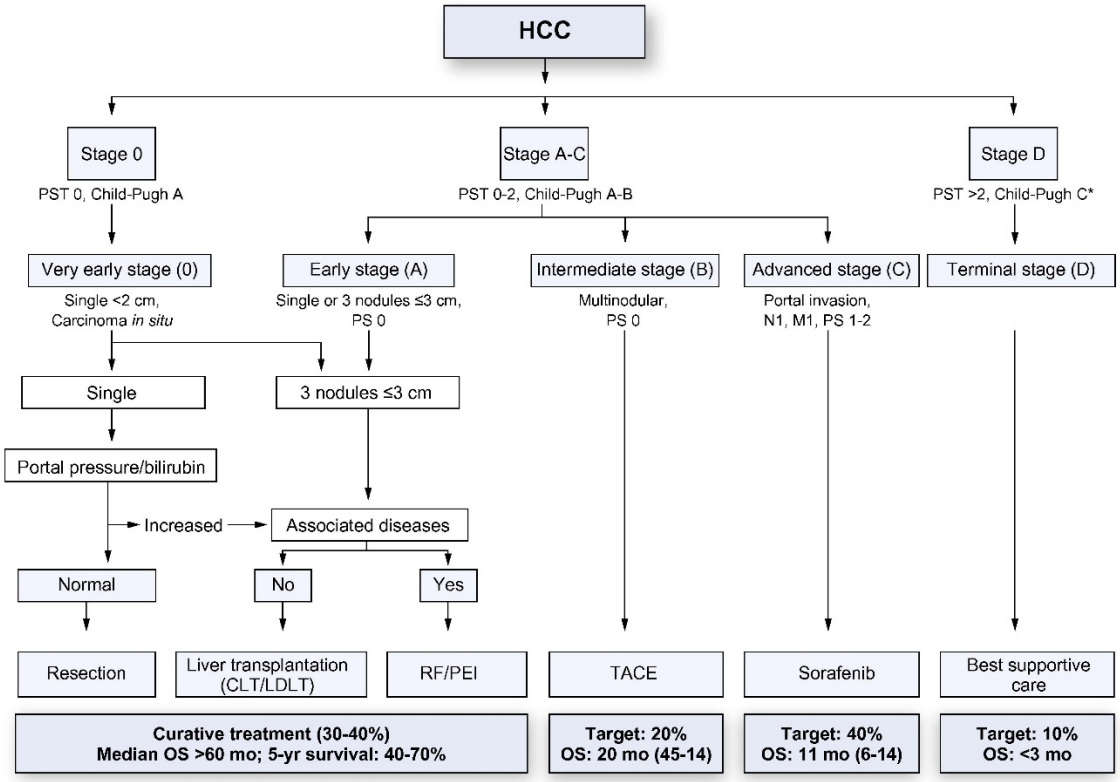
Factor	1 point	2 points	3 points
Total bilirubin (µmon/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
INR	<1.7	1.7 – 2.3	>2.3
Ascites	None	Mild	Moderate-Severe
Encephalopathy	None	Grade I-II	Grade III-IV

A variety of important risk factors for the development of HCC have been identified. Among the most important are hepatitis B carrier state, chronic hepatitis C virus infection, hereditary hemochromatosis and aflatoxin exposure.

2.2 Accepted Clinical Practice

Although there are many staging systems used for HCC, the BCLC staging system is the most widely used prognostic and treatment algorithm for HCC by Canadian clinicians (Figure 1). The staging system includes prognostic factors related to tumour status, liver function and performance status. Per the BCLC algorithm, the prognosis for patients with advanced, unresectable HCC with preserved hepatic reserve is poor with a median overall survival of less than one year.[10]

Figure 1:



HCC is considered to be a chemo-refractory tumour. Sorafenib is an oral multi-tyrosine kinase inhibitor that inhibits the RAF-kinase and VEGFR intracellular kinase pathways. The SHARP trial was a multicenter, European, randomized, double-blinded placebo controlled study in patients with advanced, inoperable HCC and Child-Pugh class A hepatic reserve comparing sorafenib therapy to placebo.[11] The median OS in the sorafenib arm was 10.7 months vs 7.9 months in the placebo arm (HR = 0.69; 95% CI, 0.55–0.87; p < 0.0001). In addition, sorafenib showed a significant benefit in terms of TTP assessed by independent radiological review with a median TTP of 5.5 months for sorafenib and 2.8 months for placebo (p<0.0001). It is of note that this represents a selected patient population – in the SHARP trial 602/902 (67%) of screened patients were eligible for randomization.[11]

The magnitude of survival benefit with sorafenib in SHARP was similar to that demonstrated in a parallel phase III trial conducted in the Asian-Pacific population, in which hepatitis B was the main cause of HCC.[12] In this later trial, the median overall survival was 6.5 months in the sorafenib arm versus 4.2 months in the placebo (HR = 0.68; 95% CI, 0.50–0.93; p = 0.014). The inferior survival outcome observed in this patient population compared with the SHARP investigation, is believed to be due to the fact that the patients had a higher proportion of Hepatitis B and more advanced disease (ECOG 1–2 or metastatic disease). The most common grade 3 drug-related adverse events with sorafenib included hand-foot syndrome and diarrhea which occurred in 8-10.7% and 8-6% respectively. [11,12] Based on these data, sorafenib is currently approved and funded across Canada for the first-line systemic treatment of Child-Pugh A class patients with advanced HCC.

There are currently no standard treatment options for patients beyond sorafenib therapy. Regorafenib is also an oral multikinase inhibitory, structurally similar to sorafenib, and targets a number of angiogenic kinases (including VEGFR), stromal and oncogenic receptor TKIs. In the phase 3 RESORCE trial[1], a survival benefit for regorafenib (160mg p.o. daily for 3 weeks on and 1 week off) was demonstrated in patients progressing after first-line treatment with sorafenib who maintained an ECOG performance status of 0-1 and Child-Pugh A liver function. When compared to placebo, regorafenib was associated with a statistically significant improvement in OS (10.6 mos vs 7.8 mos, HR = 0.63) in addition to increased disease control rates (65% vs 36%). Grade 3-4 adverse events included hypertension (15% vs 5%), hand-foot skin reaction (13% vs 1%) fatigue (9% vs 5%) and diarrhea (3% vs 0%).[1] Despite these adverse events, quality of life as assessed by EQ-5D and FACT-Hep, was not significantly worse with regorafenib compared to placebo. [1]

2.3 Evidence-Based Considerations for a Funding Population

The expected population for regorafenib use would be patients with advanced, inoperable hepatocellular carcinoma with previous sorafenib-treatment failure who have maintained Child-Pugh class A hepatic reserve, based upon the eligibility criteria in the RESORCE trial. Given the associated toxicities of regorafenib, its use would not be considered in patients with an ECOG PS of 2 or worse, or a Child-Pugh score of greater than 6. In a recent analysis in a Japanese population, it is estimated that up to 37% of sorafenib-treated patients may be eligible for second-line regorafenib. [13]

2.4 Other Patient Populations in Whom the Drug May Be Used

There are no currently other HCC patient populations that would be considered for regorafenib therapy.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Canadian Liver Foundation (CLF), provided input on regorafenib (Stivarga) for the treatment of patients with unresectable hepatocellular carcinoma who have been previously treated with sorafenib and their input is summarized below.

CLF gathered information from an online questionnaire that was modelled on the CADTH, CDR and pCODR programs submission template, which was promoted on the CLF website via CLF social media channels and to CLF patient, caregiver and health care professional contacts across the country. The online questionnaire was opened from October 6 to October 22, 2017. The survey was available in English, French and Chinese. CLF received a response from one male patient respondent between the ages of 55-64, however, it is unknown whether he has experience with regorafenib. CLF also included the opinion from a health professional to provide background context in managing the use of the drug under review.

In addition, CLF included additional comments obtained from CLF patient contacts through their national toll-free help line, e-mail support and other online and in-person communication channels. The additional comments from CLF patient contacts were not a direct response to the request for patient feedback through the online questionnaire for this submission. However, CLF felt that patient input from CLF patient contacts provide valuable patient insight to be considered during the review process. In total, the opinion and perspectives of 40 CLF patient contacts were included in this submission.

CLF notes that it was extremely difficult to find direct Canadian patient input for this submission as the number of patients who specifically meet criteria for the drug under review is very limited and the number of patients who have had experience with regorafenib is even more limited. Thus, to supplement the patient input, the CLF included a reference to a global survey of people living with HCC, which was conducted in 2016. The CLF was one of the participating international health charities with Canada, representing one of 13 countries in the survey. The abstract and poster were presented at the World Congress of Gastrointestinal Cancer 2017.

From a patient's perspective, fatigue has the largest impact on quality of life, followed by abdominal pain and nausea. Other factors that impact quality of life include loss of appetite, weight loss, diarrhea, skin disorders and alopecia. CLF notes that HCC is a difficult disease to treat as it is usually a result of a pre-existing and progressive underlying liver disease which means that the patient may already be experiencing the effect of living function impairment, including cirrhosis, jaundice, abdominal pain and ascites. Current treatments for intermediate and advanced stages of HCC include Transarterial Chemoembolization (TACE), systemic therapy such as sorafenib, and best supportive care.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Hepatocellular Carcinoma

CLF reported that liver cancer is the sixth most common cancer worldwide and is one of the fastest rising cancers in Canada. Hepatocellular carcinoma (HCC) is the most common type of cancer accounting for 72% of liver cancer cases in Canada. According to CLF, the increasing prevalence of HCC in Canada is due to the increasing prevalence of late-stage and end-stage liver disease driven by the aging population of individuals with Hepatitis B and Hepatitis C, and the increasing prevalence of non-alcoholic fatty liver disease (NAFLD).

According to the results of the Global Survey of People Living with HCC, of the 256 respondents, fatigue had the biggest impact on quality of life followed by abdominal pain and nausea. Survey respondents also indicated that appetite loss, weight loss, diarrhea, skin disorders and alopecia impacted their quality of life. Survey respondents living with HCC also described the mental and emotional impact of having HCC. Patients with HCC describe their disease experience with words such as fear, worry, shock, scared and sad.

Below are quotes from patient contacts related to their experiences with HCC:

"I have no social life any more. I cannot go anywhere for fear of falling asleep. I need to wear a diaper due to incontinence and feel very uncomfortable about that. I am tired all the time. – CLF patient contact #1

"My worst symptom is pain and being uncomfortable all the time. Mornings are the worst. I feel dazed and confused. I can hardly eat anything. When I eat, I throw up right away. But worst of all is knowing that there is nothing that can be done for me. I am devastated. The knowledge that I will die and leave my wife and my kids without a father is unbearable." – CLF patient contact #3

Patients with HCC also describe that they feel they are a burden to their family:

"I cannot help and participate in daily activities. I am a burden on my family. They have to do everything for me. I am in pain all the time. I cannot sleep at night and am groggy and confused during the day." – CLF patient contact #2

"I am lucky to live in the same city where I am undergoing treatment. My wife accompanies and drives me to appointments. Taking public transit is not possible for me. Hospital parking is too expensive. I do not work anymore and my wife had to take time off her work to care for me. I am a burden to my family and society." – CLF patient contact #5

3.1.2 Patients' Experiences with Current Therapy for Hepatocellular Carcinoma

CLF states that liver cancer patients have more options for treatment if diagnosed early. These include surgical resection, living transplant, ablation and chemoembolization. However, liver cancer is typically not diagnosed early, as patients often do not show symptoms of liver cancer until the later stages of liver cancer.

According to CLF, treatment with HCC depends on the stage and the speed of tumour growth. Intermediate and advanced stages of HCC are treated with palliative intent including transarterial chemoembolization (TACE) – therapy combining chemotherapy with embolization, or systemic targeted therapy such as sorafenib. CLF states that the only systemic therapy available in Canada is sorafenib, and that there is no other second line treatment available for advanced stage of HCC. Best supportive care is the only treatment option at the final stage of disease as there are no other treatment options currently available.

According to results of the Global Survey of People Living with HCC, the most common form of treatment for patients with HCC include TACE followed by liver ablation, surgery and liver transplant. Patient input indicated that TACE was the most challenging treatment to undergo, followed by systemic treatment with sorafenib. Furthermore, patients whose most recent treatment was sorafenib were more likely to rate their current quality of life as poor.

The most common side effects of current treatment as reported by respondents included pain, low energy, pruritus (itching), vomiting, light-headedness and abdominal pain.

Below are quotes from patients related to challenges with current therapy:

"I am currently being treated for my HCC and the pain is the worst. I am in pain all the time." – CLF patient contact #4

"I feel better after treatment, and was hopeful for a while that it will work out. My energy level has increased, even the itching (pruritus) got better. But then my doctor told me that the treatment has stopped working and I just wanted to die right there." – CLF patient contact #6

"Although I had surgery with the intent of getting rid of the cancer, I had to undergo, subsequent to that, first a round of radio frequency ablation (RFA) and then trans-arterial chemoembolization (TACE) twice in the last several months. TACE has a number of side effects in the first 24 hours including vomiting, light-headedness and abdominal pain. All those symptoms gradually come down and disappear in a matter of days." – CLF patient contact #7

3.1.3 Impact of Hepatocellular Carcinoma and Current Therapy on Caregivers

Although the online questionnaire was open to caregivers, no caregivers of patients with HCC that responded to the CLF survey.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Regorafenib

According to CLF, regorafenib has been used in a very limited number of clinical settings in Canada and only in a few patients. As such, feedback about experiences with regorafenib is limited.

According to CLF there are currently no other treatment options for patients who have been progressed on treatment with sorafenib. Patient input reported that the treatment intent of regorafenib is not curative; however it fulfills a current unmet need of having an additional second line systemic treatment for HCC in the palliative phase of the disease with an improvement in 3 additional months of survival.

Below are quotes from patients related to their expectations for treatment:

"*I want a treatment which will allow me to spend time with my family and friends. I want to be able to function during the day, care for myself such as take a shower on my own, dress myself, and cook for myself." – CLF patient contact #8*

"I am looking forward to receiving the new treatment. Apart from that, a spiritual commitment has helped me shed my constant worries and anxieties." – CLF patient contact #9

In reviewing the global application of regorafenib, CLF stated that the United States National Comprehensive Cancer Network (NCCN) has identified regorafenib as second line treatment for HCC and Europe will soon be updating its clinical practice guidelines.

CLF affirms that HCC survival prognosis is poor, especially if diagnosed at or progressed to an advanced stage of the disease. The possibility of adding a new treatment option at the advanced stage of HCC offers hope to patients and their families who would otherwise have no other options.

3.3 Additional Information

The CLF believes that patients and their physicians should have access to a broad range of treatment options regardless of geographic location, financial status, and treatment status or disease severity in order to ensure the best possible outcomes. It is up to the physicians to make individual treatment recommendations based on the needs of their patients.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Provides an option for patients who have failed sorafenib

Economic factors:

- Additional resources to monitor and treat serious adverse events.

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that there are no current treatments for patients with hepatic cellular carcinoma who have failed sorafenib.

4.2 Factors Related to Patient Population

PAG identified that patients who with unresectable hepatic cancer have no other options after failing treatment with sorafenib. Regorafenib is an additional line of treatment. PAG noted that very few patients would be eligible for regorafenib as the clinical trial only enrolled patients who tolerated sorafenib (e.g., >400 mg/day for past 20 of 28 days) and with Child-Pugh A liver function.

PAG identified that sorafenib is funded for patients with Child-Pugh A or B. PAG is seeking data on the use of regorafenib in patients with Child-Pugh B.

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.

4.3 Factors Related to Dosing

The recommended dose of 160mg once daily for the first 21 days with 7 days off in each 28 day cycle may be confusing for some patients. In addition, regorafenib should be taken with a meal with specific fat and calorie composition which may be difficult for some patients.

PAG noted that regorafenib are available in one tablet strength of 40mg, which would enable dose reduction without drug wastage. At full dose, pill burden is a concern as patients would need to take four tablets.

4.4 Factors Related to Implementation Costs

PAG noted that the multiple serious adverse events including severe hepatic toxicities and

hypertension. Additional resources would be required to monitor and manage these serious adverse events.

4.5 Factors Related to Health System

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

4.6 Factors Related to Manufacturer

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Four clinician inputs were provided: three from individual oncologists and one joint clinician group input from four oncologists at Cancer Care Ontario.

The clinicians providing input identified that there is a need for second line treatment for HCC patients who have been treated with sorafenib in the first line as there are currently no treatment options available.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Hepatocellular Carcinoma

The clinicians providing input indicated that there is no standard of care for second line HCC, typically best supportive care or a clinical trial is offered following progression on sorafenib.

5.2 Eligible Patient Population

According to the clinician input, the incidence of liver cancer has increased between 1992 and 2013 in Canada due to alcohol consumption, obesity and immigration from endemic areas with Hepatitis B and Hepatitis C infection. The clinicians providing input stated that the incidence rates are expected to continue to rise. Each year, approximately 1,200 patients die of advanced HCC. Patients who are not candidates for local liver directed therapies are evaluated for systemic palliative therapy consisting of sorafenib.

The clinicians providing input identified that the proportion of advanced HCC patients who are eligible for first-line sorafenib is small, and subsequently the proportion of patients who would be eligible for second-line treatment with preserved liver function (Childs Pugh A) and good performance status (ECOG 0-1) is even smaller.

The clinicians providing input also noted that 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.

5.3 Identify Key Benefits and Harms with Regorafenib

The clinicians providing input noted that there is no current standard of treatment in second line palliative care after sorafenib and that survival is poor. They noted that treatment with regorafenib prolongs survival by approximately three months based on the RESOURCE trial.

The clinicians providing input noted that patients treated with regorafenib will need to be closely monitored given the risk of toxicities including: fatigue, diarrhea, hypertension rash/hand foot syndrome. It was noted that these toxicities can be monitored and managed by dose reductions as needed.

One group of clinicians providing input indicated that the reported toxicity is not as severe as expected based on the CORRECT trial compared regorafenib to placebo for colorectal cancer.

5.4 Advantages of Regorafenib Over Current Treatments

The clinicians providing input noted that there is a significant unmet need for second-line treatment in patients previously treated with sorafenib as there are no other treatments available. There are currently no known effective treatments for patients with advanced HCC who progress on sorafenib. One group of clinicians providing input noted that there is a survival

benefit of regorafenib compared to supportive care.

One clinician noted that regorafenib should be a second line standard of care for patients that are refractory to sorafenib, with an ECOG status 0-1, and Child-Pugh A liver function.

5.5 Sequencing and Priority of Treatments with Regorafenib

The clinicians providing input identified that regorafenib should be considered for use in patients following radiological progression on sorafenib.

One group clinician input noted that the indication for regorafenib may be a transient, as there are currently immunotherapy trials underway that may change sequencing.

5.6 Companion Diagnostic Testing

Non applicable.

5.7 Additional Information

Based on experience with regorafenib in patients with advanced HCC at one centre, one clinician providing input has noted that patients with HCC who have been treated with regorafenib appear to tolerate regorafenib better in comparison to patients with advanced colorectal cancer who have been treated with regorafenib.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of regorafenib in patients with unresectable HCC who have been previously treated with sorafenib.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP 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. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3. Selection Criteria for the Resorce Trial

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators	Outcomes

Published or unpublished RCTs
 	
In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of regorafenib should be included.
	Patients with unresectable hepatocellular carcinoma (HCC) who have been previously treated with sorafenib
	
	<u>Subgroups:</u>
	• Age (<65 vs. ≥ 65 years)
	• ECOG (0 or 1 vs. 2)
	• Race (White vs. Asian vs. Black vs. Other)
	• Geographic location (Rest of the world vs Asian)
	• α-fetoprotein (≥400 ng/mL or <400 ng/mL)
	• Child-Pugh class
	  ○ A
	  ○ B
	• BCLC stage
	  ○ A (early)
	  ○ B (intermediate)
	  ○ C (advanced)
	• Liver cirrhosis (investigator assessed)
	• Aetiology of HCC
	  ○ Hepatitis B
	  ○ Alcohol use
	  ○ Hepatitis C
	  ○ Unknown
	  ○ Non-alcoholic steatohepatitis
		Regorafenib	BSC*
			
			Nivolumab**
				<u>Primary</u>
				• **OS**
				• **PFS**
				• **HRQoL**
				
				<u>Secondary</u>
				• ORR
				• DOR
				• DCR
				
				<u>Safety</u>
				• AEs
				• SAEs
				• WDAEs
				• AEs of interest
				  ○ Hand-foot syndrome
				  ○ Fatigue

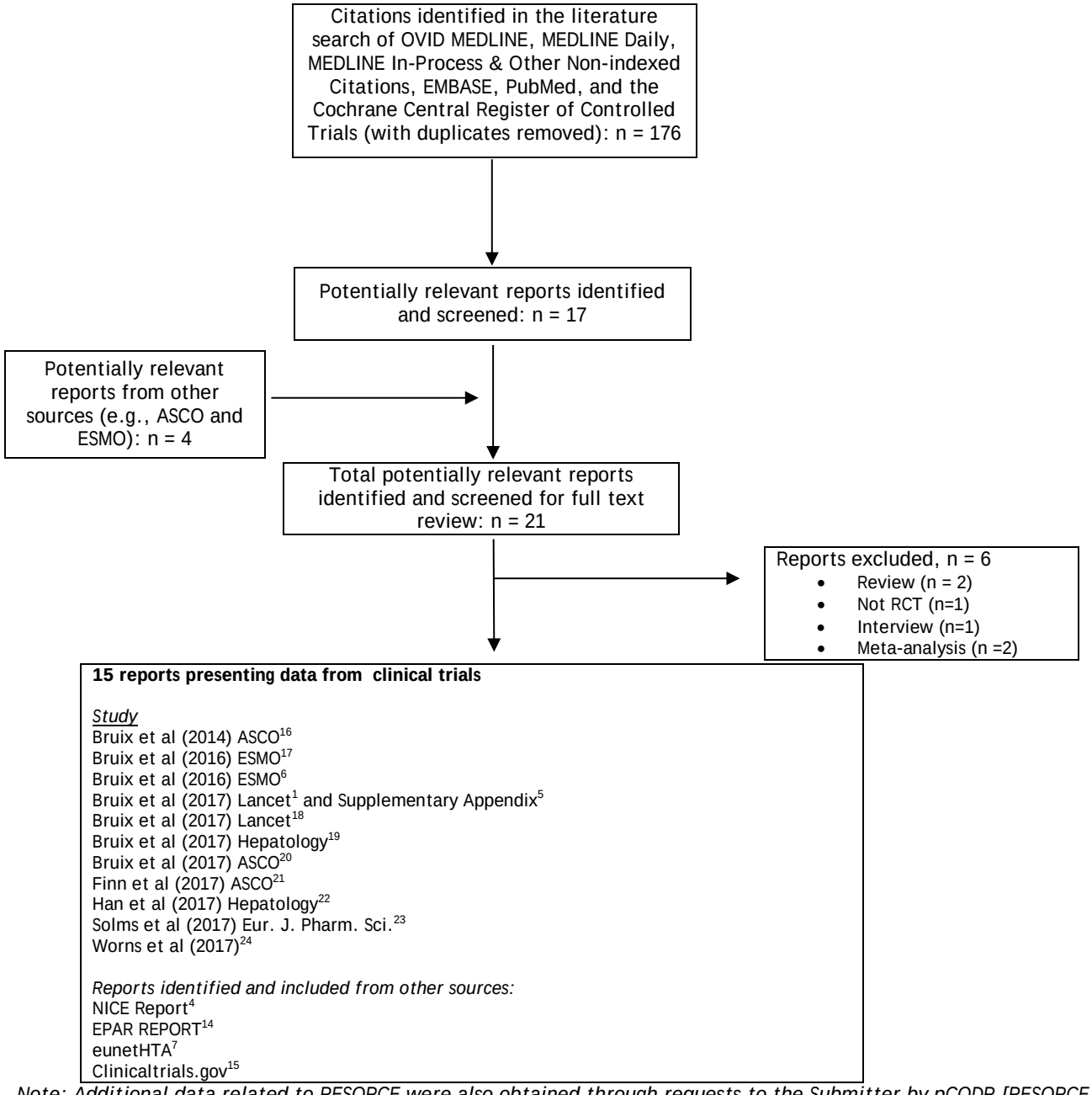
Abbreviations: MUC = metastatic urothelial carcinoma; HRQoL=Health related quality of life; RCT=randomized controlled trial; SAE=serious adverse events; AE=adverse events; WDAE=withdrawals due to adverse events; DCR=disease control rate; ORR=objective response rate; DOR=duration of response; ORR = overall response rate; BSC = best supportive care				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions). ** Not currently funded for this indication in Canada				

6.3 Results

6.3.1 Literature Search Results

Of the 176 potentially relevant reports identified, one study (RESORCE), reported in 15 citations, was included in the pCODR systematic review. [1,4-7,14-24] Six reports were excluded because one was not an RCT, one was an interview, two were reviews and two were meta-analyses. Additional reports related to the RESORCE study were obtained from the Submitter.[2,3,6,25]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to RESORCE were also obtained through requests to the Submitter by pCODR [RESORCE Protocol[2] and Checkpoint Responses[25] and Bruix et al (2017)[3], Bruix et al (2016)[6]]

6.3.2 Summary of Included Studies

The pCODR systematic review included one phase 3 RCT that assessed the safety and efficacy of regorafenib in patients with unresectable HCC who have been previously treated with sorafenib (RESORCE; N = 573).

6.3.2.1 Detailed Trial Characteristics

a) Trial

Trial Design

RESORCE was a global, multi-centre, double-blind, placebo-controlled, randomized phase 3 trial (Table 4 and Table 5).[1] The objective of the trial was to compare the treatment effects of regorafenib as compared to placebo in patients with HCC who have been previously treated with sorafenib. The trial was funded by Bayer and it conducted in 21 countries within 152 sites, including Canada.[1]

Table 4: Summary of trial characteristics of the RESORCE

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
RESORCE **Other identifiers** NCT01774344 **Characteristics** Global, multicentre, placebo-controlled, open-label, phase 3 study **Sample size** Randomized: 573 Treated: 567 **Locations** 21 countries within 152 sites **Start date:** 05/2013 to 12/2015 **Primary data cut-off:** 29-Feb-2016 **Secondary data cut-off:** 23-Jan-2017 **Final data-cut off:** Ongoing **Sponsor:** Bayer	**Key Inclusion Criteria** • Histological or cytological confirmation of HCC or non-invasive diagnosis of HCC as per AASLD criteria in patients with a confirmed diagnosis of cirrhosis. • BCLC stage Category B or C that cannot benefit from treatments of established efficacy with higher priority. • Failure to prior treatment with sorafenib. • Tolerability of prior treatment with sorafenib. • Liver function status Child-Pugh Class A. • Local or loco-regional therapy of intrahepatic tumor lesions. • ECOG of 0 or 1. • Adequate bone marrow, liver and renal function. • GFR >/= 30 ml/min/1.73 m^2 according to the Modification of diet in renal disease study equation. • At least one uni-dimensional measurable lesion by CT scan or MRI according to RECIST 1.1 or mRECIST. • Life expectancy of at least 3 months. **Key Exclusion Criteria** • Sorafenib treatment within 2 weeks of randomization. • Prior systemic treatment for HCC, except sorafenib. • Permanent discontinuation of prior sorafenib therapy due to sorafenib related toxicity. • Known history or symptomatic metastatic brain or meningeal tumors. • Uncontrolled hypertension.	**Arm A** Regorafenib (160mg/d) for the first 3 weeks of a 4 week cycle **Arm B** Matching placebo with BSC for the first 3 weeks of a 4 week cycle	**Primary** OS **Secondary** PFS ORR DCR HRQoL Safety

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Uncontrolled ascites. • Ongoing infection > Grade 2. • Hepatitis B is allowed if no active replication is present. Hepatitis C is allowed if no antiviral treatment is required. • Clinically significant bleeding NCI-CTCAE version 4.0 Grade 3 or higher. • Arterial or venous thrombotic or embolic events, deep vein thrombosis or pulmonary embolism within 6 months before the start of study medication. • ILD with ongoing signs and symptoms at the time of screening.		

Abbreviations - **HCC:** hepatocellular carcinoma; **AASLD:** American Association for the Study of Liver Diseases; **BCLC:** Barcelona Clinic Liver Cancer; **ECOG:** Eastern Cooperative Oncology Group Performance Status; **GFR:** Glomerular filtration rate; **CT:** computed tomography; **MRI:** magnetic resonance imaging; **NCI-CTCAE:** National Cancer Institute - Common Terminology Criteria for Adverse Events; **ILD:** Interstitial lung disease; **BSC:** best supportive care; **OS:** overall survival; **PFS:** progression-free survival; **ORR:** objective response rate; **DCR:** disease control rate; **HRQoL:** health-related quality of life

Table 5: Select quality characteristics of the RESORCE trial

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
RESORCE	Regorafenib VS Placebo and BSC	OS	560[A]	573	IVRS, stratified[B]	Yes	Double -blind[C]	Yes	Yes	No	Yes

Abbreviations: BSC = best supportive care, OS = overall survival

[A] The trial required a sample size of 560 patients, representing 370 deaths, to have 90% power to detect a hazard ratio (HR) of 0.70 using a one-sided level of 0.025.[2]

[B] Randomization was stratified by geographical region (Asia versus the rest of the world), ECOG performance status (0 versus 1), AFP levels (<400 ng/mL versus ≥400 ng/mL), extrahepatic disease (presence versus absence) and macrovascular invasion (presence versus absence).

[C] Investigators, patients and sponsors were blinded to treatment allocation. Regorafenib and placebo were identical in appearance. Patients took four doses of matching placebo, which was similar to the dosing schedule of regorafenib. All of the study medication used in the trial was labelled with a unique drug pack number. The unique packaging number was pre-printed on each bottle and assigned to patients using the IVRS.

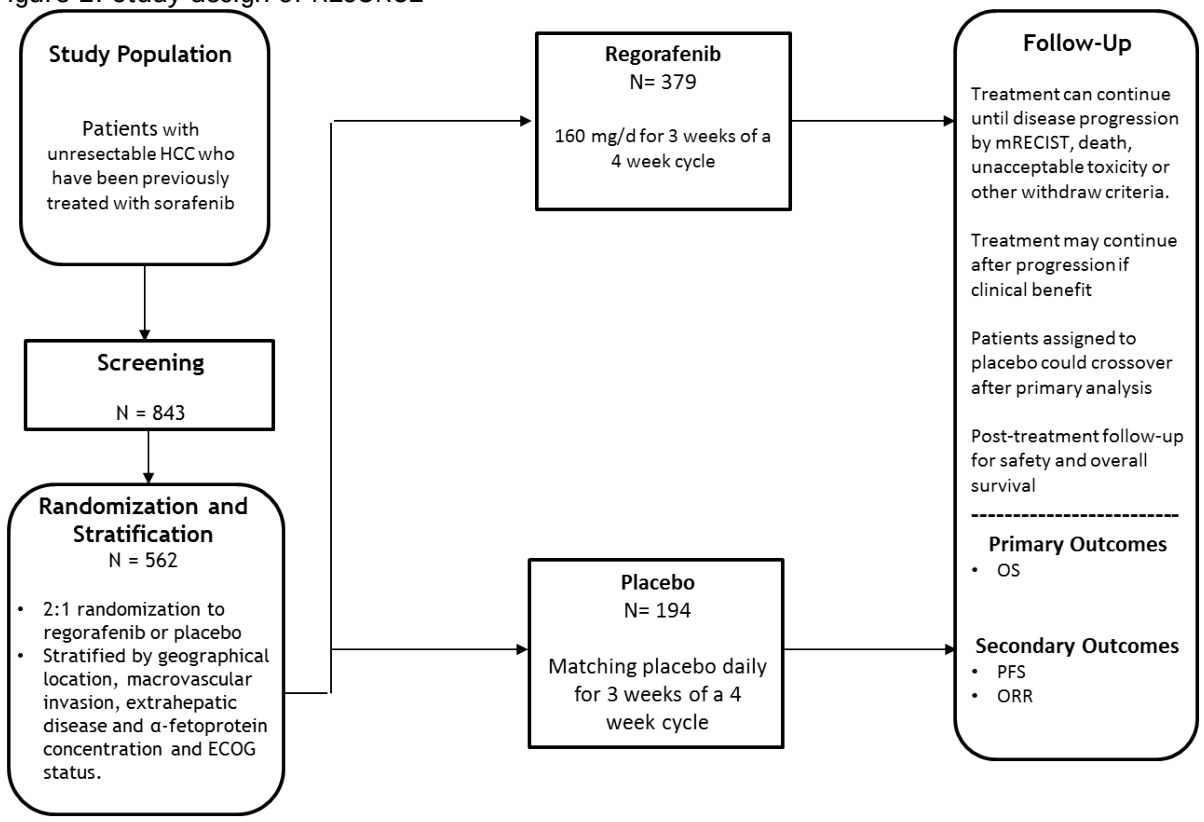
[D] The primary analysis was planned after 370 deaths had occurred, which was performed on 29-Feb-2016.

The RESORCE trial included patients aged 18 years and older who had a histological or cytological confirmation of HCC or non-invasive diagnosis of HCC using AASLD criteria in those with a confirmed diagnosis of cirrhosis; BCLC stage Category B or C that cannot benefit from treatments

of established efficacy with higher priority such as resection, local ablation, chemoembolization or systemic sorafenib; failure to prior treatment with sorafenib, which was defined as documented radiological progression according to the radiology charter; tolerability of prior treatment with sorafenib, which was defined as not less than 20 days at a minimum daily dose of 400 mg QD within the last 28 days prior to withdrawal; Child-Pugh Class A liver function; local or loco-regional therapy of intrahepatic tumor lesions must have been completed ≥ 4 weeks before first dose of study medication; ECOG performance status of 0 or 1; adequate bone marrow, liver and renal function; GFR ≥ 30 ml/min/1.73 m^2 according to the Modification of diet in renal disease study equation; at least one uni-dimensional measurable lesion by CT scan or MRI according to RECIST 1.1 or mRECIST; and a life expectancy of at least three months.[2]

Patients were excluded if they had sorafenib treatment within two weeks of randomization; prior systemic treatment for HCC, except sorafenib; permanent discontinuation of prior sorafenib therapy due to sorafenib related toxicity; known history or symptomatic metastatic brain or meningeal tumors; uncontrolled hypertension (i.e. systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management); uncontrolled ascites, which was defined as not easily controlled with diuretic or paracentesis treatment; ongoing infection > Grade 2 according to NCI-CTCAE v. 4.0; hepatitis B was allowed if no active replication is present and hepatitis C was allowed if no antiviral treatment is required; clinically significant bleeding NCI-CTCAE version 4.0 Grade 3 or higher within 30 days before randomization; arterial or venous thrombotic or embolic events, deep vein thrombosis or pulmonary embolism within 6 months before the start of study medication; and ILD with ongoing signs and symptoms at the time of screening.[2]

Figure 2: Study design of RESORCE



Abbreviations: HCC = hepatocellular carcinoma ; PFS = progression-free survival; OS = overall survival; ORR = objective response rate; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; ECOG = Eastern Cooperative Oncology Group

Data Source: METHODS pCODR

Figure 2 represents the study design of RESORCE. The trial consisted of two phases, the treatment phase and the follow-up phase.[2] These phases will be described in more detail, more specifically:

Treatment Phase[2]

- Eligible patients were assigned their treatment group using an interactive voice-response system and a computer-generated randomisation list that was prepared by the funder
- Patients were randomized on a 2:1 ratio to receive either regorafenib or placebo
- Randomization was stratified by geographical region (Asia versus the rest of the world), ECOG performance status (0 versus 1); AFP levels (<400 ng/mL versus ≥400 ng/mL), extrahepatic disease (presence versus absence) and macrovascular invasion (presence versus absence)
- Patients were assessed for tumour progression every 6 weeks for 8 cycles and then every 12 weeks thereafter
- Other investigational antitumor drugs, antineoplastic chemotherapy, hormonal therapy or immunotherapy were not permitted
- Treatment continued until disease progression using the mRECIST criteria, clinical progression (i.e. ECOG performance score of ≥ 3 or symptomatic deterioration, including increased liver function tests), death, unacceptable toxicities, withdraw consent or investigator decision.

- Treatment beyond progression was permitted if investigator judged that the patient would experience a clinical benefit
    - Clinical benefit was defined as the absence of deterioration of ECOG status (e.g. ECOG should not deteriorate from baseline status: 0 to 2 or higher, from 1 to 3 or higher) and/or absence of deterioration of liver function (jaundice, uncontrolled ascites, encephalopathy).
- Patients receiving placebo could cross-over and received regorafenib after the primary analysis

Follow-up Phase[2]

- Overall survival data was collected every month until death or the study closed
- Other post-discontinuation information was also documented, such as: date of disease progression, documentation of any subsequent anti-cancer and the date of death

Statistical Analysis

Sample size: The trial required a sample size of 560 patients, representing 370 deaths, to have 90% power to detect a HR of 0.70 using a one-sided level of 0.025. [2] As a results of a protocol amendment, the trial increased the sample size from 530 to 560 patients.[2] This was done to allow 150 patients from China to be recruited in the study and adhere to the 40% cap for Asian patients.

Outcomes: The primary efficacy endpoint assessed in the RESORCE trial was OS. Secondary endpoints included: PFS, TTP, ORR and DCR. It was reported in the eunetHTA Report that ORR and DOR were descriptive only.[7] Tertiary efficacy outcomes were DOR, duration of stable disease, HRQoL and safety.

Analysis Sets: The efficacy set used an ITT analysis which included all randomized patients. The safety set consisted of patients who received at least one dose of the study medication.

Interim Analysis: The trial was designed to perform one interim futility analysis. The interim analysis was planned when 111 deaths occurred and a one-sided overall beta was used for OS. However, an interim analysis was not performed.[4] The interim analysis was conducted by an independent DMC who used a stopping boundary.

Missing data: Missing data or unevaluable tumor assessments were not used in the efficacy analyses.[14] Furthermore, no imputation was performed for missing lesion or tumor response assessments.[14]

Multiplicity: It was reported in the eunetHTA Report that the trial did not implement hierarchical testing or other multiplicity analyses to control for type 1 error.[7]

Protocol Amendments

Five global amendments were made to the protocol, more specifically:[14]

Amendment #1 (02-May-2013) - clarification of the inclusion and exclusion criteria.

Amendment #2 (13-Dec-2013) - increase the time from last sorafenib treatment at randomization from 8 to 10 weeks, clarification of exclusion criteria and add continuation of tumour evaluation for patients stopping treatment due to other reasons than disease progression.

Amendment #3 (11-Nov-2014) - increase the sample size from 530 to 560 to allow for the inclusion of 150 patients from China which adhered to the 40% cap for Asian patients and clarification of the inclusion criteria.

Amendment #4 (02-Nov-2015) - remove the second interim analysis but the second interim analysis would have been conducted before full accrual.

Amendment #5 (1-Dec-2015) - add information on the interaction of regorafenib with neomycin, breast cancer resistance protein UGT1A1, UGT1A9, P-glycoprotein substrates and bile salt-sequestering agents.

b) Populations

Baseline characteristics for patients enrolled in RESORCE are presented in Table 6. The baseline characteristics appeared to be balanced across all treatment groups. Although the trial enrolled patients with Child-Pugh A, there were 11 patients with Child-Pugh B. It was stated in Bruix et al (2017) that these patients progressed to Child-Pugh B after screening and were included in the ITT population.[1] In addition, Child-Pugh class was missing for one patient in the regorafenib group.[1] 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.[1]

Table 6: Baseline characteristics of patients enrolled in RESORCE

	15982 RESORCE (FAS)	
	Placebo N=194	Regorafenib N=379
Number of Target Lesions (RECIST [a])		
1	31 (16.0%)	67 (17.7%)
2	88 (45.4%)	175 (46.2%)
3	37 (19.1%)	68 (17.9%)
3-5	--	--
4	26 (13.4%)	43 (11.4%)
5	12 (6.2%)	19 (5.0%)
6-10	--	--
Time since Initial diagnosis to Start of Study Treatment (weeks)		
n	173	335
Mean (±StD)	115.9 (±94.9)	127.3 (±121.3)
Median (range)	87.9 (10.9-531.1)	92.7 (8.7-1129)
Time since the First Progression [b] to Start of Study Treatment (weeks)		
n	180	338
Mean (±StD)	52.8 (±55.2)	64.4 (±75.0)
Median (range)	34.2 (1.4-326.4)	38.9 (1.0-486.9)
Type of the First Progression [b] Assessment		
Measurement proven	180 (92.8%)	334 (88.1%)
Clinical judgment	5 (2.6%)	13 (3.4%)
Pathology proven	6 (3.1%)	16 (4.2%)
Measurement and pathology proven	3 (1.6%)	13 (3.4%)
TNM stage at initial diagnosis		
Stage I	38 (19.6%)	83 (21.9%)
Stage II	44 (22.7%)	89 (23.5%)
Stage IIIA	32 (16.5%)	65 (17.2%)
Stage IIIB	22 (11.3%)	39 (10.3%)
Stage IIIC	2 (1.0%)	12 (3.2%)
Stage IV	--	--
Stage IVA	12 (6.2%)	22 (5.8%)
Stage IVB	30 (15.5%)	47 (12.4%)
Unknown	--	--
TNM stage at study entry		
Stage I	0	2 (0.5%)
Stage II	12 (6.2%)	27 (7.1%)
Stage IIIA	16 (8.3%)	36 (9.5%)
Stage IIIB	18 (9.3%)	41 (10.8%)
Stage IIIC	0	5 (1.32%)
Stage IVA	17 (8.76%)	22 (5.80%)
Stage IV	--	--
Stage IVB	130 (67.0%)	245 (64.6%)
Unknown	--	--

			15982 RESORCE (FAS)	
			Placebo N=194	Regorafenib N=379
HCC diagnosis per AASLD[c] [n(%)]	Biopsy		124 (63.9%)	264 (69.7%)
	Non-invasive	Lesion >2 cm and 1 dynamic imaging technique	60 (30.9%)	98 (25.9%)
		Lesion 1-2 cm and two coincidental dynamic techniques	10 (5.2%)	16 (4.2%)
		Missing	0	1 (0.3%)
Hepatitis B Surface Antigen at Study Entry				
Negative			121 (62.4%)	244 (64.4%)
Positive			69 (35.6%)	125 (33.0%)
Hepatitis C Antibody at Study Entry				
Negative			149 (76.8%)	290 (76.5%)
Positive			41 (21.1%)	72 (19.0%)
Etiology of HCC [d]				
Alcohol use			55 (28.4%)	90 (23.8%)
Hepatitis B			73 (37.6%)	143 (37.7%)
Hepatitis C			41 (21.1%)	78 (20.6%)
Genetic / Metabolic			6 (3.1%)	16 (4.2%)
Non-alcoholic steatohepatitis (NASH)			13 (6.7%)	25 (6.6%)
Unknown			32 (16.5%)	66 (17.4%)
Other			4 (2.1%)	12 (3.2%)
BCLC stage at study entry				
A (Early Stage)			0	1 (0.3%)
B (Intermediate Stage)			22 (11.3%)	53 (14.0%)
C (Advanced Stage)			172 (88.7%)	325 (85.8%)
Alpha-fetoprotein (AFP) (ng/mL) (CRF)				
Missing			--	--
< 400 ng/mL			107 (55.2%)	217 (57.3%)
≥ 400 ng/mL			87 (44.9%)	162 (42.7%)
Macrovascular invasion (CRF)				
Absence			140 (72.2%)	269 (71.0%)
Presence			54 (27.8%)	110 (29.0%)
Extrahepatic disease (CRF)				
Absence			47 (24.2%)	114 (30.1%)
Presence			147 (75.8%)	265 (69.9%)
Macrovascular invasion and extrahepatic spread status (CRF)				
Macrovascular invasion present, but not extrahepatic spread			15 (7.7%)	39 (10.3%)
Extrahepatic spread present, but not macrovascular invasion			108 (55.7%)	194 (51.2%)
Both conditions present			39 (20.1%)	71 (18.7%)
Both conditions not present			32 (16.5%)	75 (19.8%)
Child-Pugh Score				
Missing			0	1 (0.3%)
5			118 (60.8%)	244 (64.4%)
6			70 (36.1%)	129 (34.0%)
7 [e]			5 (2.6%)	5 (1.3%)
8			1 (0.5%)	0
Child-Pugh Score				
Missing			0	1 (0.3%)
A			188 (96.9%)	373 (98.4%)
B [e]			6 (3.1%)	5 (1.3%)
Liver Cirrhosis (Medical History)				
No			50 (25.8%)	94 (24.8%)
Yes			144 (74.2%)	285 (75.2%)

Abbreviations: AASLD = American Association for Study of Liver Disease; AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer ; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; HCC = hepatocellular carcinoma; mRECIST = modified RECIST for HCC; NASH = non-alcoholic steatohepatitis; R0 = Complete tumor resection with all margins histologically negative; R1 = Incomplete tumor resection with microscopic surgical resection margin involvement (margins grossly uninvolved); R2 = Incomplete tumor resection with gross residual tumor that was not resected (primary tumor, regional nodes, macroscopic margin involvement); RECIST = Response Evaluation Criteria in Solid Tumors; StD = standard deviation; TNM = tumor, node, metastasis

a; mRECIST evaluation criteria for Study 15982.

b; "First progression" did not necessarily mean first progression while on sorafenib.

c; Non-invasive diagnosis of HCC was documented only when diagnosis was not proven by biopsy.

d; Subjects may have had more than one etiology of HCC.

e; The information in this table is based on the last observations on or before the first study drug intake. Changes may have occurred between the screening of subjects and their first day of study drug intake. During the study it was found that 3 subjects were on anticoagulant medication which, according to the study protocol, led to Child-Pugh classification of B.Baseline data were taken from the non-missing observation before or on the first day of study drug intake. Baseline values for ECOG, AFP, macroscopic vascular invasion and extrahepatic spread status collected on CRF were based on randomization date.

		Placebo N=194 (100%)	Regorafenib N=379 (100%)
Time (days) from start of sorafenib to start of study medication	n	193	374
	N missing	1	5
	mean (±StD)	380.6 (324.4)	385.3 (344.6)
	median (range)	279 (56-2217)	261 (53-2204)
Time (days) from progression [a] while on sorafenib to start of study medication [b]	n	193	374
	N missing	1	5
	mean (±StD)	54.6 (53.1)	55.0 (42.7)
	median (range)	43.0 (8-522)	42.5 (4-299)
Time (days) from permanent discontinuation of sorafenib to start of study medication	n	193	374
	N missing	1	5
	mean (±StD)	31.1 (14.6)	31.5 (14.8)
	median (range)	26.0 (15-71)	26.5 (14-78)
Time (days) from start of sorafenib to progression while on sorafenib	n	193	374
	N missing	1	5
	median (95% CI)	217 (176, 266)	217 (184,245)
	(range)	(19-2185)	(1-2183)

Data Source: EPAR Report[14]

Bruix et al (2017) reported that the duration of sorafenib and time to progression prior to receiving the study medication was well balanced between the two treatment groups. That the median time on sorafenib was 7.8 months (IQR: 4.2 to 14.5) in the regorafenib group and 7.8 months (IQR: 4.4 to 14.7) in the placebo group.[1] The median time from progression was also similar between groups (regorafenib: 1.4 months [IQR: 0.9 to 2.3] and placebo: 1.4 months [IQR: 0.9 to 2.2]).[1] Likewise, the median time to sorafenib discontinuation was also similar between the two treatment groups (0.9 months [IQR: 0.7 to 1.3] for both groups).[1]

c) Interventions

Treatment Dosing Schedule

The dosing schedule for the two treatment arms in the RESORCE trial are presented below:

- *Regorafenib and BSC*
  - Regorafenib at an oral dose of 160 mg every day for 3 weeks of a 4 week cycle plus BSC. Each 160 mg dose consisted of four 40 mg tablets.
  - BSC included any concomitant medication or treatment, such as: antibiotics, analgesics, radiation therapy for pain control (i.e. limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immunotherapy.
- *Placebo and BSC*
  - Placebo at an oral dose of four matching placebo tablets for 3 weeks of a 4 week cycle plus BSC.
  - BSC included any concomitant medication or treatment, such as: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemo/hormonal/immunotherapy.

Dose delays, reductions or modifications

Dose interpretations and reductions were permitted for patients receiving regorafenib to manage toxicities. Regorafenib was reduced from 160 mg to 120 mg and to 80mg.[14] Once toxicities were resolved, regorafenib could be re-escalated to a maximum of 160 mg.[14] However, if a patient required further dose reductions then treatment would be discontinued.

d) Patient Disposition

Patient disposition for the RESORCE trial is summarized in Figure 3. In total, there were 573 patients enrolled in the trial and included in the ITT population. Patients were randomized to either regorafenib (N=379) or placebo (N=194).[1] Overall, six patients were not treated with their assigned therapies ($N_{regorafenib}$ = 5 and $N_{placebo}$ = 1) (Figure 3).[1]

At the 29-Feb-2016 cut-off date, most patients had discontinued from their assigned therapies. [1] Here, 83% of patients in the regorafenib group and 95% in the placebo group had discontinued.[1] The most common reasons for termination in the regorafenib group were radiological progression (48.2%), adverse events associated with disease progression (18.1%), adverse events not associated with disease progression (15.2%) and withdraw by patient (8.4%). On the other hand, patients were more likely to discontinue placebo therapy because of radiological disease progression (65.0%), adverse events associated with disease progression (15.3%).[1]

Figure 3: Patient disposition for patients enrolled in the RESORCE trial

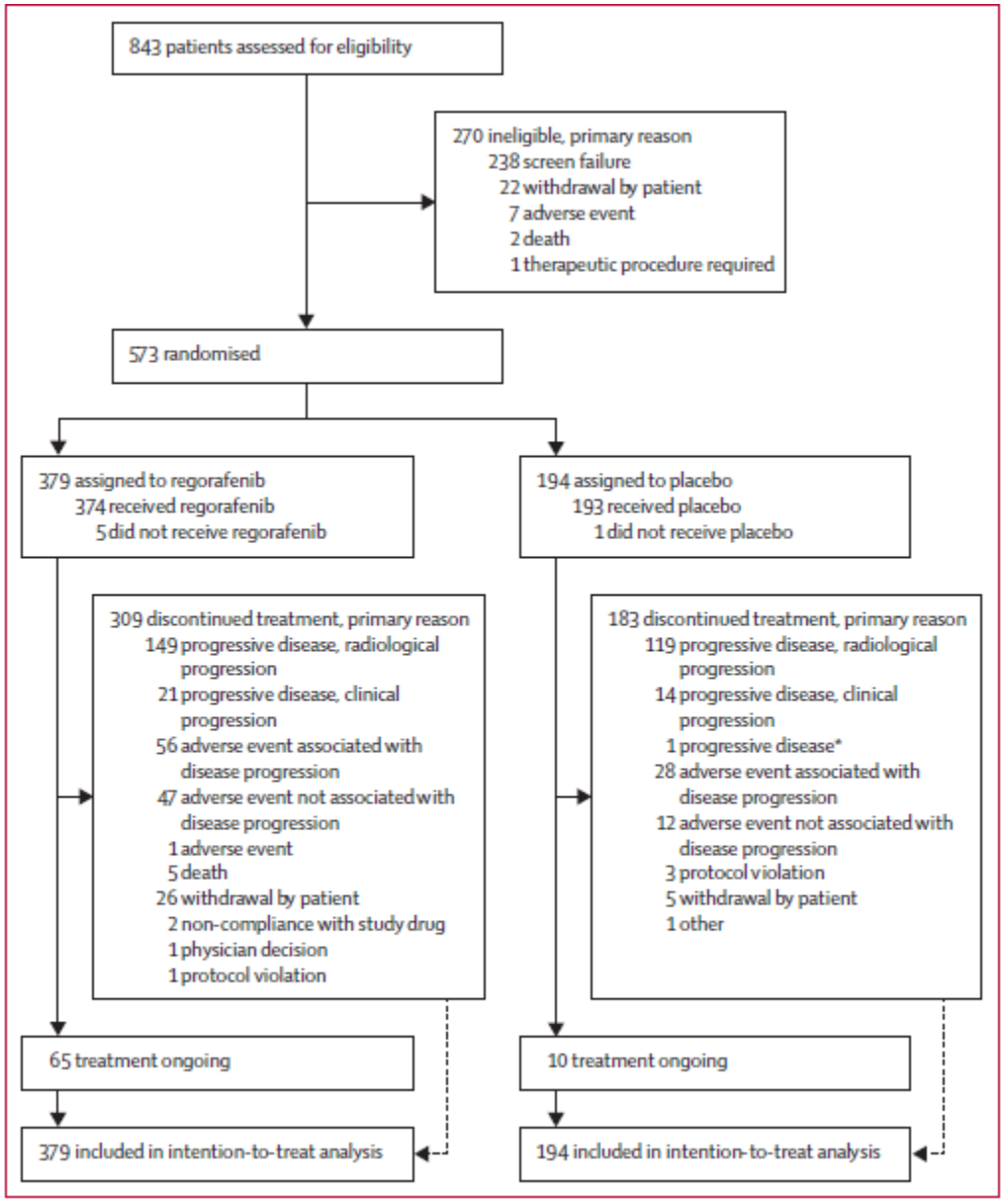


Figure 1: **Trial profile**
*Patient had radiological progression but continued treatment, and terminated treatment when the investigator judged that the patient was no longer experiencing clinical benefit.

Data Source: Bruix et al (2017) Lancet [1]

e) Limitations/Sources of Bias

Overall, RESORCE was a well-designed double-blind, placebo-controlled RCT. There was minimal risk of selection, performance, detection, attrition and reporting bias. However, there are few limitations that should be considered when interpreting the results of the trial, more specifically:

- After the primary analysis (29-Feb-2016), patients originally randomized to the placebo arm could cross over and receive regorafenib. The results in Bruix et al (2017) will not be impacted because patient crossover was implemented after the primary analysis was performed.[1] However, an unplanned interim analysis of the trial was conducted on 23-Jan-2017.[3] Thus, the updated OS estimates from this unplanned analysis may be confounded because patients were permitted to cross over from the placebo arm to the regorafenib arm.

- The trial implemented strict eligibility criteria, such that patients who were intolerant to sorafenib (i.e. unable to tolerate sorafenib at ≥400 mg/day for ≥20 of the last 28 days of treatment), patients who had Child-Pugh class B or patients who had an ECOG performance status ≥ 2 were excluded. The authors indicate that only patients with Child-Pugh A liver function and were included to avoid the potential confounding effect of impaired liver function on survival. Based on the PAG input these criteria are not representative of the clinical population and PAG anticipates that many patients in the clinical setting will not qualify for this treatment. If as a result of these factors patients in the clinical setting are likely to have worse outcomes on treatment, the generalizability of the trial results become uncertain. The relevance of the trial data into the Canadian setting is addressed by the CGP in section 1.2.3.

- It was noted by the CGP that current Canadian clinical practice differs from the time interval used defined in the protocol for preforming radiographic assessment of progression. The trial protocol assessed radiographic progression every 6 weeks during the treatment duration of the trial; however, in Canada, it is more common to scan for progression every 3 months in clinical practice. Thus, it is anticipated that patients will be on treatment longer in clinical practice relative to RESORCE trial because of the sustained intervals used to perform radiographic assessment for progression. Furthermore, the frequent monitoring may have obscured differences between the intervention and control groups, resulting in an underestimation of the effect sizes.

- It was reported in the eunetHTA Report that the trial did not implement hierarchical testing or other multiplicity analyses to control for type 1 error.[7] A type 1 error leads to false-positives, such that a study may report a treatment difference between two groups (p-value ≤ 0.05), when in fact, there is no true difference.[8]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The cut-off for the final analysis occurred on 29-Feb-2016, which represents a median follow-up of 7.0 months (IQR: 3.7 to 12.6).[1] An unplanned interim analysis was also performed on 23-Jan-2017, which represents an additional year of follow-up.[3] The unplanned analysis only provides an update on OS.

Overall Survival

OS was the primary outcome in the trial and it was defined as the time from randomization to death due to any cause.[2] Bruix et al (2017) used Kaplan-Meier analyses to obtain the estimates of OS for each treatment group with corresponding 95% CI.[1] Stratified Cox proportional hazards models were also used to estimate HRs with their corresponding 95% CI. Effect estimates were compared using a log-rank test with a one-sided alpha of 0.025.[2]

At the 29-Feb-2016 data cut-off, there were 373 deaths.[1] Sixty-one percent of patients in the regorafenib group died (N=233) while 72% (N=140) of patients in the placebo group died.[1] The Kaplain-Meier curves of OS are presented in Figure 4. Median OS was longer in the regorafenib arm (10.6 months [95% CI: 9.1 to 12.1]) as compared to the control arm (7.8 months [95% CI: 6.3 to 8.8]). Regorafenib associated with a significantly prolonged OS relative to placebo in patients with HCC (HR: 0.63, 95% CI: 0.50 to 0.79; $p \leq 0.0001$).[1] The NICE Report stated that sensitivity analyses of confirmed the robustness of the OS effect estimates.[4]

An unplanned interim analysis occurred on 23-Feb-2017.[3] Seventy-seven percent of patients in the regorafenib group died (N=290) while 87% (N=169) of patients in the placebo group died.[3] Median OS was longer in the regorafenib arm (10.7 months [95% CI: 9.1 to 12.2]) as compared to the control arm (7.9 months [95% CI: 6.4 to 9.0]). Regorafenib associated with a significantly prolonged OS relative to placebo in patients with HCC (HR: 0.61, 95% CI: 0.50 to 0.75; $p \leq 0.0001$).[1]

Bruix et al (2017) also performed pre-specified subgroup analyses for OS.[1] The results of the subgroup analysis showed a consistent protective effect of regorafenib relative to the placebo (Figure 5). However, the trial was not powered to test subgroup effects and these analyses should be considered exploratory.

Figure 4: Kaplain-Meier curves for OS, PFS as assessed by mRECIST and TTP from patients enrolled in the RESORCE trial

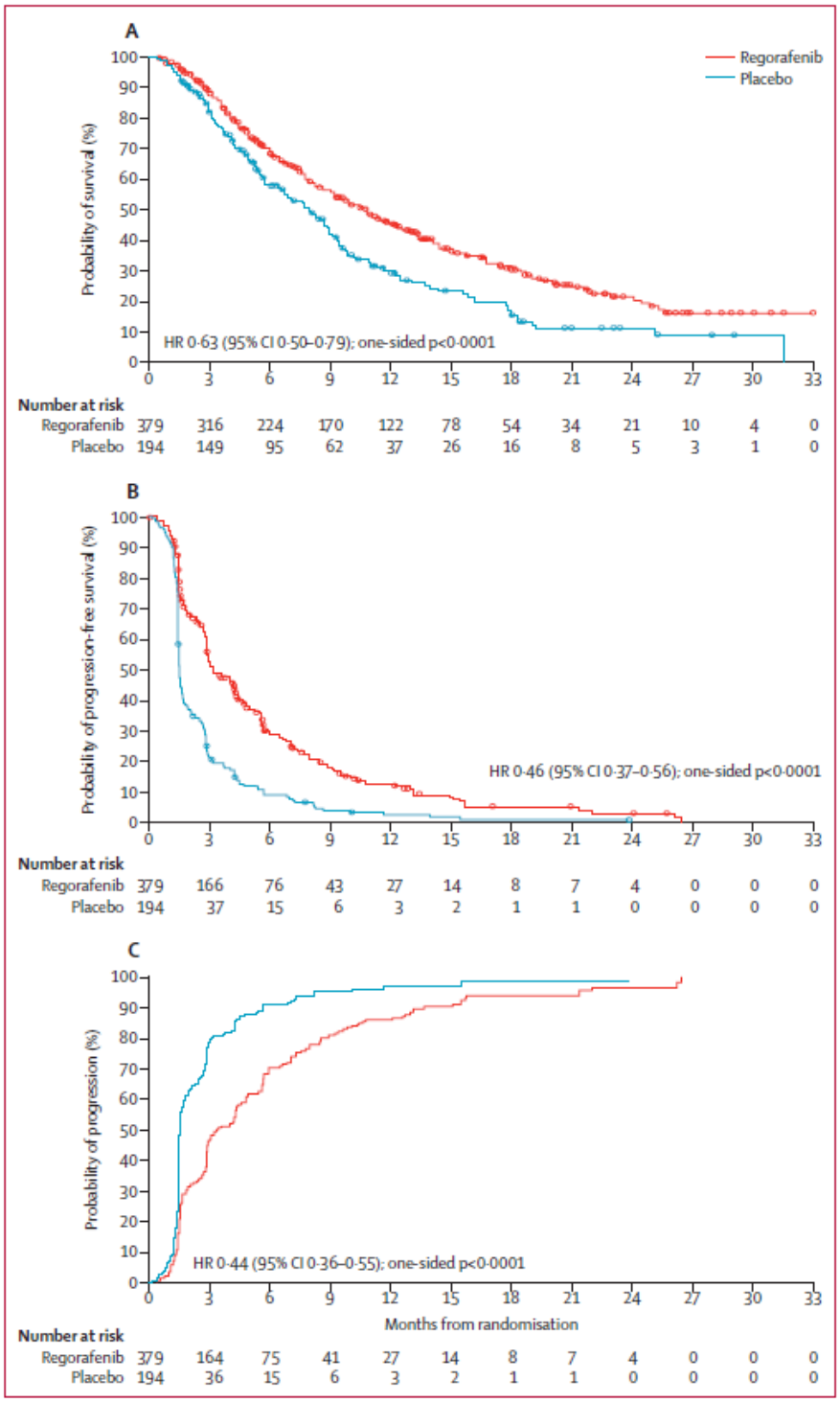
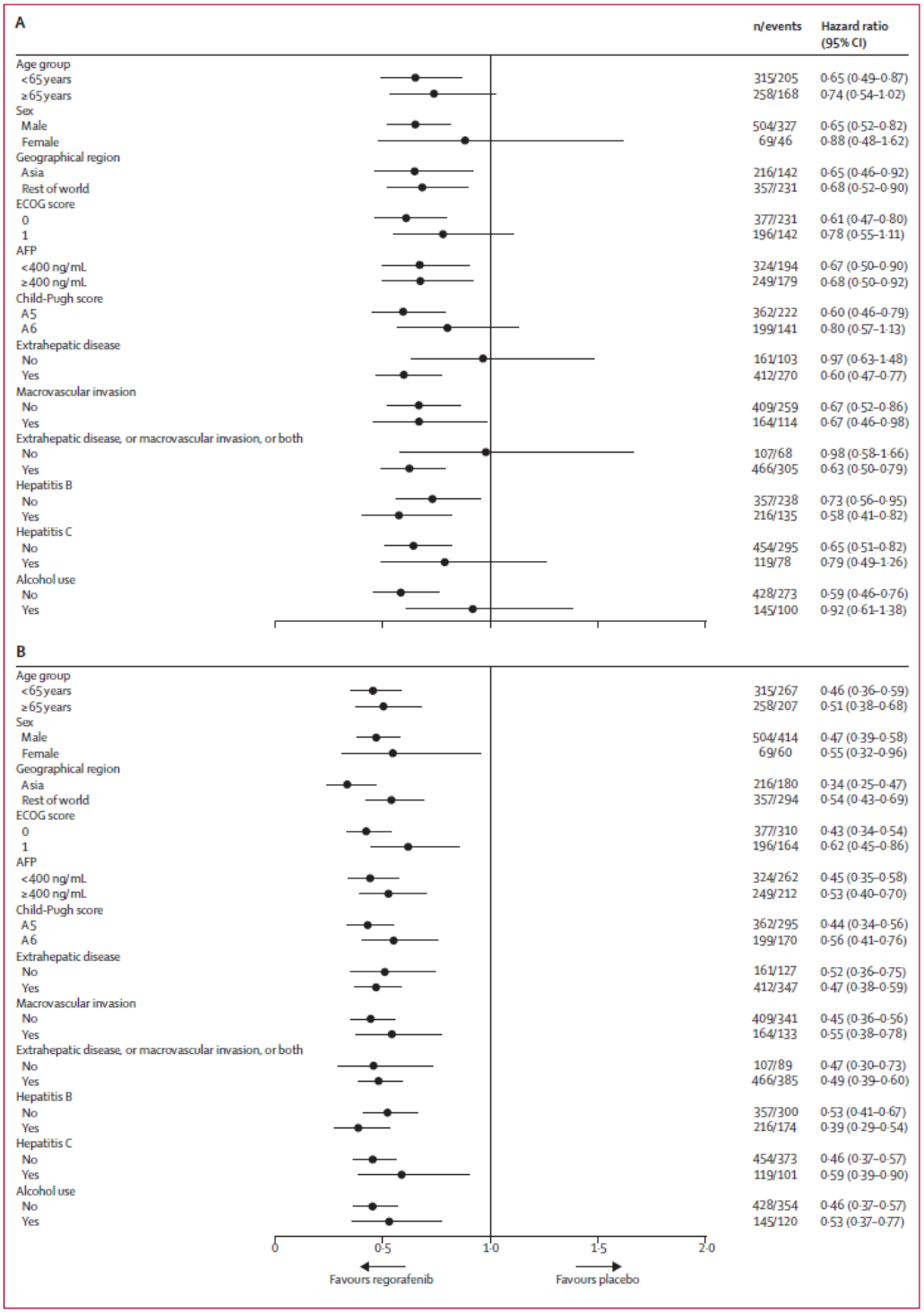
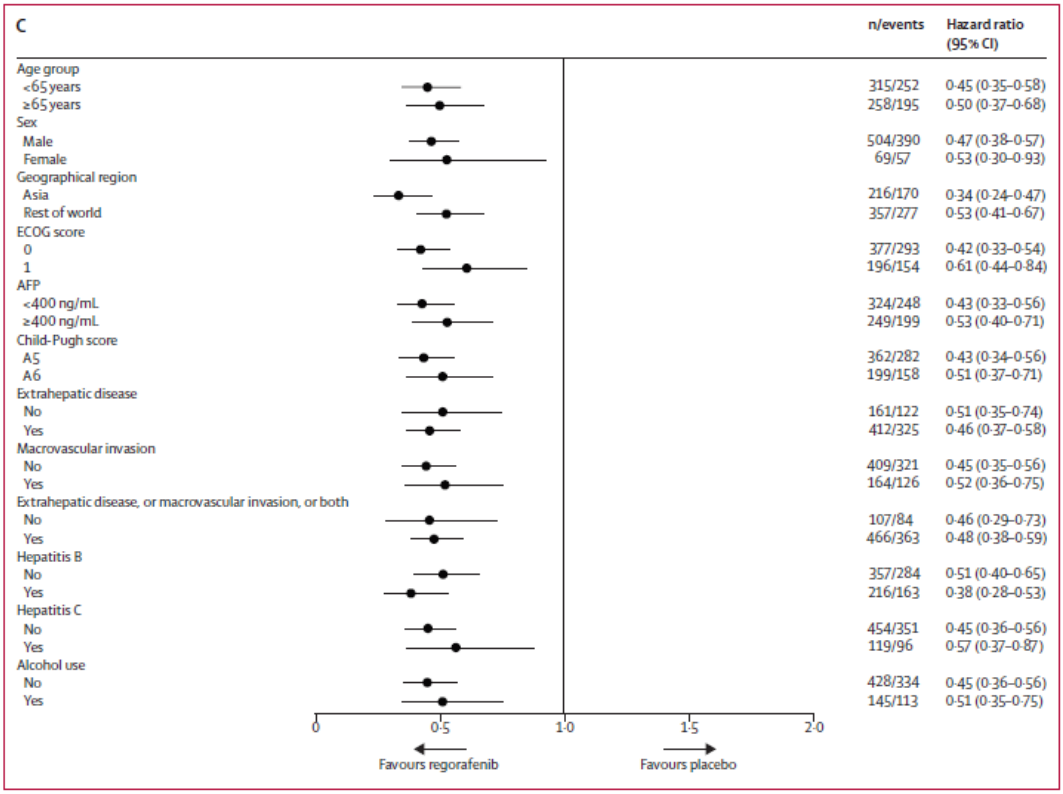


***Figure 2*: Kaplan-Meier analysis of overall survival (A), progression-free survival (mRECIST; B), and time to progression (mRECIST; C)**
mRECIST=modified RECIST for hepatocellular carcinoma.

Data Source: Bruix et al (2017) Lancet [1]

Figure 5: Effect estimates of (A) OS, (B) PFS and (C) time to progression using mRECIST criteria for patients enrolled in the RESORCE trial





Data Source: Bruix et al (2017) Lancet [1]

Progression-Free Survival

PFS was a secondary outcome and it was defined as the time from randomization until disease progression (clinical or radiological) or death due to any cause.[2] PFS assessments were performed by the study investigator and it was based on radiological review using mRECIST and RECIST 1.1 criteria.[1] The mRECIST criteria is an amended version of the RECIST 1.1 criteria that provides a more reliable method to assess tumour response in patients with HCC.[26] Bruix et al (2017) reported that the mRECIST differs from the RECIST 1.1 criteria because it requires cytopathological confirmation of malignancy to classify pleural effusion or ascites as progression, it has modified criteria to define progression due to lymph node involvement at the hepatic hilum or new intrahepatic sites and it considered complete tumour necrosis on dynamic imaging studies.[5]

Bruix et al (2017) used Kaplan-Meier analyses to obtain the estimates of PFS for each treatment group with corresponding 95% CIs.[1] Stratified Cox proportional hazards models were also used to estimate HRs with their corresponding 95% CIs. Effect estimates were compared using a log-rank test with a one-sided alpha of 0.025. However, it was stated in the eunetHTA Report that the trial did not implement hierarchical testing or other multiplicity analyses to control for type 1 error.[7]

At the 29-Feb-2016 cut-off, more patients in the placebo group (93.3%; N =293) had disease progression or died as compared to those in the regorafenib group (77.3%; N =181).[4] The Kaplain-Meier curves are presented in Figure 4. The median PFS for the regorafenib group was 3.1 months (95% CI: 2.8 to 4.2) and 1.5 months (95% CI: 1.4 to 1.6) in the placebo group.[1] The authors reported that regorafenib was associated with prolonged PFS as compared to placebo using mRECIST criteria (HR: 0.46, 95% CI: 0.37 to 0.56; p-value ≤ 0.0001).[1] Similar PFS estimates were

reported using the RECIST 1.1 criteria (HR: 0.43, 95% CI: 0.35 to 0.52; p<0·0001).[5]The NICE Report stated that sensitivity analyses confirmed the robustness of the PFS effect estimates.[4]

Bruix et al (2017) also performed pre-specified subgroup analyses for PFS (Figure 5).[1] The results of the subgroup analysis showed a consistent protective effect of regorafenib relative to the placebo. However, the trial was not powered to test subgroup effects and these analyses should be considered exploratory.

Table 7 shows the systemic therapies that patients could have received during follow-up. Slightly more patients in the placebo arm received an antineoplastic and immunomodulating agent as compared to those in the regorafenib arm (27.8% vs. 20.1%).[14]

Table 7: Systemic anti-cancer therapy during follow up for patients enrolled in the RESORCE trial

ATC CLASSIFICATION SUBCLASS WHO-DD Version 3q2005	Placebo N=194 (100%)	Regorafenib 160 mg N=379 (100%)	Total N=573 (100%)
Number of subjects (%) with at least one medication	59 (30.4%)	88 (23.2%)	147 (25.7%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	54 (27.8%)	76 (20.1%)	130 (22.7%)
ANTINEOPLASTIC AGENTS	54 (27.8%)	73 (19.3%)	127 (22.2%)
ENDOCRINE THERAPY	1 (0.5%)	2 (0.5%)	3 (0.5%)
IMMUNOSTIMULANTS	1 (0.5%)	2 (0.5%)	3 (0.5%)
IMMUNOSUPPRESSIVE AGENTS	2 (1.0%)	5 (1.3%)	7 (1.2%)

Data Source: EPAR Report[14]

Time to Progression

TTP was a secondary outcome and it was defined as the time from randomization to clinical or radiological disease progression.[2] TTP assessments were performed by the study investigator and it was based on radiological review using mRECIST and RECIST 1.1 criteria.[1] Bruix et al (2017) used Kaplan-Meier analyses to obtain the estimates of TTP for each treatment group with corresponding 95% CIs.[1] Stratified Cox proportional hazards models were also used to estimate HRs with their corresponding 95% CIs. Effect estimates were compared using a log-rank test with a one-sided alpha of 0.025. However, it was stated in the eunetHTA Report that the trial did not implement hierarchical testing or other multiplicity analyses to control for type 1 error.[14]

More patients in the placebo group had disease progression (89.2%) as compared to those in the regorafenib group (72.3%).[4]The Kaplain-Meier curves are presented in Figure 4. The median TTP for the regorafenib group was 3.2 months (95% CI: 2.9 to 4.2) and 1.5 months (95% CI: 1.4 to 1.6) in the placebo group.[1] The authors reported that regorafenib was associated with a longer TTP as compared to placebo using mRECIST criteria (HR: 0.44, 95% CI: 0.36 to 0.55; p-value ≤ 0.0001).[1] Similar estimates were reported using the RECIST 1.1 criteria (HR: 0.41, 95% CI: 0.34 to 0.551; p<0·0001).[5] Subgroup analysis for TTP demonstrated a consistent protective effect of regorafenib relative to the placebo. However, the trial was not powered to test subgroup effects and these analyses should be considered exploratory.

Objective Response Rate

ORR was a secondary outcome and it was defined as the rate of patients with a CR or PR divided by all randomized patients.[2] ORR assessments were performed by the study investigator and it was based on radiological review using mRECIST and RECIST 1.1 criteria.[1] Stratified Point estimates of ORR with corresponding 95% CIs were compared using a CMH test with a one-sided alpha of 0.025.[2]

The ORR was significantly higher for patients treated with regorafenib versus those treated with placebo using mRECIST criteria (11% [N = 40/379] vs. 4% [N = 8/194]; p-value: 0.0047) (Table 8).[1] Similar ORR estimates were reported using the RECIST 1.1 criteria (p-value: 0.02).[5] However, it was stated in the eunetHTA Report that the trial did not implement hierarchical testing or other multiplicity analyses to control for type 1 error.[14]

Table 8: Response rates for patients enrolled in the RESORCE trial

	Regorafenib (n=379)	Placebo (n=194)
Best overall response*		
Complete response	2 (1%; <1–2)	0
Partial response	38 (10%; 7–14)	8 (4%; 2–8)
Stable disease	206 (54%; 49–59)	62 (32%; 26–39)
Non-complete response/ non-progressive disease	1 (<1%; 0–2)	0
Progressive disease	86 (23%; 19–27)	108 (56%; 48–63)
Not evaluable	19 (5%; 3–8)	8 (4%; 2–8)]
Not assessed	27 (7%; 5–10)	8 (4%; 2–8)
Clinical progression†	86 (23%; 19–27)	40 (21%; 15–27)
Objective response (complete response + partial response)*	40 (11%)‡	8 (4%)‡
Disease control*	247 (65%)§	70 (36%)§

Data are n (%; 95% CI). *Based on radiological review using modified Response Evaluation Criteria in Solid Tumors for HCC (mRECIST).[22] †Defined as worsening of ECOG performance status or symptomatic deterioration including increase in liver function tests. ‡One-sided p=0·0047. §One-sided p<0·0001.

Table 2: Tumour response (efficacy population)

Data Source: Bruix et al (2017) Lancet [1]

Disease Control Rate

DCR was a secondary outcome and it was defined as the rate of patients whose best response was not disease progression (i.e. CR, PR or SD for ≥ 6 weeks) divided by all randomized patients.[2] DCR assessments were performed by the study investigator and it was based on radiological review using mRECIST and RECIST 1.1 criteria.[1] Stratified Point estimates of DCR with corresponding 95% CIs were compared using a CMH test with a one-sided alpha of 0.025.

The DCR was significantly higher for patients treated with regorafenib versus those treated with placebo using mRECIST criteria (65% [N = 247/379] vs. 36% [N = 70/194]; p-value≤ 0.0001) (Table 8).[1] Similar ORR estimates were reported using the RECIST 1.1 criteria (p-value ≤ 0.0001).[5]

However, it was stated in the eunetHTA Report that the trial did not implement hierarchical testing or other multiplicity analyses to control for type 1 error.[7]

Duration of Response

DOR was a tertiary outcome in the trial and it was defined as the time from first documented ORR of PR or CR to disease progression or death.[2] DOR assessments were performed by the study investigator and it was based on radiological review using mRECIST criteria.[1] Stratified Point estimates of DOR with corresponding 95% CIs were compared using a CMH test with a one-sided alpha of 0.025. The median DOR for patients in the regorafenib arm was 3.5 months (95% CI: 1.9 to 4.5) and was 2.7 months (1.9 to not estimable) for those in the placebo arm.[5]

Quality of Life

HRQoL was measured using four different patient-reported outcome measures from two questionnaires, which includes the FACT-G, the FACT-Hep, the EQ-5D-3L (i.e. EQ-5D) and the EQ-5D VAS questionnaires.[6]

The FACT-G instrument is a 27-item questionnaire that assesses general HRQoL for patients with any type of cancer using four domains. These include: physical well-being, social well-being, emotional well-being and functional wellbeing. [6,27] The FACT-Hep is a 45-item questionnaire that includes the FACT-G and an 18-item Hepatobiliary Cancer subscale that captures specific concerns related to QoL in patients with hepatobiliary cancers.[6,27] Both the FACT-G and the FACT-Hep questionnaires rate each item using a 5-point Likert scale that ranges from "0 (Not at all) to 4 (Very much)" and higher scores indicate a better QoL and higher scores indicate a better HRQoL.[27] The MID for FACT-G is 6-7 and it is 8-9 for the FACT-Hep.[6]

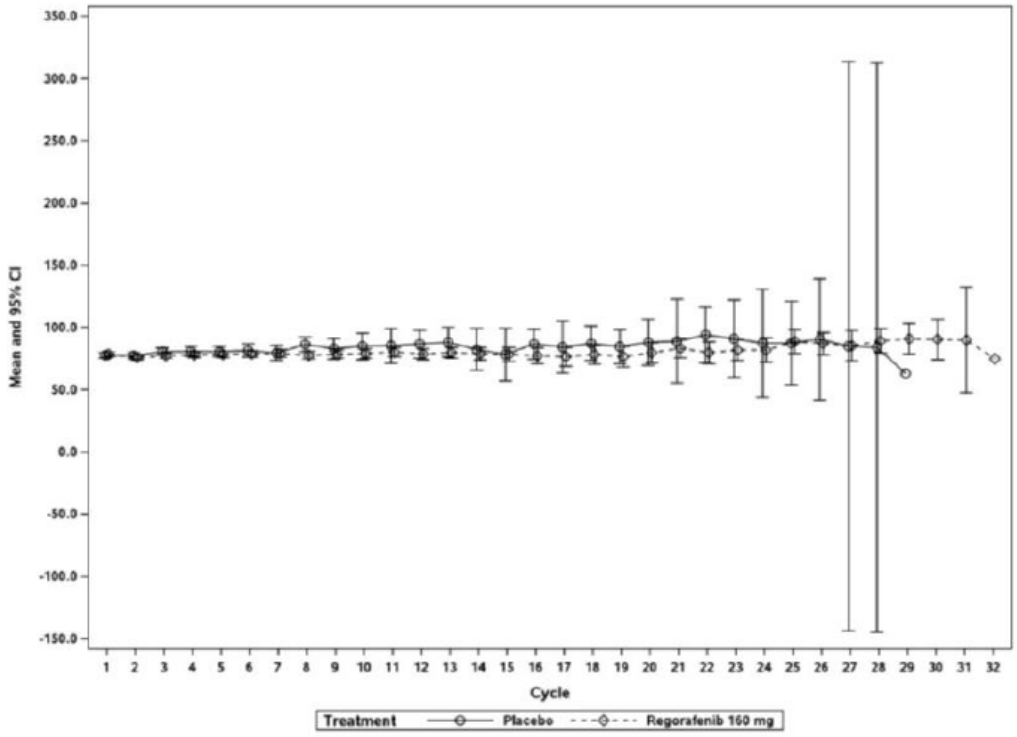
The EQ-5D instrument is a questionnaire that measures five dimensions of health, which includes: mobility, self-care, usual activity, pain/discomfort and anxiety/depression.[6] The EQ-5D VAS measures patients self-rated health status using a vertical graduated VAS that ranges from 0 (i.e. worst imaginable health state) to 100 (i.e. best imaginable health state). Higher scores on both the EQ-5D and the EQ-5D VAS indicate a better HRQoL. The MIDs for EQ-5D and the EQ-5D VAS are 0.1 and 10, respectively.[6]

All instruments were self-administered to the patients at the start of each study visit.[2] Questionnaires were administered at baseline, at every cycle, and at the end of treatment visit.[2] An ANOCOVA model that adjusted for baseline HRQoL score and stratification factors was used to compare the time-adjusted AUCs for both treatment groups.[2] The LSM with 95% CI was presented for each treatment group and for the difference between groups.[2]

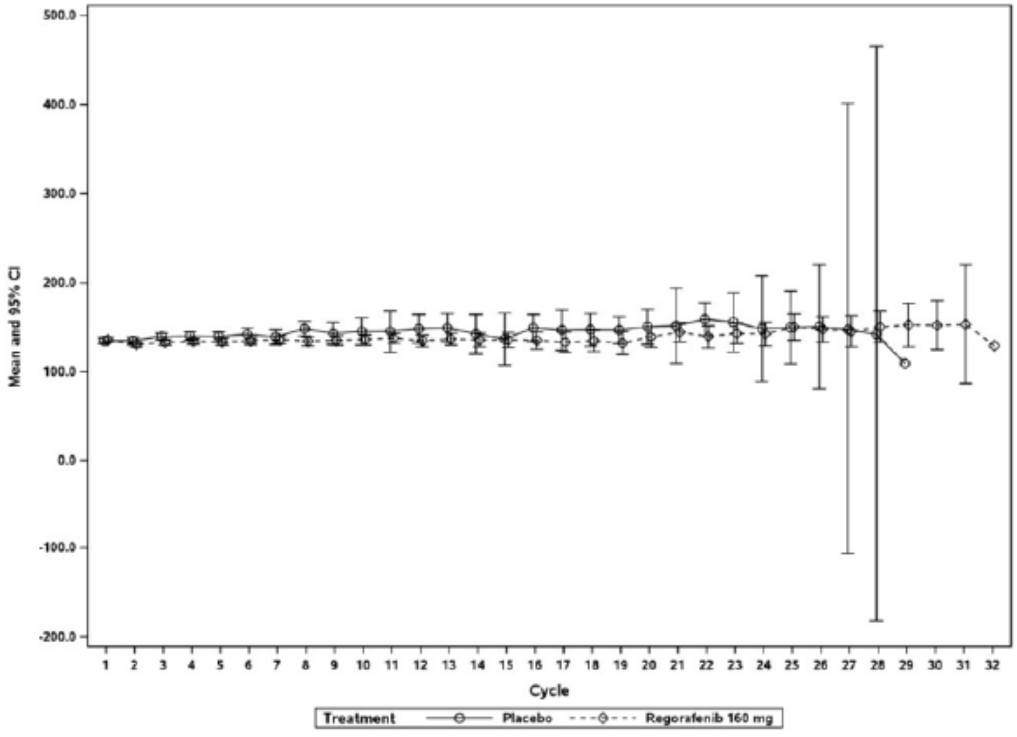
The summary statistics and plots of the four instruments are presented in Table 9 and Figure 6.

Figure 6: The corresponding means and 95% CIs for (A) the FACT-G, (B) the FACT-Hep total, (C) the EQ-5D and (D) the EQ-5D VAS.

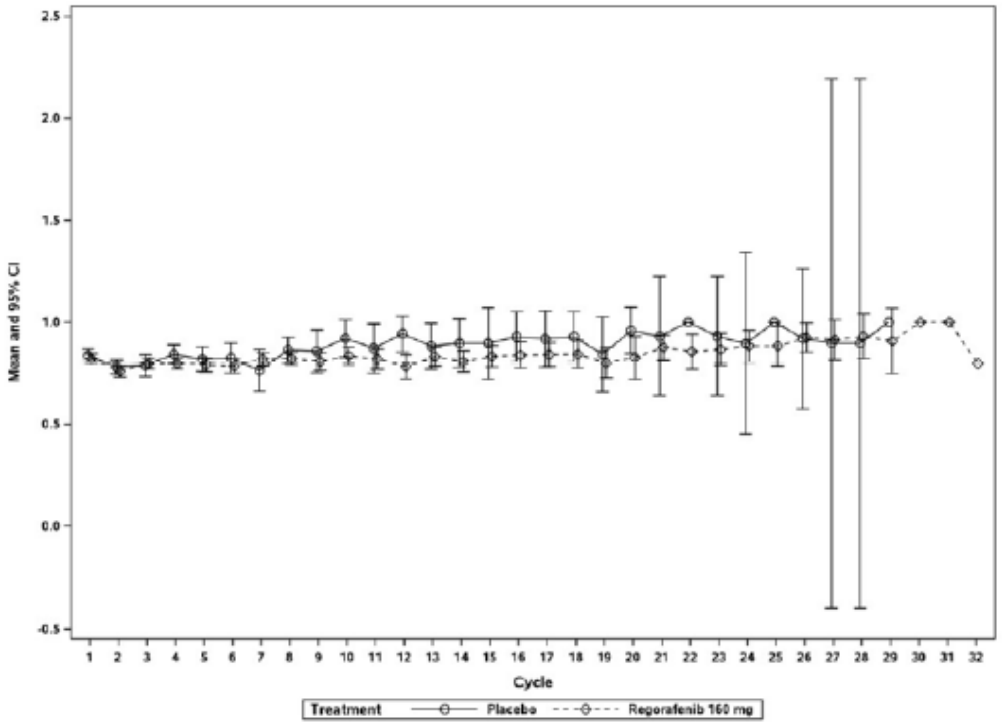
(A) The FACT-G



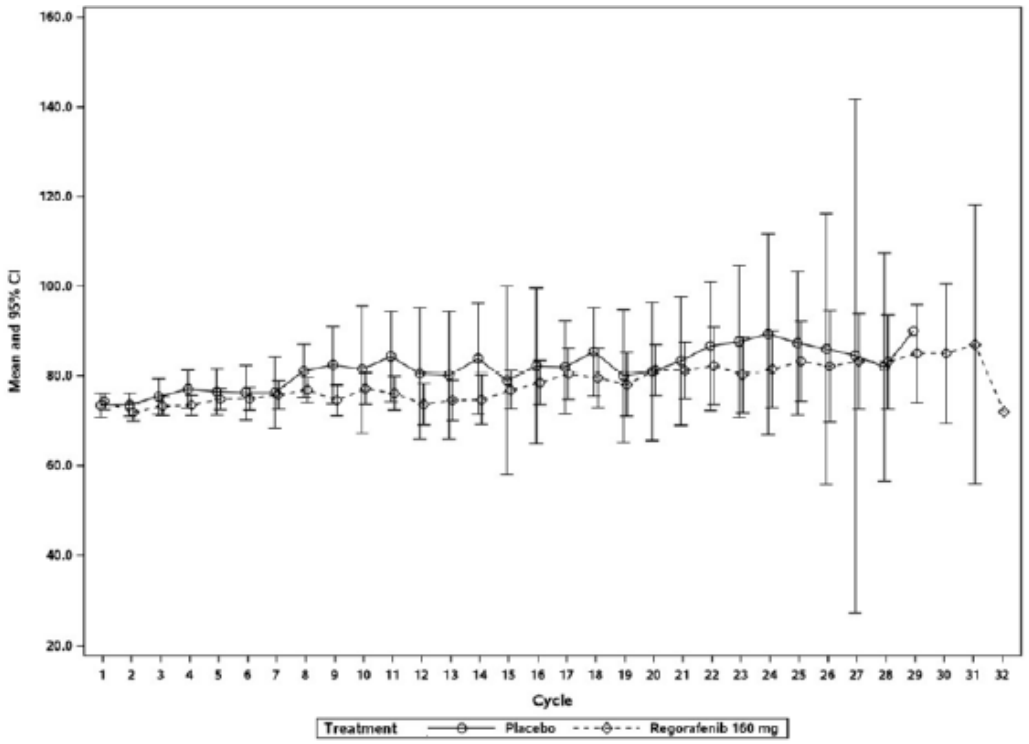
(B) The FACT-Hep Total



(C) EQ-5D



(D) EQ-5D VAS



Data Source: Data Source: eunetHTA Report[7]

The EPAR Report stated that at least 80% of patients in both arms completed the survey and 90% of these responses were valid for analysis.[14] The eunetHTA Report stated that the completion rate for the EQ-5D at the EOT was 56.7% in the placebo group and 47.0% in the regorafenib group while it was 57.7% in the placebo group and 47.5% in the regorafenib group for EQ-5D VAS and 57.2% in the placebo group and 47.0% in the regorafenib group for FACT-Hep scale.[7,14] The completion rate at EOT was not reported for the FACT-G scale.

Bruix et al (2016) reported that there were no statistical differences between regorafenib and placebo for the FACT-G, EQ-5D or EQ-5D VAS scales ($p > 0.05$ for all).[1] Furthermore, there was no clinically meaningful differences for these scales because the MID was not met. For the FACT-Hep Total scale, the LSM time-adjusted AUC analysis favoured placebo (p=0.0006); however, the difference is not clinically meaningful since the MID threshold was not met.[5]

Table 9: Patient-reported outcomes from patients enrolled in the RESORCE Trial

LSM time-adjusted AUC (95% CI)	Regorafenib	Placebo	Difference	P-value	MID[3,6]
EQ-5D index	0·76 (0·75, 0·78)	0·77 (0·75, 0·79)	–0·01 (–0·03, 0·02)	0·4695	0·1
EQ-5D VAS	71·68 (70·46, 72·90)	73·45 (71·84, 75·06)	–1·77 (–3·58, 0·04)	0·0558	10
FACT-General (FACT-G)	75·14 (74·12, 76·16)	76·55 (75·20, 77·90)	–1·41 (–2·93, 0·11)	0·0698	6–7
FACT-Hep total	129·31 (127·84, 130·79)	133·17 (131·21, 135·12)	–3·85 (–6·06, –1·65)	0·0006	8–9
Trial Outcome Index	91·47 (90·30, 92·64)	95·52 (93·98, 97·07)	–4·05 (–5·79, –2·31)	<0·0001	7–8

AUC=area under the curve. CI=confidence interval. FACT=Functional Assessment of Cancer Therapy. LSM=least squares mean. MID=minimally important difference. VAS=visual analogue scale.

Data source: Bruix et al (2017) Lancet Supplementary Appendix [5]

Harms Outcomes

A large proportion of patients from the RESORCE trial were included in the safety analysis, with 98.7% of patients from the regorafenib arm (N=374/379) and 99.5% from the control arm (N=193/194).[4]

Bruix et al (2017) stated that the median duration of regorafenib treatment was 3.6 months (IQR: 1.6 to 7.6) and 1.9 months (range: 1.4 to 3.9) for placebo.[1] The mean daily dose in the regorafenib arm was 144.1mg (SD = 21.3) and 49% of patients received the full dose of 160 mg/d.[1] Patients in the placebo group received a mean daily dose of 157.4 mg (SD= 10.3).[1]

Adverse Events

All Grades and Grade 3 or 4 Adverse Events

The majority of patients enrolled in RESORCE had at least one TEAE (regorafenib: 100% and placebo: 93%) (Table 10) as well as for grade 3 to 4 TEAEs (regorafenib: 67% and placebo: 39%).[1] More patients in the regorafenib arm had a drug-related TEAE (93%) versus those treated with placebo (52%) (Table 10).[1] Likewise, more patients in the regorafenib group (50%) had at least one Grade 3 or higher drug-related TEAE as compared to the control group (17%).[1]

The most common drug-related TEAEs for ≥ 10% of patients were hand-foot skin reaction (regorafenib: 52% and placebo: 7%); diarrhoea (regorafenib: 33% and placebo: 9%); fatigue (regorafenib: 29% and placebo: 19%); hypertension (regorafenib: 23% and placebo: 5%); anorexia (regorafenib: 24% and placebo: 6%); increased blood bilirubin (regorafenib: 19% and placebo: 4%); nausea (regorafenib: 11% and placebo: 7%) and oral mucositis (regorafenib: 11% and placebo: 3%).[1]

Table 10: Summary of TEAE and drug-related TEAEs that occurred in the RESORCE safety population

	Treatment-emergent						Treatment-emergent drug-related					
	Regorafenib (n=374)			Placebo (n=193)			Regorafenib (n=374)			Placebo (n=193)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any adverse event	374 (100%)	208 (56%)	40 (11%)	179 (93%)	61 (32%)	14 (7%)	346 (93%)	173 (46%)	14 (4%)	100 (52%)	31 (16%)	1 (1%)
Hand-foot skin reaction	198 (53%)	47 (13%)	NA	15 (8%)	1 (1%)	NA	196 (52%)	47 (13%)	NA	13 (7%)	1 (1%)	NA
Diarrhoea	155 (41%)	12 (3%)	0	29 (15%)	0	0	125 (33%)	9 (2%)	0	18 (9%)	0	0
Fatigue	151 (40%)	34 (9%)	NA	61 (32%)	9 (5%)	NA	110 (29%)	24 (6%)	NA	37 (19%)	3 (2%)	NA
Hypertension	116 (31%)	56 (15%)	1 (<1%)	12 (6%)	9 (5%)	0	87 (23%)	48 (13%)	1 (<1%)	9 (5%)	6 (3%)	0
Anorexia	116 (31%)	10 (3%)	0	28 (15%)	4 (2%)	0	88 (24%)	10 (3%)	0	12 (6%)	0	0
Increased blood bilirubin	108 (29%)	37 (10%)	2 (1%)	34 (18%)	15 (8%)	6 (3%)	70 (19%)	24 (6%)	1 (<1%)	7 (4%)	4 (2%)	0
Abdominal pain	105 (28%)	13 (3%)	NA	43 (22%)	8 (4%)	NA	34 (9%)	5 (1%)	NA	5 (3%)	0	NA
Increased AST	92 (25%)	37 (10%)	4 (1%)	38 (20%)	19 (10%)	3 (2%)	48 (13%)	16 (4%)	3 (1%)	15 (8%)	9 (5%)	1 (1%)
Fever	72 (19%)	0	0	14 (7%)	0	0	14 (4%)	0	0	4 (2%)	0	0
Nausea	64 (17%)	2 (1%)	NA	26 (13%)	0	NA	40 (11%)	1 (<1%)	NA	13 (7%)	0	NA
Constipation	65 (17%)	1 (<1%)	0	22 (11%)	1 (1%)	0	24 (6%)	0	0	3 (2%)	0	0
Ascites	58 (16%)	16 (4%)	0	31 (16%)	11 (6%)	0	8 (2%)	3 (1%)	0	1 (1%)	1 (1%)	0
Anaemia	58 (16%)	16 (4%)	2 (1%)	22 (11%)	10 (5%)	1 (1%)	23 (6%)	5 (1%)	1 (<1%)	2 (1%)	1 (1%)	0
Limb oedema	60 (16%)	2 (1%)	NA	24 (12%)	0	NA	12 (3%)	1 (<1%)	NA	1 (1%)	0	NA
Increased ALT	55 (15%)	10 (3%)	2 (1%)	22 (11%)	5 (3%)	0	29 (8%)	6 (2%)	2 (1%)	8 (4%)	2 (1%)	0
Hypoalbuminaemia	57 (15%)	6 (2%)	0	16 (8%)	1 (1%)	0	9 (2%)	2 (1%)	0	0	0	0
General disorders and administration site conditions, other	53 (14%)	16 (4%)	2 (1%)	29 (15%)	6 (3%)	3 (2%)	8 (2%)	5 (1%)	0	2 (1%)	1 (1%)	0
Weight loss	51 (14%)	7 (2%)	NA	9 (5%)	0	NA	27 (7%)	4 (1%)	NA	3 (2%)	0	NA
Oral mucositis	47 (13%)	4 (1%)	0	6 (3%)	1 (1%)	0	42 (11%)	4 (1%)	0	5 (3%)	1 (1%)	0
Vomiting	47 (13%)	3 (1%)	0	13 (7%)	1 (1%)	0	27 (7%)	1 (<1%)	0	5 (3%)	0	0
Investigations, other	40 (11%)	4 (1%)	0	11 (6%)	1 (1%)	0	18 (5%)	1 (<1%)	0	0	0	0
Back pain	42 (11%)	6 (2%)	1 (<1%)	17 (9%)	2 (1%)	0	2 (1%)	1 (<1%)	0	2 (1%)	0	0
Thrombocytopenia	39 (10%)	13 (3%)	1 (<1%)	5 (3%)	0	0	19 (5%)	7 (2%)	1 (<1%)	2 (1%)	0	0
Cough	40 (11%)	1 (<1%)	NA	14 (7%)	0	NA	4 (1%)	0	NA	2 (1%)	0	NA
Hypophosphataemia	37 (10%)	30 (8%)	2 (1%)	4 (2%)	3 (2%)	0	22 (6%)	16 (4%)	2 (1%)	2 (1%)	1 (1%)	0
Hoarseness	39 (10%)	0	NA	1 (1%)	0	NA	34 (9%)	0	NA	0	0	NA

Data are n (%). Adverse events were graded using NCI-CTCAE version 4.03. ALT=alanine aminotransferase. AST=aspartate aminotransferase. NA=not applicable. NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. *Events listed are treatment-emergent adverse events occurring in at least 10% of patients in either treatment group.

Table 3: **Treatment-emergent adverse events and treatment-emergent drug-related adverse events* (safety population)**

Data source: Bruix et al (2017) Lancet [1]

Serious Adverse Events

Treatment-emergent serious SAE were similar between the regorafenib (44%) and the placebo group (47%).[1] However, more drug-related SAEs occurred in the regorafenib (10%) than in the placebo group (3%).[1]

Dose modification, reductions, delays or discontinuations

Patients in the regorafenib group were twice as likely to have a dose modification (i.e. dose interruption or dose reduction) than those in the placebo group (68% [N = 255/374] vs. 31% [N = 60/193]).[1] A quarter of patients treated with regorafenib discontinued due to an AE (25%; N = 93/374) while 19% treated receiving placebo discontinued (N=37/193).[1] The most common AEs that led to a dose discontinuation were AST concentration (regorafenib: 2% and placebo: 2%); hand-foot skin reaction (regorafenib: 2% and placebo: 0%); and ALT increase (regorafenib: 1% and placebo: 0%).[1]

Deaths

Bruix et al (2017) reported that nine drug-related deaths occurred in the trial (Table 11).[1] Seven deaths occurred in the regorafenib group [myocardial infarction (n=1), gastric perforation (n=1), upper gastrointestinal haemorrhage (n=1), death not otherwise specified (n=1), other general disorders and administrative site conditions (n=1), hepatic failure (n=1), intracranial haemorrhage (n=1) and encephalopathy (n=1)] and two occurred in the placebo group [hepatic failure (n=2)].[5]

Table 11: Deaths that occurred in the RESOURCE trial

	Regorafenib (n=374)	Placebo (n=193)
Any	7 (2%)	2 (1%)
Myocardial infarction	1 (<1%)	0
Gastric perforation	1 (<1%)	0
Upper gastrointestinal haemorrhage	1 (<1%)	0
Death not otherwise specified	1 (<1%)	0
General disorders and administrative site conditions, other, specify	1 (<1%)	0
Hepatic failure	0	2 (1%)
Intracranial haemorrhage	1 (<1%)	0
Encephalopathy	1 (<1%)	0

Data are n (%).

Data source: Bruix et al (2017) Lancet Supplementary Appendix [1]

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified.

8 COMPARISON WITH OTHER LITERATURE

The Methods Team did not identify any relevant information to be summarised as supplemental material.

9 ABOUT THIS DOCUMENT

This 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 Hepatocellular Carcinoma. 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 CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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 revision was made in between posting of the Initial and Final Clinical 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 CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

Literature Search Methods

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 Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Regorafenib (Stivarga) and Hepatocellular Carcinoma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was limited to the English language, but not limited by publication year.

The search is considered up to date as of March 5, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies, clinical trial registries and relevant conference abstracts. Searches of conference abstracts 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.

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.

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.

Data Analysis

Additional data analyses are not expected for pCODR reviews. If they are required, as determined in consultation with pCODR, provide details on any additional statistical analyses and details on software programs used. If additional data analyses are not conducted, insert the following:

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

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 clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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