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ORIGINAL REPORT

Cost-Effectiveness Analysis of Regorafenib for Metastatic Colorectal Cancer

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ABSTRACT

Purpose
Regorafenib is a standard-care option for treatment-refractory metastatic colorectal cancer that increases median overall survival by 6 weeks compared with placebo. Given this small incremental clinical benefit, we evaluated the cost-effectiveness of regorafenib in the third-line setting for patients with metastatic colorectal cancer from the US payer perspective.

Methods
We developed a Markov model to compare the cost and effectiveness of regorafenib with those of placebo in the third-line treatment of metastatic colorectal cancer. Health outcomes were measured in life-years and quality-adjusted life-years (QALYs). Drug costs were based on Medicare reimbursement rates in 2014. Model robustness was addressed in univariable and probabilistic sensitivity analyses.

Results
Regorafenib provided an additional 0.04 QALYs (0.13 life-years) at a cost of $40,000, resulting in an incremental cost-effectiveness ratio of $900,000 per QALY. The incremental cost-effectiveness ratio for regorafenib was > $550,000 per QALY in all of our univariable and probabilistic sensitivity analyses.

Conclusion
Regorafenib provides minimal incremental benefit at high incremental cost per QALY in the third-line management of metastatic colorectal cancer. The cost-effectiveness of regorafenib could be improved by the use of value-based pricing.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer death in men and women in the United States.[1] In 2010, $14 billion was spent in the United States on management of CRC.[2] Multiple drug regimens are available for the treatment of metastatic CRC (mCRC), including combination therapies with fluorouracil, oxaliplatin, irinotecan, bevacizumab, cetuximab, and panitumumab. Before 2012, there was no approved treatment available for patients who had experienced progression after these standard regimens.

Regorafenib is an oral multikinase inhibitor that targets angiogenic, stromal, and oncogenic receptor tyrosine kinases.[3] The CORRECT (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) trial compared the effects of regorafenib with those of placebo in patients who experienced progression after standard regimens.[4] The trial demonstrated a median overall survival (OS) benefit of 1.4 months for regorafenib when compared with placebo. Grade 3 to 4 treatment-related adverse events (AEs) occurred in 54% of patients assigned to treatment with regorafenib and 14% of patients assigned to placebo. The most frequent grade 3 to 4 AEs occurring more commonly with regorafenib than placebo were hand-foot skin reaction (17% *v* 1%), fatigue (10% *v* 6%), diarrhea (7% *v* 1%), hypertension (7% *v* 1%), and rash or desquamation (6% *v* 0%). Regorafenib was subsequently approved by the US Food and Drug Administration in September 2012 and has become a standard-care option for mCRC refractory to standard regimens.

Given that regorafenib has a significant AE profile, provides a small incremental benefit, and is associated with a high cost, the value of this treatment relative to its benefit remains unclear. To address this issue, we developed a Markov model to evaluate the cost-effectiveness of regorafenib as third-line therapy in patients with mCRC from the perspective of the US payer.

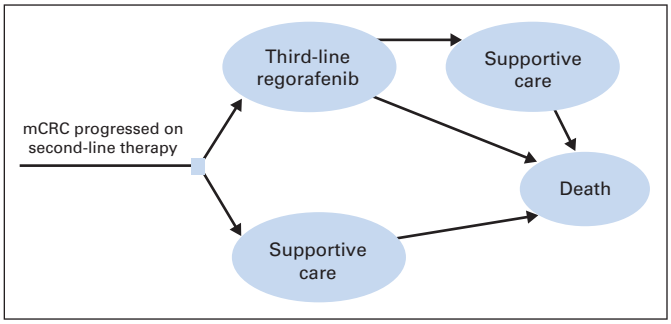

Fig 1. Markov model. mCRC, metastatic colorectal cancer.

METHODS

The structure of the Markov model consisted of an initial decision regarding treatment with regorafenib or best supportive care. Patients who initially received regorafenib could end therapy because of disease progression or intolerance of grade 3 to 4 AEs. Patients who experienced progression after regorafenib could receive best supportive care. All patients in each health state could experience progression to death (Fig 1).

Each model cycle represented 4 weeks, because in clinical practice, patients receive regorafenib daily for 3 weeks followed by a 1-week break. The primary outputs of the model included cost, life-years (LYs), and quality-adjusted LYs (QALYs), which were used to calculate the incremental cost-effectiveness ratio (ICER). The Markov model was implemented in TreeAge Pro 2013 software (https://www.treeage.com),[5] and statistical analyses were performed in R software (http://www.r-project.org).

Model Survival Estimates

We based our assumption describing the survival benefits associated with regorafenib on the results of the CORRECT trial.[4] The overall mortality rate, which corresponded to the probability of death, was derived from the OS curves for treatment with regorafenib and placebo published in the CORRECT trial. Engauge Digitizer software (version 4.1; http://digitizer.sourceforge.net) was used to extract the data points from the OS curves, and these data points were then used to fit parametric survival models.[6] We found that Weibull and log-logistic models provided a good fit for all curves according to the Akaike information criterion and the Schwarz–Bayesian criterion.[7] We used a Weibull distribution to model survival because it can have an increasing hazard rate and is suitable for modeling the events occurring early during follow-up periods. On the basis of the fitted Weibull OS model, denoted as S(t), we computed the cause-specific mortality M at cycle t as: $M = (S[t] - S[t + 1])/S(t)$.

Progression Risk

In the regorafenib treatment group, treatment discontinuation due to AEs or progression on therapy was estimated assuming an exponential distribution based on the median treatment duration published in the CORRECT trial. Estimates of mortality and progression risk beyond the follow-up time in the clinical trials were extrapolated based on the fitted survival models.

Utility Estimates

Each health state was assigned a health utility score based on quality-of-life data collected in the CORRECT trial. In the trial, EQ-5D[8] index scores were 0.73 in the regorafenib group and 0.74 in the placebo group at baseline. At the end of treatment, both groups had a score of 0.59. In the model, we assigned all patients a utility of 0.66, which is the mean of these values. We used 0.59 and 0.735 as the boundaries of the range in sensitivity analyses. To compute the total QALYs in the Markov model, survival time was adjusted by the utility. We included grade 3 to 4 AEs in the model that had significantly different rates between the arms of the CORRECT trial, which were hand-foot syndrome, hypertension, diarrhea, and fatigue. Disutilities associated with AEs were estimated based on established values in the literature.[9] For the temporary health states associated with AEs modeled in this study (fatigue, hand-foot syndrome, diarrhea, and hypertension), the measured decreases in utilities from the published literature and the unmeasured decreases in utilities for these same health states in the CORRECT study were expected to be similar. The duration of AEs was estimated based on clinical experience. Hand-foot syndrome was assumed to last for 14 days, with a disutility of −0.116. Hypertension was assumed to last for 5 days, with a disutility of zero. Diarrhea was assumed to last for 5 days, with a disutility of −0.103. Fatigue was assumed to last for 10 days, with a disutility of −0.115. The duration-adjusted disutility was subtracted from the baseline utility to calculate the overall utility of each health state.

Cost Estimates

Only direct medical costs were considered and stated in 2014 US dollars. To estimate the unit price of each drug, we used 2014 average wholesale price (AWP) data from the Centers for Medicare and Medicaid Services, as described by the Academy of Managed Care Pharmacy.[10] Regorafenib is dosed in 40-mg tablets, and the recommended starting dose is 160 mg. The AWP is $147.26 per 40-mg tablet. The CORRECT trial states that the mean daily dose received was 147 mg. We performed analyses in the model with three different dosing strategies: 120, 160, and 147 mg daily. Although 147 mg is not a realistic dose in clinical practice, it provides an average value for assessing the expected cost of regorafenib in a patient cohort.

Assumptions for management of AEs were based on recently published guidelines.[11] Hand-foot syndrome was assumed to be managed with 0.05% clobetasol cream and 4% lidocaine cream. Hypertension was assumed to be managed with amlodipine 5 mg daily. Diarrhea was assumed to be managed by a physician visit and lomotil and loperamide. Fatigue was assumed to have no specific medical management. AE costs were calculated according to the Medicare physician fee schedule for 2014. The fees for outpatient physician visits were based on current procedural terminology codes.[12] The methods used for these cost calculations were previously described by Tumeh et al.[13] We did not perform annual discounting of the costs and benefits in this analysis, because the OS rate was 24% at 1 year for both groups.

Sensitivity Analysis

We performed internal model validations demonstrating that the OS curves generated by the Markov model simulation closely approximated those presented in the CORRECT trial (Appendix Fig A1, online only). A series of sensitivity analyses were performed to evaluate the robustness of the model and address uncertainty in the estimation of model parameters. Utilities were varied over their 95% CIs. Drug costs were varied within ± 20% of their baseline values, in accordance with established approaches.[14,15] In univariable sensitivity analyses, we varied the value of one parameter at a time over its defined range and examined the effect on the ICER. We used the lower boundary for 120-mg dosing ($7,422 for one cycle of therapy) and the upper boundary for 160-mg dosing ($14,843 for one cycle of therapy) to provide the range of costs of regorafenib. In probabilistic sensitivity analyses, we performed 10,000 Monte Carlo simulations, each time randomly sampling from the distributions for all parameters simultaneously. We used gamma distribution for the cost parameters and beta distribution for utility and probability parameters. The baseline values, ranges, and distributions of model parameters are listed in Table 1.

RESULTS

Base Case Results

The base case model results are listed in Table 2. The use of regorafenib compared with best supportive care produced a gain of 6 weeks of life (0.13 LYs). When adjusted for quality of life, use of regorafenib produced a gain of 2 quality-adjusted life-weeks (0.04 QALYs). On the basis of the dosing strategy used, the incremental cost

Table 1. Model Parameters: Baseline Values, Ranges, and Distributions for Sensitivity Analysis

Variable	Value	Range	Reference	Distribution
AEs with regorafenib				
Hand-foot syndrome	0.17	0.136 to 0.204	CORRECT	Beta
Fatigue	0.09	0.072 to 0.108	CORRECT	Beta
Diarrhea	0.07	0.056 to 0.084	CORRECT	Beta
Hypertension	0.07	0.056 to 0.084	CORRECT	Beta
AEs with best supportive care				
Hand-foot syndrome	0	0 to 0	CORRECT	Beta
Fatigue	0.05	0.04 to 0.06	CORRECT	Beta
Diarrhea	0.01	0.008 to 0.012	CORRECT	Beta
Hypertension	0.01	0.008 to 0.012	CORRECT	Beta
AE disutilities				
Hand-foot syndrome	−0.116	−0.093 to −0.139	Lloyd et al[9]	Beta
Fatigue	−0.115	−0.093 to −0.139	Lloyd et al[9]	Beta
Diarrhea	−0.103	−0.082 to −0.123	Lloyd et al[9]	Beta
Hypertension	0	0 to 0		
AE duration, days				
Hand-foot syndrome	14	11.2 to 16.8	Estimated	Gamma
Fatigue	10	8 to 12	Estimated	Gamma
Diarrhea	5	4 to 6	Estimated	Gamma
Hypertension	5	4 to 6	Estimated	Gamma
AE cost, $				
Hand-foot syndrome	134.48	107.58 to 161.38		Gamma
Fatigue	0	0 to 0		Gamma
Diarrhea	81.60	65.28 to 97.92		Gamma
Hypertension	59.10	47.28 to 70.92		Gamma
Other				
Cost of regorafenib dose, $ per 28-day cycle				
120 mg	9,277	7,422 to 11,132		Gamma
147 mg	11,364	9,091 to 13,639		Gamma
160 mg	12,369	9,896 to 14,843		Gamma
Utility	0.66	0.59 to 0.735	CORRECT	Beta

Abbreviations: AE, adverse event; CORRECT, Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy.

of a course of treatment with regorafenib was $32,000 (120-mg dosing) to $43,000 (160-mg dosing). The ICER for regorafenib compared with best supportive care was between $730,000 and $980,000 per QALY.

Sensitivity Analyses

The results of univariable sensitivity analyses are presented in the tornado diagram (Fig 2). The parameters with the greatest influence on the ICER were cost of regorafenib, probability of stopping regorafenib before death because of an AE, and baseline utility value. Across broad variation in the ranges for each parameter, the ICER remained > $550,000 per QALY. The duration, cost, and disutility for AEs had a minor influence on the ICER.

Table 2. Base Case Results

Cost/Effect	Incremental Difference With Regorafenib		
Dose, mg	120	147	160
Cost, $	32,141	39,391	42,838
ICER, $ per LY	253,663	310,881	338,090
ICER, $ per QALY	732,242	897,411	975,954

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

The results of the probabilistic sensitivity analyses are shown in the cost-effectiveness acceptability curves in Figure 3. These curves show the probability that regorafenib is cost-effective across increasing willingness-to-pay (WTP) values. These results demonstrated nearly 0% probability that regorafenib is cost-effective at WTP values < $600,000 per QALY. There was a 50% chance that regorafenib is cost-effective at a WTP value of approximately $900,000 per QALY.

DISCUSSION

A fluoropyrimidine in combination with either oxaliplatin or irinotecan is an established treatment for mCRC, with good clinical effectiveness at a favorable cost.[15] In the past decade, advances have been made by pairing chemotherapy with biologic agents. By targeting angiogenesis, efficacy has been demonstrated with the addition of bevacizumab in the first-line, second-line, and maintenance settings.[16-20] Ziv-aflibercept, which also targets the angiogenesis pathway, produced a 1.4-month median OS benefit when added to FOLFIRI (fluorouracil, leucovorin, and irinotecan) compared with FOLFIRI alone in the second-line setting.[21] The RAISE trial recently demonstrated a 1.6-month median OS benefit when ramucirumab was added to chemotherapy in the second-line setting.[22] By targeting the epidermal growth factor receptor, alternative monoclonal antibodies

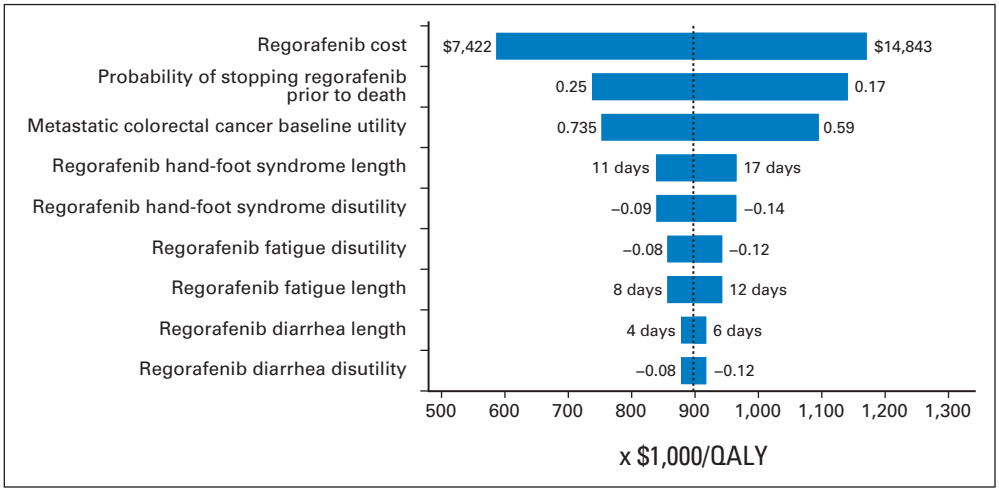

Fig 2. Univariable sensitivity analyses. QALY, quality-adjusted life-year.

have been paired with chemotherapy. Moreover, there are meaningful data to support the addition of either cetuximab (chimeric immunoglobulin G1 isotype antibody) or panitumumab (human immunoglobulin G1 isotype antibody) to chemotherapy in patients with *RAS* wild-type disease.[23-32]

These biologic agents, however, are not without significant cost, and their value remains under scrutiny.[33,34] Cost-effectiveness analyses provide a standard methodology for examining the cost of a drug, in the context of the survival benefit, quality of life, costs of administration and AEs, and duration of therapy. Bevacizumab has recently been shown to have an ICER > $350,000 per QALY in both the first- and second-line settings.[15] The value of ziv-aflibercept was evaluated from the perspective of a payer in the United Kingdom and found to have an ICER > £62,000 per QALY ($95,000 per QALY).[35] In this evaluation, the authors reported that the cost estimate for ziv-aflibercept was based on a patient access schema but did not report the direct cost of the drug, which may be significantly lower in the United Kingdom than in the United States. There are multiple published estimates of the cost-effectiveness of *EGFR*-targeted therapies.[36-43] These studies have involved a variety of methodologies, across multiple countries, with ICERs ranging from $20,000 to $3 million per LY.[44] These data provide useful reference points for assessing the total cost of therapy and the value of regimens for mCRC, but it remains challenging to compare cost data from different health systems because of the wide variations among countries and the scope of costs considered in individual studies.[45]

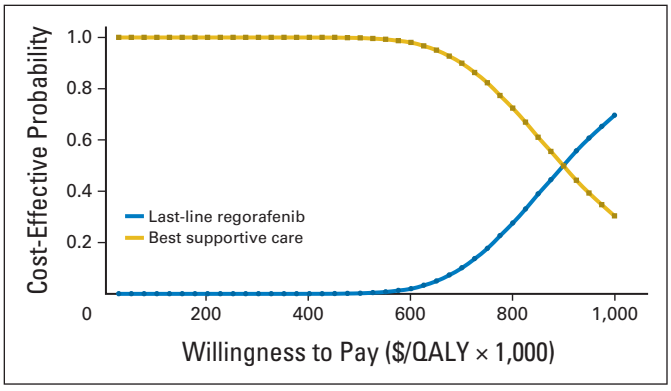

Fig 3. Cost-effectiveness acceptability curves. QALY, quality-adjusted life-year.

The CORRECT trial demonstrated that by targeting angiogenic, stromal, and oncogenic receptor tyrosine kinases, survival could be prolonged for some patients with mCRC who had exhausted other systemic options. However, given the modest incremental benefit and significant AEs associated with this therapy, the role of regorafenib has been controversial. We performed the first study to our knowledge examining the cost-effectiveness of regorafenib in patients with mCRC who had experienced progression with standard regimens. On the basis of our model, regorafenib provides modest incremental benefit at high incremental cost per QALY. Even when using assumptions favorable to regorafenib in univariable sensitivity analyses, the ICER remained > $550,000 per QALY. The probabilistic sensitivity analyses, varying all model parameters in 10,000 Monte Carlo simulations, revealed that it was highly unlikely that regorafenib would be considered cost-effective at any WTP threshold < $600,000 per QALY and suggested that regorafenib exceeds the usually accepted values for cost-effective health care interventions.[46-49]

Moreover, patients who do not have supplemental insurance to cover Medicare Part D drugs are required to cover approximately 20% of drug costs. These patients would incur an average out-of-pocket expense of $7,000 for the total cost of regorafenib therapy. We recommend a careful discussion between physicians and patients regarding the additional benefit and potential total drug cost before starting regorafenib.

Our analysis was limited by data availability and our assumptions.[50] Quality of life was reported at the beginning and end of treatment in the CORRECT trial. We used these values to estimate the quality of life during treatment. Although this estimation is not ideal, actual variations in health-related quality of life would be accounted for by the range of utility values used in the sensitivity analyses. It was challenging to simulate real-life dosages of regorafenib within the model, because the average dose was 147 mg, but the drug is available in 40-mg tablets. With an average dose of 147 mg, we feel that our alternative analyses using both 120 and 160 mg provide appropriate estimations for the average dosing that would occur in a population and the practical range of dosing that could occur in practice. We

recognize that some clinicians initiate therapy with an 80-mg dose, despite the lack of efficacy data to support this dosing strategy. If we were to assume the same level of efficacy as with the standard dose, the ICER for regorafenib dosed at 80 mg per day would be $488,524 per QALY.

We used the AWP[51] to ascertain drug cost; however, an alternative approach would have been to use the average sales price.[52] Although there may be slight variations in cost when using the AWP as opposed to the average sales price as an estimate for drug cost, these variations in cost are subsumed in the ranges and probability distributions examined in the sensitivity analyses. In addition, we obtained the average sales price for regorafenib using the described method[52] and found that the value fell within the range of values used in our sensitivity analyses. These variations in drug cost would not alter the general conclusions drawn from our model. Substantial variation in the cost of regorafenib would be necessary for it to be considered cost-effective by commonly applied thresholds.[46-49]

In addition, although the OS curves remained close together throughout the follow-up period, the progression-free survival curves for the CORRECT trial split after 50 days of therapy. This suggests the presence of a patient population that may benefit more from regorafenib. Currently, there is no biomarker available to identify patients who are most likely to benefit from regorafenib, which could improve the incremental cost-effectiveness of regorafenib. In the CORRECT trial, patients discontinued therapy because of either disease progression or AEs, with variation in the rate of discontinuation between groups. For example, the rate of discontinuation of therapy for AEs was 18% in the regorafenib group and 13% in the group receiving placebo. Irrespective of the reason for discontinuing treatment, the drug and AE costs incurred in the model would not change, and as a result, the ICER also would not change. For this reason, we did not explicitly use the reason for stopping therapy as a parameter in the model. Treatment discontinuation because of AEs or disease progression during therapy was estimated assuming an exponential distribution based on the median treatment duration published in the CORRECT trial. The published median treatment duration was used to estimate the time on treatment until discontinuation. Estimates of mortality and progression risk beyond the follow-up time in the clinical trials were extrapolated based on the fitted survival models.

Our study demonstrates the high incremental cost with low incremental benefit of regorafenib in mCRC over wide variations in the assumptions incorporated into the models. On the basis of our analysis, regorafenib provides low value at its current cost. New pricing and payment systems are needed to support delivery of cost-effective care, and many have been suggested. These include value-based pricing,[53,54] third-party buy and bill,[55] indication-specific pricing,[56] bundled payment,[57] pathway adherence,[55] payment by results,[58] and inclusive shared savings.[59] With increasing deductibles and copays, our patients are now bearing a significant burden of the cost of drugs. Novel approaches to drug discovery and development have dramatically increased the number of targets for cancer therapies. The advent of these agents presents a challenge in terms of timeline for drug development and health care costs. New enrichment strategies are needed in patient selection for clinical trials, guideline development, and payer coverage determination that address clinical value in addition to statistically significant clinical benefit. These strategies are necessary to guide delivery of high-value interventions to our patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cost-Effectiveness Analysis of Regorafenib for Metastatic Colorectal Cancer

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Appendix

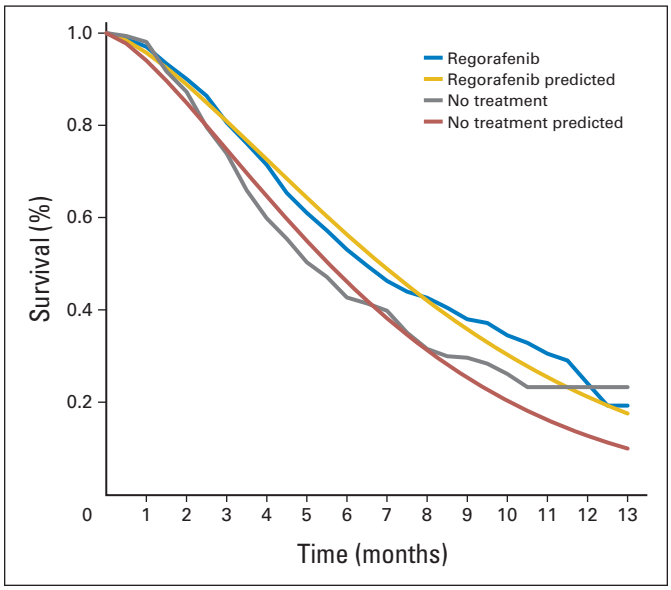

Fig A1. Internal validation of overall survival model.