Cost-Effectiveness of Regorafenib as a Second Line Therapy for Patients with Advanced Hepatocellular Carcinoma

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Precis: Regorafenib has been shown to confer a survival benefit as a second line systemic treatment for advanced hepatocellular carcinoma. This study examines the cost-effectiveness of regorafenib in this setting.

Abstract

Background: Regorafenib, a multikinase inhibitor, has been shown to prolong survival by 2.8 months as a 2nd line agent in patients with hepatocellular carcinoma (HCC) who progress on sorafenib therapy. We aimed to examine the cost-effectiveness of regorafenib for the treatment of HCC.

Methods: We constructed a Markov simulation model of patients with unresectable HCC and Child Pugh A cirrhosis treated with regorafenib versus best supportive care. Model inputs for regorafenib effectiveness and rates of adverse events in HCC patients were based on published clinical trial data and literature review. We calculated quality adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) of regorafenib therapy. We conducted one-way sensitivity analyses on all model parameters and Monte-Carlo simulation varying model parameters simultaneously. We determined at which regorafenib cost threshold, cost-effectiveness would be achieved.

Results: Regorafenib provided an increase of 0.18 QALYs at a cost of $47,112. The ICER for regorafenib compared to best supportive care was $224,362. In one-way sensitivity analyses, there were no scenarios in which regorafenib was cost effective. In cost threshold analysis, regorafenib would need to be priced at or below $67 per pill to be cost-effective at an ICER of $100,000.

Conclusion: Regorafenib is not cost-effective as a second-line agent in the treatment of HCC with a marginal increase in QALYs at a high cost. Lowering costs of regroafenib or improving selection of patients with maximal survival benefit would improve its value as a second-line treatment option for patients with HCC.

Keywords: HCC, Markov, ICER, QALY, RESORCE

INTRODUCTION

Hepatocellular carcinoma (HCC) is an increasingly incident malignancy in the United States associated with significant morbidity and mortality.[1-3] Despite improvement over time, the majority of HCC patients continue to present at advanced stages, when curative treatment options are not possible and prognosis is poor.[4, 5] In the most recent 10-year period assessed by SEER, primary liver cancer had the largest relative increase in mortality among all solid tumors.[6]

Systemic therapy is the primary treatment modality for patients with advanced HCC, including those with portal vein invasion or extra-hepatic spread.[7] Similarly, there is increasing recognition of systemic therapy's role for patients who progress after treatment with locoregional therapy, such as transarterial chemoembolization (TACE). Sorafenib, an oral multikinase inhibitor, is the only FDA-approved first-line therapy for patients with advanced HCC.[8, 9] Sorafenib was approved in patients with unresectable HCC based on results from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) Trial, which showed patients treated with sorafenib experienced significantly prolonged time-to-radiologic progression (5.5 vs. 2.8 months, $p<0.001$) and improved overall survival (10.7 vs. 7.9 months $p<0.001$).[10] Based on these data, sorafenib is the most commonly used systemic therapy in patients with advanced HCC, including expanded use in patients with Child Pugh B and even some patients Child Pugh C cirrhosis.[9] Cost-effectiveness analyses have demonstrated that sorafenib is cost-effective in patients with Child Pugh A cirrhosis, including in elderly patients, although it is no longer cost-effective in patients with hepatic decompensation.[8]

Until recently, there have not been any approved alternate therapies for patients who experience tumor progression or severe adverse events on sorafenib. Several therapies appeared promising in phase II studies but failed to improve survival when evaluated in larger phase III studies.[11-13]

Regorafenib is also a multikinase inhibitor that has been previously approved for use in patients with metastatic colorectal cancer and advanced gastrointestinal stromal tumors.[14, 15] The RESORCE trial, a double blind phase III randomized control trial recently evaluated the efficacy of regorafenib compared to best supportive care in patients who experienced progression on sorafenib.[16] Patients who received regorafenib had a median survival of 10.6 months versus 7.8 months for placebo ($p<0.001$).

An analysis of the cost-effectiveness of regorafenib as a 3rd line agent in patients with metastatic colorectal cancer demonstrated that it is not cost-effective compared to placebo with an incremental cost-effectiveness ratio (ICER) of $900,000 per quality life year (QALY) gained in the base model, and the ICER did not reach $550,000 in any of the sensitivity analyses.[17] The authors concluded the cost-effectiveness of regorafenib should be improved with use of value-based pricing. With its new indication for HCC treatment, we aimed to examine the cost-effectiveness of regorafenib as a second line agent in the treatment of advanced HCC.

METHODS

We constructed a Markov model of patients with advanced HCC in the setting of Child Pugh A cirrhosis and an Eastern Cooperative Oncology Group (ECOG) status of 0-1. Rates of disease progression for patients who progressed on sorafenib were based on results from the RESORCE Trial.[16] This model tracked health states of patients as outlined in Figure 1. Patients treated with regorafenib continued on regorafenib until they experienced a grade 3-4 AE or radiographic HCC progression. Treated patients moved in weekly cycles to best supportive care or death.

The model was constructed using Microsoft Excel and tracked costs, QALYs, and the ICER comparing regorafenib versus best supportive care. Cost-effectiveness was calculated from a health system perspective.

Model Inputs

Progression Rates

HCC progression rates in the model were calculated to match the median overall survival, median progression-free survival, and median time-to-progression observed in the RESORCE Trial.[16] We assumed constant HCC progression rates over time.

Adverse Events

We included the impact of hypertension, hand-foot skin reaction, fatigue, and diarrhea, as these side-effects were the most common clinically relevant grade 3 or 4 events in the trials of regorafenib for both HCC and colorectal cancers.[14, 16] Rates of side effects were based on data from the RESORCE Trial.[16] For management of grade 1-2 AEs, we modeled use of amlodipine 5 mg daily for hypertension, Eucerin cream for hand-foot skin reaction, and atropine / diphenoxylate and loperamide for diarrhea. Any occurrence of grade 3-4 AE resulted in regorafenib discontinuation with resultant resolution of the AE.

Health Utilities

We calculated health utilities based upon the quality of life data (EQ-5D, FACT-Hep) presented in the RESORCE trial.[16] Although the study found a significant decrease in quality of life of patients treated with regorafenib, the quality of life decrement did not meet the threshold for a minimally important difference. RESORCE did not compare quality-of-life for patients with and without tumor progression, so we assumed quality-of-life was not different between progressed and non-progressed health states;

however, health utilities in patients with and without HCC progression were varied in sensitivity analyses. Health utilities were aggregated over weekly periods to calculate overall QALYs.

Costs

Both arms included costs of side effects and best supportive care, including general liver disease management. Costs in the regorafenib arm included regorafenib medication costs as well as surveillance imaging associated with regorafenib monitoring. Regorafenib costs were based on weighted average costs from the Red Book ($165 per 40mg)[18], and adjusted based on mean daily dose observed in the RESORCE Trial (144mg per day). Patients on regorafenib were modeled to receive three weeks on and one week off therapy, which is consistent with treatment schedule detailed in the RESORCE Trial. Discontinuation rates were modeled to match what was reported in the RESORCE Trial. In addition to drug costs, patients on regorafenib were assumed to have contrast-enhanced abdominal CT imaging at baseline and every 12 weeks until drug discontinuation or death. All costs were updated to 2016 dollars using the GDP deflator. Cost-effectiveness of regorafenib was defined as an ICER (i.e. difference in cost of two possible treatments divided by the difference in effect) of $100,000 compared to best supportive care.[19-22]

Sensitivity Analysis

We derived parameter ranges from the literature and performed one-way sensitivity analyses on all parameters as well as multi-way sensitivity analysis on key parameters of interest. We also conducted a Monte-Carlo simulation of the model simultaneously drawing all parameter values and their ranges to evaluate overall uncertainty in results. Using data from 10,000 iterations, we created cost-effectiveness acceptability curves representing the likelihood that regorafenib would be considered cost-effective at various levels of willingness-to-pay for health gains (QALYs). We modeled the potential impact of HCC progression on health utilities, given that HCC progression may negatively affect health related quality of

life. We also conducted a cost threshold analysis to determine at which pill cost regorafenib would become cost-effective.

RESULTS

Base Case

The model inputs, including baseline values, ranges included in sensitivity analyses, costs and utilities and their sources are shown in Table 1. Our model's progression-free and overall survival curves for both the regorafenib and placebo arms matched results of the RESORCE Trial. (Supplemental Figure 1A and 1B) The overall results of the base case analysis are shown in Table 2. Regorafenib provided an additional 0.18 QALYs (65 quality-adjusted days) compared to best supportive care. The cost incurred with regorafenib treatment was $47,112 vs $7,408 with best supportive care. Regorafenib was not cost-effective with an ICER of $224,362 compared to best supportive care in our base case analysis.

Sensitivity Analysis

In one-way sensitivity analyses, the parameters with the most influence on ICER were related to HCC progression, particularly overall survival, and cost of regorafenib. (Figure 2) However, the ICER remained above $140,000 per QALY in each one-way sensitivity analysis.

In the sensitivity analysis where we modeled decrease in health utility with HCC progression, we found the ICER rose to above $1,200,000 when the health utility associated with HCC progression was decreased to 0. If patients without HCC progression had improved health utility compared to the base case, the ICER decreased but did not fall below $210,000. (Supplemental Table 1).

In two-way sensitivity analyses, we varied the median overall survival with both regorafenib and best supportive care. With the most optimistic survival for regorafenib (12 months) and pessimistic for best supportive care (6 months) the ICER became approximately $98,000 per QALY, and thus considered cost-effective. (Table 3) All shorter survival differences between the two arms, would result in ICERs above the $100,000 threshold.

The Monte-Carlo simulation showed that regorafenib therapy was unlikely to be cost-effective, with an ICER exceeding $150,000 compared to best supportive care. The ICER was at least $100,000 per QALY in 99% of simulations and exceeded $200,000 per QALY in 61% of simulations. (Figure 3) If the willingness-to-pay for QALYs increases dramatically, then regorafenib becomes a more acceptable treatment strategy.

Cost-threshold analysis

Finally, we conducted a cost threshold analysis to determine the pill cost of regorafenib where it would become cost-effective as a second-line therapy for HCC. Supplemental Figure 2 illustrates the ICER vs. cost of regorafenib, and it crosses $100,000 per QALY at a cost of $67 per pill.

DISCUSSION

Although regorafenib can provide an additional 2 quality-adjusted life months compared to best supportive care for advanced HCC patients who progress on sorafenib, we found it is not a cost-effective therapy. Regorafenib consistently had ICERs > $100,000 per QALY in all one-way sensitivity analyses and every iteration of cost-effectiveness acceptability curves. In a cost threshold analysis, we found regorafenib pill cost would need to be reduced to $67 from its current price of $165 per pill to be cost-effective.

Two-way sensitivity analysis showed regorafenib could be cost-effective if the survival benefit over best supportive care was 6 months or greater. Although this exceeds the survival benefit seen in all-comer patients who progress on sorafenib, it may be possible to select a subgroup of patients in whom this survival benefit would be observed. It is increasingly clear that HCC is a heterogeneous tumor with differences in tumor biology and treatment responsiveness between patients. Similarly, the RESORCE Trial focused on patients who progressed on sorafenib, selecting for patients who did not respond to multikinase inhibitor therapy, but it is possible regorafenib may have a greater benefit for patients who were intolerant to sorafenib or sorafenib-naïve patients (i.e. as first-line therapy). Unfortunately, we lack clinically useful biomarkers to predict response to systemic therapy in patients with HCC. In a secondary analysis of SHARP data, high s-c-KIT and low hepatocyte growth factor concentration at baseline showed a trend toward predicting improved survival among sorafenib-treated patients[23], however there are not any prognostic biomarkers which have been validated and/or adopted for routine clinical use.[24-27] Therefore, discovery of clinically useful biomarkers that predict response to regorafenib may improve its value as a second line treatment for HCC.

Cost-effectiveness incorporates several important factors for deciding therapies including cost, clinical effectiveness, and tolerability; however, fails to consider patient preferences and availability of other treatment regimens. The importance of pill cost and clinical effectiveness (survival benefit) on regorafenib's cost effectiveness has been discussed above. Although regorafenib can have a high rate of AEs, it appears to have minimal detrimental impact on health-related quality of life, as the regorafenib and placebo arms had no meaningful differences in quality of life scores.[16] These data were derived from efficacy trial-based data so it will be important to monitor if regorafenib is equally well tolerated in post-marketing studies, as has been done for sorafenib in the Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON).[9] As with all discussions regarding cancer treatment, it will be important for providers to discuss and weigh potential pros and

cons of second-line treatment with regorafenib. Decisions regarding the role of regorafenib must be determined considering each patient's preferences, goals of care, and quality of life. Importantly, there are currently not any effective alternative treatments for patients who progress on sorafenib, thus regorafenib is the only option for these patients and fills an important niche in HCC therapy. However, there are currently several promising agents, including immunotherapy, that are undergoing evaluation in phase II-III studies.[28] Given the rapidly changing landscape of HCC therapeutics, cost-effectiveness will be increasingly important when considering potentially forthcoming second-line treatment options for HCC.

Our study has notable strengths and weaknesses. We relied on modeling data from the RESORCE Trial, which may not reflect real world practice. Patients in the RESORCE Trial were highly selected with excellent functional status and liver function. Real world effectiveness is likely to be worse, as has been shown with sorafenib therapy, and thus this would make the ICERs for regorafenib even higher so would not change the overall conclusion of our study.[8] Patients in RESORCE also had a higher burden of extrahepatic versus intrahepatic disease, which has been shown to impact outcomes in HCC.[29] To address this limitation, we performed robust one-way and two-way sensitivity analyses, which showed regorafenib was not cost-effective across a wide range of model inputs. This was also confirmed in our Monte-Carlo analysis and cost-effectiveness acceptability curves. Finally, our study evaluates regorafenib in all-comer patients who progress on sorafenib. Although not cost-effective when considered as a group, our analysis cannot account for potential individual differences in treatment responsiveness.

In summary we have shown that while clinically effective, regorafenib may provide low value as a second line therapy for HCC. High costs, coupled with modest clinical effectiveness, are important considerations when considering palliative second line therapies for HCC. Significant reduction in

regorafenib cost, to better reflect its overall clinical value, or better selection of patients in whom survival benefit is maximized would greatly impact regorafenib cost effectiveness.

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FIGURE LEGENDS

Figure 1. Markov model structure with health states

Figure 2. One-way sensitivity analyses showing the ICER as model parameters are varied over their ranges. PFS – progression free survival, TTP – time to progression, USD – US dollars

Figure 3. Cost-effectiveness acceptability curves

ONLINE ONLY

Supplemental Figure 1A – Model generated progression free survival curve for regorafenib and best supportive care

Supplemental Figure 1B – Model generated overall survival for regorafenib and best supportive care

Supplemental Figure 2 – Cost-threshold analysis of regorafenib pill cost

Table 1: Base case model parameters and one-way sensitivity analysis ranges derived from prior literature

Parameter	Value (Range)	Source
Outcomes		
Regorafenib		
Median Overall Survival	10.6 (9.1 to 12.1) months	[16]
Median Progression-Free Survival	3.1 (2.4 to 3.8) months	[16]
Median Time to Progression	3.2 (2.6 to 3.9) months	[16]
Best Supportive Care		
Median Overall Survival	7.8 (6.6 to 9.1) months	[16]
Median Progression-Free Survival	1.5 (1.4 to 1.6) months	[16]
Median Time to Progression	1.5 (1.4 to 1.6) months	[16]
Proportion of Patients with Adverse Events		
Regorafenib		
Hypertension	0.152 (0.116 to 0.188)	[16]
Hand-foot skin reaction	0.126 (0.092 to 0.16)	[16]
Fatigue	0.091 (0.062 to 0.12)	[16]
Diarrhea	0.032 (0.014 to 0.05)	[16]
Best Supportive Care		
Hypertension	0.047 (0.017 to 0.077)	[16]
Hand-foot skin reaction	0.005 (-0.005 to 0.015)	[16]
Fatigue	0.047 (0.017 to 0.077)	[16]
Diarrhea	0 (0 to 0)	[16]
Weekly Costs		
Regorafenib (per week on drug)	$4,156 (3138 to 5174)	[18]
Computed Tomography Imaging	$234 (177 to 291)	[30]
Other care	$174 (131 to 216)	[31]
Hypertension	$8.70 ($6.57 to $10.83)	[18]
Hand-foot skin reaction	$5 ($3.78 to $6.23)	[3]
Fatigue	$0 ($0 to $0)	
Diarrhea	$14.84 ($11.2 to $18.48)	[21]
Utilities		
HCC Progression-Free	0.76 (0.59 to 0.93)	[14, 16, 17]
HCC Progressed	0.76 (0.59 to 0. 93)	[14, 16, 17]
Disutilities from Adverse Events		
Hypertension	-0.025 (-0.031 to -0.019)	[32]
Hand-foot skin reaction	-0.116 (-0.144 to -0.088)	[33]
Fatigue	-0.115 (-0.143 to -0.087)	[33]
Diarrhea	-0.103 (-0.128 to -0.078)	[33]
Duration of Disutilities		
Hypertension	5 (3.8 to 6.2) days	[17]
Hand-foot skin reaction	14 (10.6 to 17.4) days	[17]
Fatigue	10 (7.6 to 12.5) days	[17]

Diarrhea	5 (3.8 to 6.2) days	[17]
Discount Rate	3%	

Table 2. Cost effectiveness of Regorafenib in the base case scenario. ICER – incremental cost effectiveness ratio; QALY – quality adjusted life years

	Costs	QALYs	ICER
Best Supportive Care	$7,408	0.63	
Regorafenib	$47,112	0.81	$224,362

Table 3. Incremental cost effectiveness ratios (ICERs) from two-way sensitivity analysis varying median overall survival for regorafenib and best supportive care.

Median Overall Survival		Best Supportive Care			
		6 months	**7 months**	**8 months**	**9 months**
Regorafenib	**9 months**	$ 191,041	$ 301,969	$ 753,008	*
	10 months	$ 145,736	$ 199,395	$ 321,341	$ 1,380,784
	11 months	$ 118,888	$ 150,696	$ 208,009	$ 397,501
	12 months	$ 98,386	$ 118,102	$ 148,779	$ 220,488

*-dominated ,i.e. more expensive and fewer QALYs

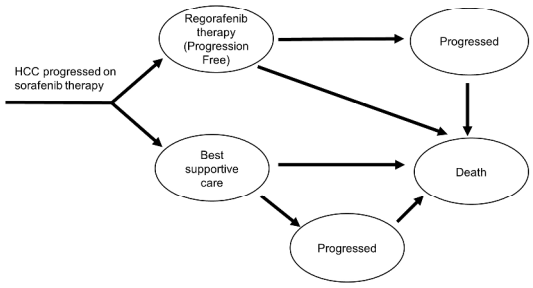

Figure 1

Figure 1

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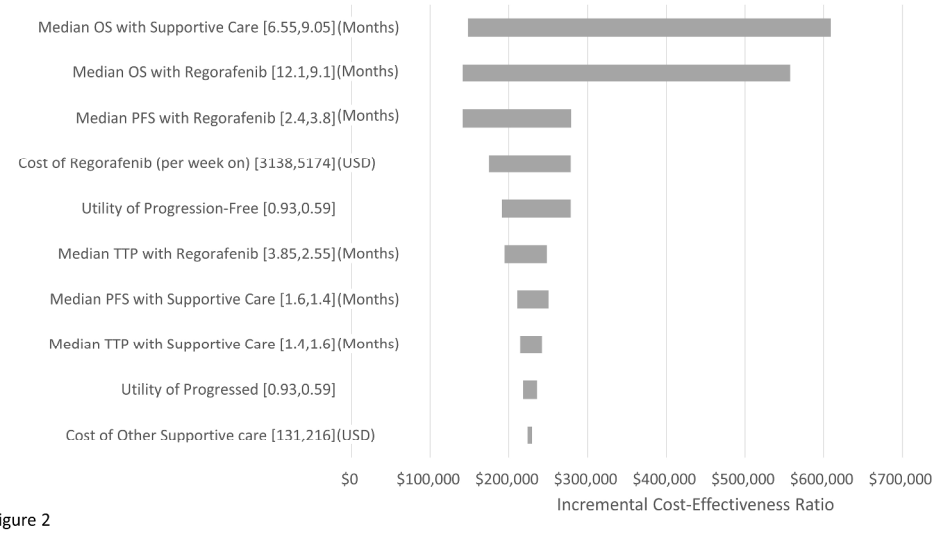

Figure 2

Figure 2

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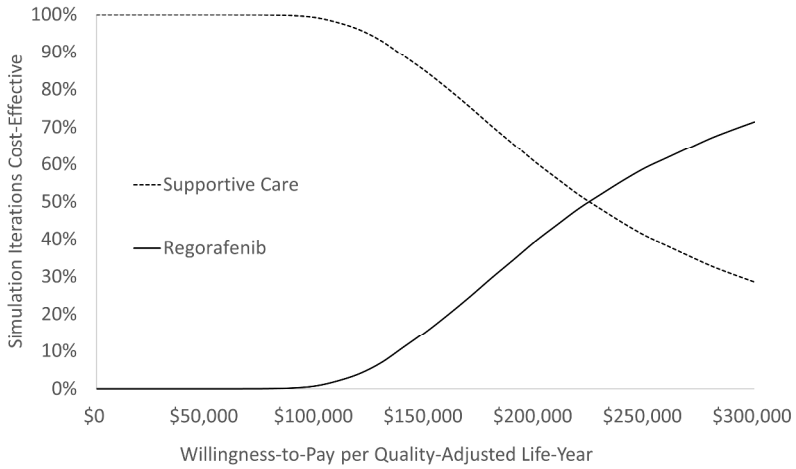

Figure 3

Figure 3

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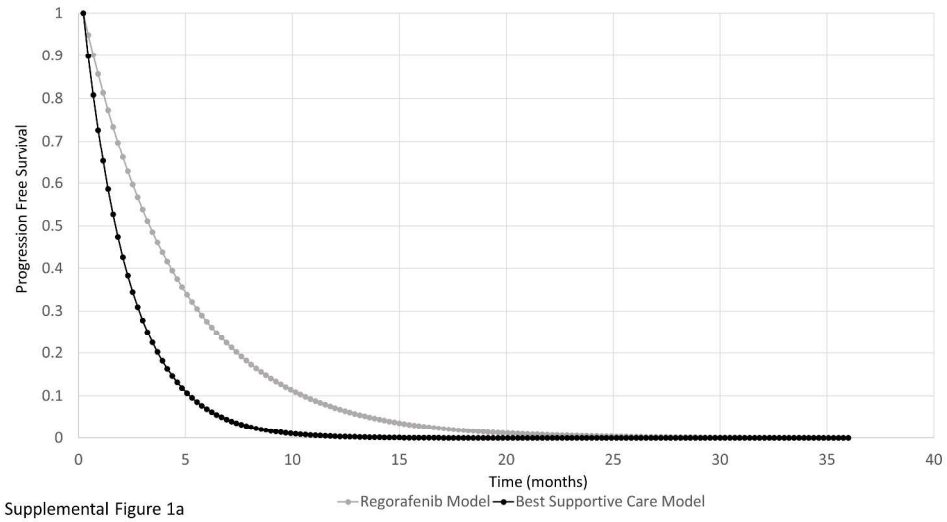

Supplemental Figure 1A

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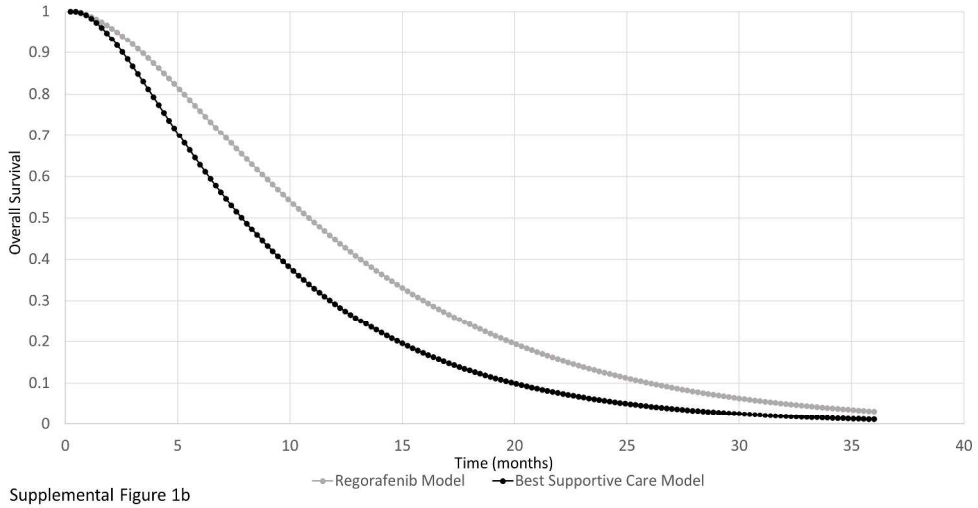

Supplemental Figure 1b

Supplemental Figure 1B

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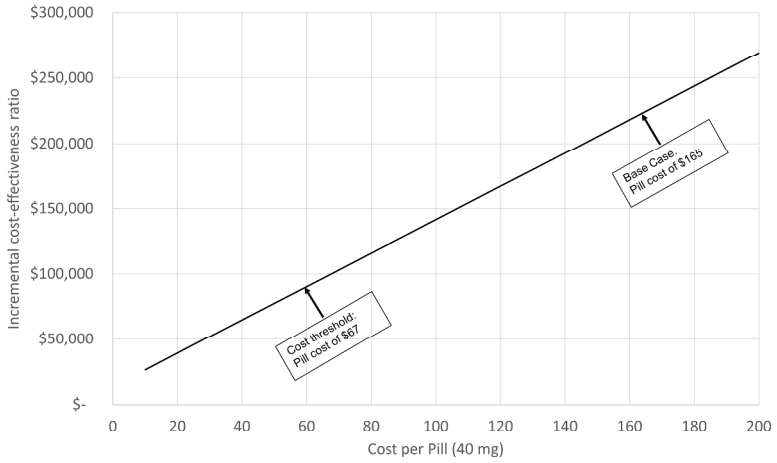

Supplemental Figure 2

Supplemental Figure 2

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Sensitivity analysis varying HCC progression-associated quality adjusted life year; ICER – incremental cost effectiveness ratio; QALY – quality adjusted life years

QALY for patients with HCC progression	**ICER**	**QALY for patients without HCC progression**	**ICER**
0.76 (base case)	$224,362	0.76 (base case)	$224,362
0.66	$251,674	0.86	$219,184
0.56	$286,556	0.96	$214,240
0.46	$332,664	1	$212,324
0.36	$396,455		
0.26	$490,515		
0.16	$643,091		
0.06	$933,439		
0	$1,280,249		