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REVIEW

Cost-Effectiveness Analysis of Regorafenib versus Other Third-Line Treatments for Metastatic Colorectal Cancer

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Background: Regorafenib, a novel multikinase inhibitor, has been approved by the US Food and Drug Administration as a standard treatment choice for metastatic colorectal cancer (mCRC). Nonetheless, its substantial cost places a significant burden on social health resources and patients. However, the cost-effectiveness (CE) of regorafenib compared to other third-line therapies is still undetermined.

Objective: This study aims to assess the CE of regorafenib compared to other third-line therapies for the treatment of mCRC.

Methods: We conducted a comprehensive literature search in PubMed, Medline, Scopus, Embase, Cochrane Library, as well as nine other databases to identify relevant studies published up to October 2023, focusing on patients with mCRC and examining the cost-effectiveness of regorafenib. Following the screening and extraction of pertinent data, the study quality was assessed using the Quality of Health Economic Studies (QHES) checklist.

Results: The literature search yielded 751 records, and after applying the inclusion criteria, 13 studies from 7 different countries were included. Of these, 7 studies evaluated the cost-effectiveness of regorafenib compared to trifluridine/tipiracil (TAS-102), 3 studies compared regorafenib with best supportive care (BSC), and 3 studies compared regorafenib with fruquintinib, serplulimab, and regorafenib dose optimization (ReDo).The quality of the included studies was high with an average QHES scores of 85.62. Regorafenib standard dose proves to be less cost-effective than alternative third-line therapies. Implementing a dose optimization strategy could potentially rectify this disparity and enhance the cost-effectiveness of regorafenib.

Conclusion: The use of the standard dose of regorafenib is generally regarded as not cost-effective when compared to other third-line therapies for patients with mCRC. However, implementing a dose-escalation strategy may enhance regorafenib's cost-effectiveness. Consequently, significant price reductions or optimizing the dose of regorafenib are required to achieve cost-effectiveness.

Keywords: regorafenib, metastatic colorectal cancer, cost-effectiveness, incremental cost-effectiveness ratios

Introduction

Colorectal cancer (CRC) is the third most common type of cancer and a prominent cause of cancer-related deaths worldwide.[1] In 2023, approximately 153,020 new cases of CRC and 52,550 deaths in the United States.[2] In the past decades, the incidence of CRC in individuals under the age of 50 years has increased rapidly, and this trend has been observed globally in both men and women.[3] Among all initial CRC diagnoses, approximately 25% of patients have metastatic CRC (mCRC) at the first diagnosis and at least 50% of patients eventually develop metastases.[4,5] The prognosis of mCRC is poor, with a 5-year survival rate of less than 15%.[6] Although surgery with or without adjuvant chemotherapy can cure early-stage CRC, mCRC cannot be eradicated due to the substantial burden of disseminated cancer cells, which are composed of therapy-resistant metastasis-competent cells.

For decades, major therapeutic advances involving chemotherapy (fluoropyrimidine, oxaliplatin, and irinotecan) as a backbone combined with monoclonal antibodies targeting specific molecular subtypes have been achieved in mCRC, resulting in clinically relevant survival improvement.[4,7] In recent years, drugs targeting elevated processes or pathways in tumor cells, such as angiogenesis and the epidermal growth factor receptor (EGFR)-mediated mitogen-activated protein kinase (MAPK) pathway, have been successfully employed in clinical practice.[8] In 2012, regorafenib was approved by the

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United States Food and Drug Administration (FDA) as a third-line therapy for mCRC refractory to fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, prior anti-VEGF therapy, and if KRAS wild-type, previous anti-EGFR therapy.[9]

With the substantial price reduction of regorafenib and updates to relevant guidelines, several scholars have conducted comparative studies on the cost-effectiveness of regorafenib for patients with mCRC compared to other third-line or further treatment options. However, due to variations in the economic level, healthcare environment, and pricing of regorafenib in different countries, there may be differences in the methodologies or results of its economic evaluation. Therefore, this study aimed to evaluate the cost-effectiveness of regorafenib compared with other third-line or further treatments for mCRC to comprehensively assess its cost-effectiveness and provide guidance for clinical applications and healthcare decision-makers.

Materials and Methods

Sources and Search Strategy

This study conformed to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10] Eligible studies were searched using PubMed, Medline, Scopus, Embase, Cochrane Library, and nine other databases to identify relevant articles published in English from January 1, 2012, to October 31, 2023, with an abstract available for review. Titles and abstracts were initially searched using the following search algorithm: "Regorafenib OR Stivarga AND metastatic colorectal cancer OR mCRC AND cost-effectiveness OR cost-utility or pharmacoeconomics or economic evaluation or cost".

Eligibility Criteria

The inclusion criteria were as follows: (a) adopting cost-effectiveness analysis or cost-utility analysis (CUA); (b) patients diagnosed with mCRC and treatment with regorafenib; (c) incremental cost-effectiveness ratios (ICERs) adopted to compare treatments. The exclusion criteria were as follows: (a) not published in English; (b) not related to economic evaluation; and (c) non-specific drug studies (studies about screening strategies, intervention thresholds, medication adherence, etc.).

Data Extraction and Quality Assessment

Eligible studies were independently screened by two researchers to extract relevant data for inclusion in the study. Cross-validation was conducted to ensure accuracy, and discrepancies were discussed and reconciled. The extracted content included basic information on the research (first author, publication date, country, perspective, research type/model, and outcome index), study design (intervention, health outcomes, time horizon, and discounting), study outcomes, sensitivity analysis, and other necessary parameters. Importantly, ICERs were extracted as reported in the original article, and no adjustment for year or purchasing power parity was performed.

The Quality of Health Economic Studies (QHES) Checklist was used to evaluate the quality of the included studies.[11] The QHES is a validated grading system designed to assess the quality of economic health analyses. It evaluates each study across 16 criteria and assigns a score between 0 and 100, where 0 indicates the lowest quality and 100 represents the highest. The point values for each criterion were determined using regression analysis. After calculating the points for all 16 criteria, the studies were categorized into four categories: extremely poor quality (0–24), poor quality (25–49), fair quality (50–74), and high quality (75–100).[12]

Results

Literature Search

A total of 751 potentially relevant articles obtained from both manual and gray literature searches were identified in the databases. After screening, 738 articles were excluded as they were outside the scope of this study. Thirteen articles met our inclusion criteria. A flow diagram of the search and selection strategy is shown in Figure 1.

Study Descriptions

As indicated in Table 1, these 13 studies were from seven different countries, four studies were conducted in the US,[13–16] three studies were from China,[17–19] two studies were from Japan[20,21] and the rest were from Italy,[22] England and Wales,[23] Greece,[24]

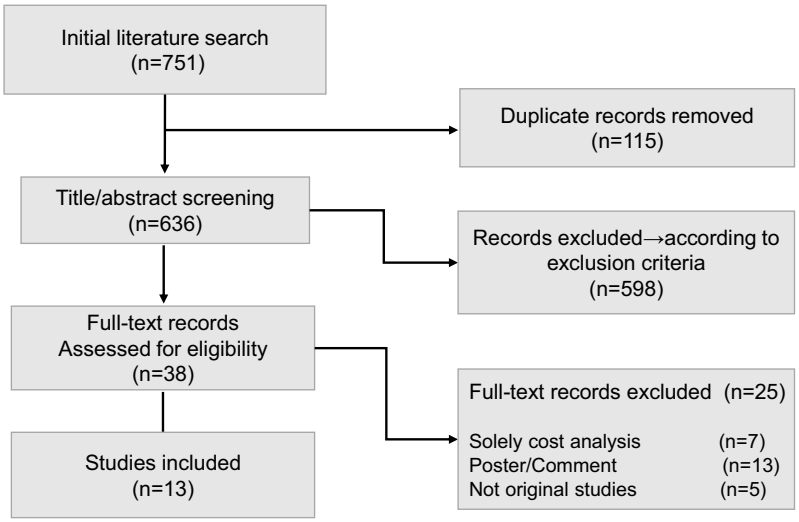

Figure 1 A flow diagram of articles identified and selection strategy based on inclusion criteria.

and the Czech.[25] The most commonly adopted perspective in the reviewed economic evaluation was the payer perspective; of the nine studies with the perspective of governmental healthcare, one used the third-party payer perspective. The majority of studies (11 of 13) incorporated cost-utility analysis (CUA), of which seven utilized the Markov model, whereas the remaining

Table 1 General Characteristics of the Included Records

Author (Publication Year)	Country	Perspective	Evaluation Techniques	Model Analysis	Outcome Index
Kashiwa M et al (2018)[20]	Japan	Japanese health care payer	Cost-utility Analysis, CUA	Partitioned survival model	LYs, QALYs, ICER, Cost
Barzi A et al (2019)[16]	USA	US payer perspective	Cost-utility Analysis, CUA	Markov model	ICER
Guan X et al (2021)[17]	China	Chinese health care perspective	Cost-utility Analysis, CUA	Markov model	LYs, QALYs, ICER, Cost
Cho SK et al (2018)[13]	USA	US payer perspective	Cost-utility Analysis, CUA	Markov model	QALYs, ICER, Cost
Bullement A et al (2018)[23]	England and Wales	UK National Health Service perspective	Cost-utility Analysis, CUA	Partitioned survival model	LYs, QALYs, ICER, Cost
Goldstein DA et al (2015)[14]	USA	US payer perspective	Cost-utility Analysis, CUA	Markov model	LYs, QALYs, ICER, Cost
Kimura M et al (2016)[21]	Japan	NA	Cost-utility Analysis, CUA	Partitioned survival model	ICER, CER
Giuliani J et al (2021)[22]	Italy	NA	Cost-utility Analysis, CUA	Partitioned survival model	Cost
Gourzoulidis G et al (2021)[24]	Greece	A third-party payer perspective	Cost-effective Analysis	Partitioned survival model	LYs, QALYs, ICER, Cost
Ma Y et al (2023)[18]	China	Chinese health care perspective	Cost-effective Analysis	Markov model	LYs, QALYs, ICER, Cost
Zhang S et al (2020)[19]	China	Chinese health care perspective	Cost-utility Analysis, CUA	Markov model	LYs, QALYs, ICER, Cost
MIcoch T et al (2018)[25]	Czech Republic	Czech Republic health care perspective	Cost-utility Analysis, CUA	Markov model	LYs, QALYs, ICER, Cost
Cho SK et al (2022)[15]	USA	United States (US) payer perspective	Cost-utility Analysis, CUA	Markov model	LYs, QALYs, ICER, Cost

Abbreviations: LYs, life years; QALYs, quality adjusted life-years; ICER, incremental cost-effectiveness ratio, NA, not applicable.

five adopted the partitioned survival model. Most studies selected life years (LYs), quality-adjusted life-years (QALYs), incremental cost-effectiveness ratio (ICER), and cost as the health output index. The results of the QHES assessment revealed that the overall quality of the included studies was relatively high, with an average QHES score of 85.62 (Table 2).

Cost-Effectiveness Analysis

Clinical data included in the records were mainly selected from randomized controlled trials (RCT), meta-analyses, and clinical trials. Progression-free survival (PFS) and/or overall survival (OS) were used as the outcomes in these 11 studies with a model, two studies used no model. Eight studies applied a fixed time horizon, such as 2.5, 3, 5, or 10 years, whereas the others did not indicate the time horizon. Six studies applied a 5% discount rate for both costs and QALYs, two studies used 3.5%, and one study applied 3%, while the other three studies did not. All the 13 studies only considered the direct medical cost, including drug, pallicare per day, adverse drug reactions (ADRs) related management, outpatient chemotherapy, terminal care, and other non-medical-related expenses. Clinical data selection and cost analyses are presented in Table 3.

Regorafenib versus BSC

As shown in Table 4, three studies evaluated the CE of regorafenib in a third-line setting in patients with mCRC. Goldstein et al[14] assessed the cost-effectiveness of regorafenib for mCRC from the US payer perspective and found that regorafenib provides minimal incremental benefit at a high incremental cost per QALY, with a 50% chance that regorafenib is cost-effective at a willingness-to-pay (WTP) value of approximately $900,000 per QALY. Zhang S et al[19] compared the cost-effectiveness of regorafenib with placebo plus best supportive care (BSC) in Chinese patients with mCRC, and indicated that regorafenib is not cost-effective at the WTP threshold of $27,576 when compared with the placebo group. Mlcoch et al[25] examined the cost-effectiveness of regorafenib using a propensity score-weighted cohort from the Czech Registry. They concluded that, based on data from the registry and RCTs in the Czech Republic, regorafenib represents a cost-effective therapeutic option for patients with mCRC at a WTP threshold of €47,000 per QALY.

Regorafenib versus Trifluridine/Tipiracil

As indicated in Table 4, seven studies evaluated the cost-effectiveness of regorafenib compared to trifluridine/tipiracil (TAS-102) for the treatment of patients with mCRC. Two studies were from the USA[13,15] two studies were from Japan 21,26[20,21] and the rest were from Italy,[22] England and Wales,[23] and Greece.[24] Five studies evaluated the cost-effectiveness of regorafenib standard dose with TAS-102 and concluded that TAS-102 is more clinically and cost-effective than regorafenib.[13,20,21,23,24] Two additional studies examined the cost-effectiveness of regorafenib dose optimization (ReDo) in comparison to TAS-102. They concluded that the optimal dosing strategy for regorafenib has enhanced its benefit-to-toxicity ratio and relative cost-effectiveness when compared to TAS-102.[15,22] Cho SK et al[15] conducted a cost-effectiveness

Table 2 Results Form the Quality of Health Economic Studies (QHES) Evaluation

Author (Publication Year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Score
Kashiwa M et al (2018)[20]	√	√	√	×	√	√	√	×	√	√	√	√	√	√	√	×	89
Barzi A et al (2019)[16]	√	√	√	×	√	√	×	√	√	√	√	√	×	×	√	×	78
Guan X et al (2021)[17]	√	√	√	×	√	√	√	√	√	√	√	√	×	√	√	√	90
Cho SK et al (2018)[13]	√	√	√	×	√	√	√	√	√	√	√	√	√	×	√	×	90
Bullement A et al (2018)[23]	√	√	√	×	√	√	√	√	√	√	√	√	√	×	√	√	91
Goldstein DA et al (2015)[14]	√	√	√	×	√	√	√	×	√	√	√	√	√	×	√	√	84
Kimura M et al (2016)[21]	√	×	√	×	×	√	√	√	√	√	√	√	√	×	√	×	77
Giuliani J et al (2021)[22]	√	×	√	×	×	√	√	×	√	√	√	√	√	×	√	√	73
Gourzoulidis G et al (2021)[24]	√	√	√	×	√	√	√	√	√	√	√	√	√	√	√	√	99
Ma Y et al (2023)[18]	√	√	√	×	√	√	√	√	√	√	√	√	√	√	√	×	96
Zhang S et al (2020)[19]	√	√	√	×	√	√	×	√	√	√	√	√	×	×	√	×	78
Mlcoch T et al (2018)[25]	√	√	√	×	√	√	×	√	√	√	√	√	×	×	√	×	78
Cho SK et al (2022)[15]	√	√	√	×	√	√	√	√	√	√	√	√	√	×	√	×	90
Average score																	85.62

Table 3 Cost Analysis of the Included Publications

Author (Publication Year)	Types of Clinical Trials	Health Outcomes	Time Horizon (Years)	Discounting	Cost Expense	
					Direct Cost	Indirect Cost
Kashiwa M et al (2018)[20]	RCT: CORRECT, CONCUR, RECOURSE	OS, PFS	5	2%	(1)(2)(3)(4)	NA
Barzi A et al (2019)[16]	Randomized Phase II trial	NA	NA	5%	(1)(2)(3)	NA
Guan X et al (2021)[17]	RCT: FRESCO, CONUR	PFS, OS	NA	5%	(1)(2)(3)	NA
Cho SK et al (2018)[13]	RCT: RECOURSE, CORRECT	PFS, MOS	5	5%	(1)(2)(3)(4)	NA
Bullement A et al (2018)[23]	RCT: RECOURSE, CORRECT, J003-10,040,030	OS, PFS, HRQL	10	3.5%	(1)(2)(3)(4) (5)	NA
Goldstein DA et al (2015)[14]	RCT (CORRECT)	OS	NA	NA	(1)(2)	NA
Kimura M et al (2016)[21]	RCT: CORRECT, RECOURSE	MST	<1	NA	(1)(2)(3)(4)	NA
Giuliani J et al (2021)[22]	RCT: RECOURSE, ReDOS	OS	NA	NA	(1)	NA
Gourzoulidis G et al (2021)[24]	RCT: RECOURSE, CORRECT, Phase II clinical trial	OS, PFS	10	3.5%	(1)(2)(3)(4)	NA
Ma Y et al (2023)[18]	RCT (ASTRUM-010, CONCUR)	OS, PFS	Lifetime	5%	(1)(2)(3)(4) (5)	NA
Zhang S et al (2020)[19]	RCT (CONCUR)	NA	NA	5%	NA	NA
Mlcoch T et al (2018)[25]	RCT (CORRECT)	OS, PFS	2.5	3%	NA	NA
Cho SK et al (2022)[15]	RCT: CORRECT, RECOURSE, ReDOS, Phase 2 clinical trials	OS, PFS	3	5%	(1)(2)(3)(4) (5)	NA

Notes: Cost expense: (1) drugs, (2) Adverse events, (3) Pallicare per day, (4) Outpatient chemotherapy, (5) Terminal care.
Abbreviations: RCT, randomized controlled trials; OS, overall survival; PFS, progression-free survival; MST, median survival time.

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Table 4 Health Output Assessment of Included Publications

Author (Publication Year)	Treatment Protocol	Results from Economic Evaluation				Willingness to pay Threshold
		QALYs	LYs (Years)	ICER/QALY	Cost	
Kashiwa M et al (2018)[20]	Regorafenib versus TAS-102	0.249 vs 0.344	0.280 vs 0.421	$432,734 vs $131,799	$107,781 vs $45,291	$135,869.57
Barzi A et al (2019)[16]	Regorafenib (ReDOS) versus regorafenib (standard)	NA	NA	$112,705 vs $384,687	NA	$150,000
Guan X et al (2021)[17]	Regorafenib versus fruquintinib	0.79 vs 0.74	1.10 vs 1.02	$231,697	$32,224 vs $22,888	$75,758
Cho SK et al (2018)[13]	Regorafenib versus TAS-102	0.397 vs 0.437	NA	$395,223 vs $399,740	$26,657 vs 43,264	$150,000
Bullement A et al (2018)[23]	Regorafenib versus TAS-102	0.11 vs 0.17	0.16 vs 0.26	£133,561 vs £51,194	£14,613 vs £8,479	NA
Goldstein DA et al (2015)[14]	Regorafenib versus BSC	0.04	0.13	>$550,000	$40,000	$900,000
Kimura M et al (2016)[21]	Regorafenib versus TAS-102	NA	NA	¥477,330.9/MST	¥705,330.3 vs ¥371,198.7	NA
Giuliani J et al (2021)[22]	ReDO versus TAS-102	NA	NA	Per month OS-gain: €510.41 vs €1167.50	€3,879.12 vs €5,818.68	NA
Gourzoulidis G et al (2021)[24]	Regorafenib versus TAS-102	0.50 vs 0.57	0.78 vs 0.89	€51,000 vs €49,326	€10,850 vs €10,087	€51,000
Ma Y et al (2023)[18]	Serplulimab versus Regorafenib	6.00 vs 0.69	7.43 vs 1.03	$5385.94	$68,722 vs $40,106	$36,036
Zhang S et al (2020)[19]	Regorafenib versus BSC	0.62 vs 0.44	0.85 vs 0.61	$63,154.63	$26,795.62 vs $15,184.05	$27,576
Mlcoch T et al (2018)[25]	Regorafenib versus BSC	0.572 vs 0.351	NA	€43,122	€9,904 vs €362	€47,000
Cho SK et al (2022)[15]	ReDO vs RSD	0.571 vs 0.394	NA	$104,308	$71,701 vs $ 53,323	$150,000
	ReDO vs TAS-102	0.571 vs 0.435		$37,966	$71,701 vs $ 66,545	
	ReDO vs TAS-BEV	0.571 vs 0.511		Dominant[a]	$71,701 vs $ 124,746	

Notes: [a]ReDO dominant over TAS-BEV, providing a higher QALY at a lower cost.

analysis comparing ReDo to TAS-102 in combination with bevacizumab (TAS-BEV). Their findings indicated that ReDo was more cost-effective than TAS-BEV, as it offered a higher QALY at a lower cost.

Regorafenib versus Other Molecular Target Drugs

As shown in Table 4, Two studies conducted in China investigated the cost-effectiveness of regorafenib compared to fruquintinib or serplulimab as a third-line treatment for patients with mCRC. Guan et al[17] developed a three-state Markov model to evaluate the cost-effectiveness of regorafenib versus fruquintinib in the context of China. Their study findings indicated that fruquintinib is the more cost-effective option, as it is associated with an increase of approximately 0.05 quality-adjusted life years (QALYs) and results in a cost saving of about $11,454. Ma Y et al[18] developed a three-state Markov model to estimate the costs and health outcomes of serplulimab and regorafenib in China. They concluded that serplulimab is more cost-effective than regorafenib for patients with previously treated metastatic colorectal cancer (mCRC) in China.

Sensitivity Analysis Results and Main Limitations

As shown in Table 5, most studies (11 out of 13) performed a sensitivity analysis to evaluate the uncertainty and robustness of the model, of which three studies adopted one-way and probabilistic sensitivity analyses[15,17,24] Three studies conducted univariate and probabilistic sensitivity analyses[14,16,19] Two studies used scenario analysis based on one-way and probabilistic sensitivity analyses;[18,20] one study used scenario analysis based on univariate and probabilistic sensitivity analyses,[13] the rest

Table 5 Sensitivity Analyses, Conclusions and Limitations of Included Studies

Author (Publication Year)	Sensitivity Analyses	Conclusions	Limitations
Kashiwa M et al (2018)[20]	One-way and probability sensitivity analysis, scenario analysis	Regorafenib is less cost-effective than TAS-102	1) Lack of local data and direct clinical evidence; 2) Selection of partitioned survival analysis may affected clinical and CE outcomes.
Barzi A et al (2019)[16]	Univariate and probabilistic sensitivity analyses	Regorafenib (ReDOS) was more cost-effective than regorafenib (standard)	NA
Guan X et al (2021)[17]	One-way and probabilistic sensitivity analyses	Regorafenib is less cost-effective versus fruquintinib	Lack of primary health utility data to measure patients' quality of life in the different arms.
Cho SK et al (2018)[13]	Univariate and probabilistic sensitivity analyses, scenario analysis	Neither TAS-102 nor regorafenib are cost effective at standard willingness-to-pay thresholds	1) The uncertainty of methods for fitting survival data; 2) The cost of toxicities were from of estimation, while economic and clinical impact of most toxicities were previously studied.
Bullement A et al et al (2018)[23]	One-way sensitivity analysis	TAS-102 is more clinically and cost-effective than regorafenib	Lack of directly measured HRQL data, and assumptions made regarding the comparative efficacy of regorafenib.
Goldstein DA et al (2015)[14]	Univariate and probabilistic sensitivity analyses	Regorafenib provides minimal incremental benefit at high incremental cost per QALY	The limitation of data availability, and lack of efficacy data to support dosing strategy
Kimura M et al (2016)[21]	NA	TAS-102 is more cost-effective than regorafenib	The study did not take quality of life into account, it was not possible to accurately determine the CE in the common units ¥/QALI.
Giuliani J et al (2021)[22]	NA	Regorafenib escalation-dose strategy is more cost-effective than TAS-102	NA
Gourzoulidis G et al (2021)[24]	One-way and probabilistic sensitivity analyses	Regorafenib is less cost-effective than TAS-102	Lack of local data and direct clinical evidence
Ma Y et al (2023)[18]	One-way and probability sensitivity analysis, scenario analysis	Regorafenib is less cost-effective than serplulimab in patients with previously treated mCRC in China	1) Lack of appropriate comparator; 2) The increased risk of death and other parameters were derived based on expert opinion might involve uncertainty.
Zhang S et al (2020)[19]	Univariate and probabilistic sensitivity analyses	Regorafenib is not cost-effective at the WTP threshold of $27,576 when compared with placebo group.	NA
Mlcoch T et al (2018)[25]	Probabilistic sensitivity analysis	Regorafenib is a cost-effective therapy based on registry/RCT data in the CZ.	NA
Cho SK et al (2022)[15]	One-way and probabilistic sensitivity analyses	The optimum dosing strategy for regorafenib has improved relative cost-effectiveness compared to RSD, TAS-102, and TAS-BEV.	1) Lack of head-to-head trials; 2) The study utilized published drug costs, while the actual price of the treatments may vary across health plans.

employed one-way sensitivity analyses and probabilistic sensitivity analyses, respectively.[23,25] The sensitivity analysis results revealed that drug prices, baseline utility value, and exposure to regorafenib exerted the most significant influence on the ICER. Moreover, nine studies identified the primary limitations of the study, with the lack of local data and direct clinical evidence being the most frequently cited constraints in the included studies.

Discussion

This study systematically reviewed and assessed the quality of selected economic evaluation studies on the cost-effectiveness of regorafenib versus other third-line or further molecular-targeted drugs for mCRC. The study findings indicate that administering regorafenib treatment yields marginal gains at considerably high incremental costs per QALY for patients with mCRC. Regorafenib is projected to have lower cost-effectiveness compared to other established treatment choices like TAS-102, fruquintinib, and serplulimab. Nevertheless, the implementation of a dose optimization strategy has the potential to alter this scenario, rendering regorafenib more cost-effective than TAS-102. Therefore, we performed a cost-effectiveness analysis of regorafenib versus other third-line and molecular-targeted drugs for the treatment of mCRC to facilitate treatment strategies for patients and clinicians.

As a broad-spectrum, antiangiogenic, multikinase inhibitor, regorafenib was used as third-line therapy for patients with mCRC who progressed after standard therapy.[26] In CORRECT trial, regorafenib demonstrated a median OS improvement of 1.4 months compared with placebo.[27] Three studies conducted in different countries compared the cost-effectiveness of regorafenib with that of a placebo in the third-line treatment of mCRC and presented varying outcomes. The research from the United States and the Czech Republic concluded that regorafenib is a cost-effective therapy,[14,25] and another study from China revealed that regorafenib is not cost-effective when compared with placebo group.[19] The inconsistencies in research findings may stem from variations in research perspectives, models, and data sources. Furthermore, differences in the selection of price points before and after the reduction in regorafenib price could also contribute to these inconsistencies.

TAS-102, a fluoropyrimidine-derivative drug, was approved by the FDA in 2015 as third-line therapy or beyond for unselected patients with mCRC.[7] A previous study revealed that treatment with TAS-102 significantly improved the OS of patients with mCRC compared with placebo.[28] Seven studies from five different countries compared the cost-effectiveness of TAS-102 with regorafenib in third-line or further treatment of patients with mCRC from 5 different countries. Of which, five studies shown that TAS-102 is more cost-effective than regorafenib with a standard-dose strategy. However, two studies showed that the adoption of a dose optimization strategy could reverse the situation and make regorafenib more cost-effective than TAS-102, with a low cost per month of OS-gain (510.41€) and an ICER of $37,966 relative to TAS-102.[15,22] The phase 2 trial known as C-TASKFORCE has provided data supporting the utilization of TAS-BEV as a viable treatment alternative for patients grappling with chemotherapy-refractory mCRC.[29] Cho SK et al[15] founded that ReDO was both less costly and more effective than TAS-BEV. Furthermore, two studies demonstrated that regorafenib is less cost-effective than either fruquintinib or serplulimab.

This study has several limitations. First, databases were searched in English, and studies published in other languages were not included. In addition, the 13 articles included in this study came from seven different countries, which are different in medical services, drug costs, and willingness-to-pay threshold, so it is impossible to compare the results directly. Finally, publication bias could have influenced the available evidence. This problem may be particularly important here, as most studies lack direct clinical evidence for a comparison between regorafenib and other third-line or further molecular-target drugs.

In conclusion, regorafenib has a cost-effectiveness advantage over BSC for patients with mCRC and is less cost-effective than other third-line or further molecular target drugs, while a dose optimization strategy could reverse the situation and make regorafenib more cost-effective.

Data Sharing Statement

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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