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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Regorafenib (Stivarga) for Hepatocellular Carcinoma

April 18, 2018

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FUNDING

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

INQUIRIES

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

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by **Bayer Canada,** compared Regorafenib (Stivarga) with best supportive care (BSC) as second-treatment for patients with hepatocellular carcinoma (HCC) following treatment with sorafenib. Regorafenib is an oral multikinase inhibitor that targets oncogenesis, tumour angiogenesis, metastasis, and tumour immunity.

Table 1. Submitted Economic Model

Funding Request	Regorafenib for the treatment of patients with unresectable hepatocellular carcinoma (HCC) following treatment with sorafenib (Nexavar). EGP: This aligns with the patient population that the economic model is built on.
Type of Analysis	Cost effectiveness and cost utility analysis
Type of Model	Partitioned-survival model
Comparator	Best supportive care (BSC)
Time Horizon	3 years
Perspective	Publicly funded health care system in Canada
Cost of regorafenib	Regorafenib costs $72.60 per 40mg tablet. At the recommended dose of 160 mg once daily orally for the first 3 weeks of each 4-week cycle, regorafenib costs: • $217.86 per day • $6100.08 per 28 day cycle In the economic model an adjusted daily dose which corresponded to 85% of the protocol dose was used. The submitter explained that this was based on dosing in the RESORCE trial taking into account brief breaks ("holidays") or interruptions from treatment as observed in the trial. This results in a cost of: • $185.16 per day • $5,184.45 per 28 day cycle
Cost of BSC	Costs for BSC were assumed to be the same for both treatment arms in the model and were therefore set to zero.
Model Structure	The model was comprised of 3 health states: pre-progression, progression (or post-progression), and death. Transitions between these health states were driven by the OS and PFS from the RESORCE trial; KM survival data were used directly for the first 24 cycles of the model time horizon and parametric functions were fitted onwards. Parametric extrapolation was based on lognormal curves, with dependent curves used for OS and independent curves used for PFS.
Key Data Sources	The efficacy and safety parameters were based on the RESORCE trial. Inputs for cost and resource use were taken from the trial and an Ontario population-based database analysis of health care utilization in HCC from 2002-2010. Utilities were derived from the trial.

** Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the*

economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA– accessed on February 21, 2018
All calculations are based on = 70kg and BSA = 1.7m^2

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

- Relevant issues identified by the CGP included:
  - *The RESORCE trial demonstrated an overall survival benefit in favor of regorafenib.*
  - *Toxicities observed in the RESORCE trial were as expected with a targeted agent and manageable.*
  - *No meaningful differences were observed between regorafenib and placebo in health-related QoL (EQ-5D, FACT-G) in the trial.*
  - *In the RESORCE trial, radiographic progression was assessed every 6 weeks whereas in Canadian clinical practice patients would be assessed every 3 months. Due to more frequent assessments, the CGP considered that progression may have been caught earlier on the trial. The CGP therefore agree that in Canadian clinical practice patients may continue on treatment longer until radiographic progression is assessed and detected.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered:

- There is no alternative to supportive care or clinical trial at the present time.
- Reported toxicity was not as severe as expected based on other trials which evaluated regorafenib (eg. CORRECT trial investigating regorafenib in metastatic colorectal cancer).
- Registered clinicians indicated that patients qualifying for treatment with regorafenib should adhere to the population as defined in the clinical trial;
- Survival advantage compared to supportive care. No other real treatment options
- The proportion of advanced HCC patients who are suitable for first-line sorafenib is relatively low, and subsequent proportion in the second-line is even smaller. It will be a selective patient population with preserved liver function still well enough to get additional treatment (patients who had discontinuation of prior sorafenib therapy due to sorafenib-related toxicity were excluded from the RESORCE trial).

Summary of patient input relevant to the economic analysis
Patients considered the following to be important factors as related to the economic analysis:

- Patients with HCC face a poor prognosis, and there are currently no other approved treatment options for patients following sorafenib progression. The economic model used best supportive care as a comparator which would be considered an appropriate management strategy in the absence of treatment options.
- While regorafenib is not curative, it satisfies a current unmet need and patients should have access.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for regorafenib which are relevant to the economic analysis:

- Canadian patients currently have no other options after failing treatment with sorafenib.
- Regorafenib's oral route of administration will favorably enable implementation.
- Regorafenib must be taken with a specific fat and caloric composition which may be difficult for some patients. Given that the economic model takes a public payer perspective, costs associated with out of pocket patient expenses are not accounted for in the economic model.

- Concerns raised by PAG included the dosing schedule of three weeks on and one week off which may be confusing for some patients.
- Multiple serious adverse events including severe hepatic toxicities and hypertension would require additional RESORCEs to monitor and manage. Costs due to hypertension was accounted for in the model but costs due to hepatic toxicities were not considered.

1.3 Submitted and EGP Reanalysis Estimates

This economic evaluation was performed by using the initial model provided to pCODR by the submitter on Nov 29th, 2017. The clinical data of the RESORCE trial have been updated on February 2018, and an updated economic model was provided by the submitter following this update. All the re-analyses specified in the current report have been performed with both models (initial and up-dated one), and demonstrated minimal differences between ICERs /ICURs calculated with these models (less than $1,000/QALY). The following economic report refers to results as per the initial model.

The main assumptions and limitations with the submitted economic evaluation were:
The key assumption that has the most impact on the results of the economic evaluation is the dose and the cost of regorafenib. At the full protocol dose (160 mg for 21 days), the cost of regorafenib increased from $5,185/cycle to $6,100/cycle, and produced the highest increase of the ICER/ICUR.

Utilities used in the model were derived from data collected during the clinical trial, yet CGP and EGP agreed that the utilities used in the submitted model were overestimated, as the inputs used are higher than utilities seen in patients with similar conditions. The model allowed the EGP to perform several re-analyses around utilities using values found in the literature (1, 2) in similar populations.

The submitted base case analysis assumed that all background costs were considered equivalent between regorafenib and BSC, and common parameters were used across treatment arms. A scenario analysis was provided by the submitter, where the cost of one computed tomography scan of the abdomen ($108.3) every six weeks was additionally applied to the regorafenib treatment arm for the entire time spent on treatment. Yet, the $108.3 considered only physician fee, while the actual median cost of computed tomography scan of the abdomen in Canada was estimated by the EGP at $428 (median of the unit costs in NS, QC, ON, BC and Alberta (3-9);

Another factor that impact the ICER/ICUR was the time horizon. The CGP and EGP agreed that the time horizon of 3 year considered in the submitted base case analysis was appropriate.

Lastly, based on input from the CGP, the EGP noted that patients in Canadian clinical practice may be on treatment longer than what was observed in the clinical trial due to less frequent assessment for radiographic disease progression. As noted previously, the trial assessed for radiographic progression every 6 weeks while Canadian clinical practice involves assessment every 3 months. Given that 87.8% of the incremental cost is due to drug acquisition, the EGP anticipates that prolonged duration of treatment with regorafenib would increase the incremental cost of treatment with no incremental gain in benefit and therefore likely have an impact on the ICER. The EGP therefore anticipates that the ICER is sensitive to duration of treatment. The model didn't allow the EGP to assess the impact of this input. Furthermore, it is unclear how much longer patients may be on treatment.

The following re-analyses have been performed by varying components of the model and were significant drivers of either the incremental effect or the incremental cost, such as utilities and cost.

1) Several re-analyses were performed to assess the impact of utilities on clinical outcomes. In the base case values, utilities are derived from the RESORCE trial (PFS: 0.811 and PPS: 0.763) Previous studies (1, 2) estimated the utilities in the pre-progression and progression states, for patients receiving sorafenib for unresectable advanced hepatocellular carcinoma, as 0.76 and

0.68, respectively. Based on input from the CGP, these values were considered in the EGP's re-analyses. To demonstrate the sensitivity of the ICER to utility values, the EGP also conducted one way analysis with a decrease of these values by 5% and 10%. This is provided in the full technical report (Section 2 of the Report).

2) Full protocol dose of 160 mg for 21 days (100%) was assessed over a sensitivity analysis by the submitter. The EGP included this analysis in their estimates as an assumption where all patients take the full dose indirectly accounts for potential tablet wastage when patients discontinue treatment mid-cycle.

3) The submitted model allowed for the inclusion of the cost of radiographic assessment, yet the computed tomography (CT) cost which was considered in the model was underestimated ($108.3). The submitted model didn't allow for the modification of this cost and the cost of radiographic assessment in regorafenib group. The EGP assed this impact by adding the cost of radiographic assessment to the incremental cost. As a CT scan of the abdomen was planned every six weeks during the treatment duration of regorafenib, the additional cost was estimated to be $1,027. The EGP estimated this cost using the following approach: median unit cost of $428 was multiplied by 2.4 (Median treatment duration of regorafenib: 3.6 months = 14.4 weeks / 6 weeks = 2.4). The EGP acknowledge that this is a rough estimate of including the additional cost of radiographic assessment. Notably, more intensive radiographic assessment is correlated with a shorter duration of treatment as progression will be detected earlier, and vice versa.

4) Several other re-analyses were conducted by the EGP using different approaches to estimate OS and/or PFS beyond the trial end, adverse event cost, as well as using the PFS curve used to estimate time on treatment (treatment discontinuation curve used in base case). Although not presented here, all confirmed the sensitivity analyses results performed by the submitter had minimal impact on the base case ICER/ICUR. No additional re-analyses were considered necessary by the EGP.

Table 2. Submitted and EGP Reanalysis Estimates

Estimates	Submitted	EGP Reanalysis (lower and upper bounds)
ICER estimate, $/QALY (range/point)	$138,322/QALY ($114,525/QALY to $159,732/QALY)	$152,657/QALY and $175,700/QALY
ΔE, QALY (range/point)	0.25 (0.25 to 0.32)	0.23 to 0.25
ΔE, LY (range/point)	0.31, (0.31 to 0.40)	0.31
ΔC, $ (range/point)	$34,194, ($33,002 to $39,435)	$34,084 and $40,411

EGP Reanalysis

Table 3: Detailed Description of EGP Reanalysis				
	ΔC	ΔE (QALY)	ICER $/QALY	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$34,194	0.25	$138,322/QALY	--
LOWER BOUND (discounted)				
Utilities : 0.76 pre-progression; 0.68 progressive disease	$34,084	0.23	$150,473	$12,151
Cost of radiographic assessment of progression ($1,027 over regorafenib treatment duration)	$35,111	0.25	$160,884	$22,562
Best case estimate of above 2 parameters	$35,111	0.25	$152,657	$14,335
UPPER BOUND (discounted)				
Utilities : 0.76 pre-progression; 0.68 progressive disease	$34,084	0.23	$150,473	$12,151
Dose of regorafenib (100%)	$39,384	0.24	$161,067	$22,745
Cost of radiographic assessment of progression ($1,027 over treatment duration)	$40,221	0.25	$160,884	$22,562
Best case estimate of above 3 parameters	$40,411	0.23	$175,700	$37,378

1.4 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include: number of patients eligible to be treated with regorafenib.

A budget impact analysis was conducted to evaluate the addition of regorafenib to the provincial formularies for the treatment of patients with unresectable HCC who have been previously treated with sorafenib. The submitter provided several range of scenarios, including differences in treatment duration, dose intensity, and market share.

Sales data were used to estimate the number of patients treated with sorafenib. Based on CGP opinion, the EGP estimated approximatively 384 patients annually in Canada, and 173 patients in Ontario, respectively. This is approximately 3 times higher than submitter's estimate for the market share. The EGP therefore agree that the 3-year BIA is significantly higher than what was predicted by the submitter. The CGP estimate took into account that there are approximatively 1,200 deaths annually from liver cancer, 80% on public insurance, an estimated rate of first-line treatment of 80% and with a rate of 50% receiving 2nd line treatment prior to death.

1.5 Conclusions

The EGP's best estimate of ICUR for Regorafenib when compared to BSC is:

- Between $152,657/QALY and $175,700/QALY. The EGP further notes that this range is due to the uncertainty of utility values and dose of regorafenib.
- Within this range of ICUR, the best estimate would likely be $152,657/QALY, corresponding to the scenario of utility values of 0.76 in pre-progression state and 0.68 in progressive disease state, as reported in previous studies, an adjusted incremental cost of $1,027 to account for cost of radiographic assessment of progression, and a 3-year time horizon.
- The extra cost of regorafenib is between $34,084 and $40,411. The factor that most influences the costs is regorafenib dose intensity. Notably, given that assessment for radiographic

progression in the trial was more frequent (every 6 weeks) that Canadian clinical practice (every 3 months), it is anticipated that patients in the clinic will likely be on treatment longer before disease progression is detected. The EGP was unable to explore the impact of longer treatment duration in the model but anticipates that it would be a cost driver.

- The extra clinical effect of regorafenib is between 0.23 and 0.25. The factors that most influence the incremental clinical benefit are the utility values.

Overall conclusions of the submitted model:

The submitted model included many appropriate assumptions and an extensive set of sensitivity analysis. Important drivers in this economic evaluation were the utility values, dose intensity of regorafenib and time horizon. The submitted model allowed the EGP to conduct all the re-analyses that were considered necessary. The EGP noted that current Canadian clinical practice differs from the trial protocol which performed radiographic assessment for progression every 6-weeks. This frequency might overestimate the cost of radiographic assessment which is conducted every 3 months in Canadian practice. More importantly, less frequent assessment for radiographic progression in Canadian clinical practice will mean that patients may be treated with regorafenib for a longer period of time even though they may have already experienced disease progression. This will result in longer duration of treatment and higher cost for drug acquisition. The EGP noted this to be an important limitation in the model as the ICER is sensitive to duration of treatment.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no information redacted from this publicly available Guidance Report.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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