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Cost-Effectiveness Analysis of First-Line FOLFIRI Combined With Cetuximab or Bevacizumab in Patients With RAS Wild-Type Left-Sided Metastatic Colorectal Cancer

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Abstract

Background: The FIRE-3 phase III clinical trial demonstrated the marked advantage of prolonging the median overall survival of patients with final RAS wild-type (WT) left-sided metastatic colorectal cancer (mCRC) by 38.3 months after treatment with irinotecan, fluorouracil, and leucovorin (FOLFIRI) plus cetuximab and by 28.0 months after treatment with FOLFIRI plus bevacizumab. However, the substantial cost increase and economic impact of using cetuximab imposes a considerable burden on patients and society.

Methods: A Markov model based on the data collected in the FIRE-3 trial was developed to investigate the cost-effectiveness of treating patients with FOLFIRI plus either cetuximab or bevacizumab from the perspective of the Chinese health-care system. Costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) were calculated over a lifetime horizon. One-way and probabilistic sensitivity analyses were performed by varying potentially modifiable parameters.

Results: In our analysis, the total treatment costs in the bevacizumab and cetuximab groups were $92 549.31 and $94 987.31, respectively, and the QALYs gained were 1.58 and 2.05. In the base-case analysis, compared with bevacizumab, left-sided RAS WT patients receiving cetuximab gained 0.47 more QALYs at an ICER of $5187.23/QALY ($3166.23/LY). The 1-way sensitivity analysis showed that the most influential parameter was the cost of cetuximab. Probabilistic sensitivity analysis indicated that the cost-effective probability of cetuximab group was 92.8% under the willingness-to-pay threshold of $24 081.

Conclusions: Treatment with FOLFIRI plus cetuximab in Chinese patients with left-sided RAS WT mCRC may improve health outcomes and use financial resources more efficiently than FOLFIRI plus bevacizumab.

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Introduction

Approximately 1 million new cases of colorectal cancer (CRC) are diagnosed each year.[1] In China, CRC is now the fifth most common cancer in men, with 215 700 new cases per year, and the fourth most frequent cancer in women, with 160 600 new cases per year.[2,3]

The first-line regimen for patients with metastatic colorectal cancer (mCRC) is established on the basis of the treatment goal, metastatic location, *RAS* gene status, and patient's personal preferences.[4] Recently, increasing evidence has shown that the primary tumor location is a new independent prognostic and predictive marker for mCRC because of the complex yet unclear molecular events[5-9] with which it is associated.

The initial clinical study data supported that cetuximab as a recombinant anti-epidermal growth factor receptor (EGFR) monoclonal antibody might improve the overall survival (OS) in patients with RAS wild-type (WT) mCRC undergoing chemotherapy, while bevacizumab, a monoclonal antibody against vascular endothelial growth factor A, is commonly added to the regimen, regardless of *RAS* gene status.[10-12] However, based on large clinical studies, such as the FIRE-3 trial performed in the past 2 years, current National Comprehensive Cancer Network guideline has changed: Currently, only patients having mCRC with KRAS/NRAS WT and primary distal (left-sided) colon cancer are administered chemotherapy in combination with an EGFR inhibitor (cetuximab or panitumumab) as the first-line treatment.[4,13]

The multicenter phase III FIRE-3 study is the first to directly compare biologics (bevacizumab vs cetuximab) in combination with the FOLFIRI chemotherapy regimen (fluorouracil plus leucovorin in combination with irinotecan) as a first-line mCRC treatment. Although the progression-free survival (PFS; 10.7 vs 10.7 months, hazard ratio [HR] = 0.90, P =.38) was similar among the 2 arms, the magnitude of the OS benefit was even greater than that observed in the left-sided RAS WT cohort (38.3 vs 28.0 months, HR = 0.63, P = .002).[10,13,14]

To date, 3 cost-effectiveness analysis (CEA) studies have compared the 2 drugs in the United States and Canada. Shankaran et al[15] assessed the cost-effectiveness of cetuximab versus bevacizumab in the United Sates and concluded that cetuximab was dominant over bevacizumab. Ewara et al[16] and Lawrence et al[17] conducted 2 similar cost-effectiveness studies in Canada and demonstrated superior cost-effectiveness of bevacizumab over cetuximab. The conclusions they obtained were different. Although some studies have evaluated the cost-effectiveness of cetuximab and bevacizumab treatment, limited data exist on the cost-effectiveness or the potential cost savings independent of the impact of the primary tumor location in China.

FIRE-3 is an open-label, randomized, phase III trial, which plays a very important role in the development of standard treatment for mCRC. Cost-effectiveness analysis based on randomized controlled phase III clinical trials is widely used and recommended by the Chinese Pharmacoeconomics Guidelines.[18] With the rigorous randomized controlled design of clinical trials, strong credibility and high-internal validity can be obtained. Moreover, in this study, we used FIRE-3 data to estimate the cost-effectiveness of cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI treatment in patients with left-sided RAS WT mCRC in China.

Materials and Methods

Model Structure

A deterministic cohort model was developed to mimic the FIRE-3 protocol of the phase III trial[10] and to compare the long-term impact of cetuximab treatment (cetuximab plus FOLFIRI) versus bevacizumab treatment (bevacizumab plus FOLFIRI) for patients with left-sided RAS WT mCRC from the health-care system's perspective of China. Direct medical costs, life years (LYs), and quality-adjusted life years (QALYs) were estimated in each treatment arm and then the incremental cost-effectiveness ratios (ICERs) were calculated. The model structure and data were based primarily on the results of the FIRE-3 trial[10,13,14] and were supplemented with data collected from publicly available Chinese databases and published literature. The model was developed using TreeAge Pro 2012 (TreeAge Software, Inc, Williamstown, Massachusetts).

The model structure included 3 states to represent the progression of mCRC: PFS, progressive disease (PD), and death (Figure 1). The model cycle length was 1 month, and we calculated outcomes for 10 years. Patients in the PFS state were treated with FOLFIRI plus bevacizumab or FOLFIRI plus cetuximab until disease progression. Patients could experience treatment-related adverse events (AEs), PD treated with second-line therapy, or death. Adverse events were included if they were grade 3 or 4 occurred in the patients enrolled in FIRE-3. The proportion of patients on each second-line treatment was based on FIRE-3 data.[10]

Clinical Inputs

The FIRE-3 trial was a randomized phase III trial comparing first-line FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab in patients with KRAS WT mCRC. The patients were recruited from centers in Germany and Austria and met the following criteria: aged 18 to 75 years with stage IV, histologically confirmed CRC, an Eastern Cooperative Oncology

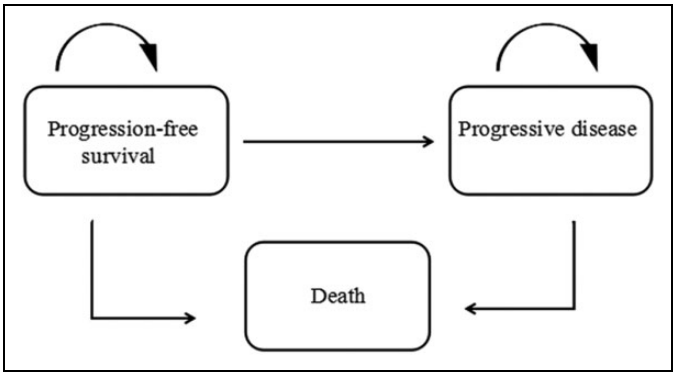


Figure 1. Markov states. Used to illustrate the disease development process of metastatic colorectal cancer.

Table 1. Rates of Second-Line Treatment in the Study.[10]

Second-Line Therapy	Cmab, n (%)	Bmab, n (%)
Bmab + FOLFOX	60 (24.7)	22 (9.4)
Bmab + FOLFIRI	25 (10.3)	1 (0.4)
Bmab + 5-Fu	9 (3.7)	9 (3.8)
Cmab	10 (4.1)	11 (4.7)
Cmab + FOLFOX	13 (5.3)	35 (14.9)
Cmab + IRI	4 (1.6)	29 (12.3)
5-Fu	13 (5.3)	11 (4.7)
FOLFOX	53 (21.8)	58 (24.7)
None	56 (23.0)	59 (25.1)

Abbreviations: Bmab, bevacizumab; Cmab, cetuximab; FOLFIRI, irinotecan, leucovorin, and fluorouracil; FOLFOX, oxaliplatin, leucovorin, and fluorouracil; IRI, irinotecan; 5-Fu, fluorouracil.

Group performance status of 0 to 2, an estimated life expectancy of greater than 3 months, and adequate organ function.[10] An evaluation of the expanded RAS status suggested an increased treatment effect in terms of the cetuximab-conferred OS and PFS benefits.[13] Progression rates were dependent on FIRE-3 data.[10,14] Eligible patients had measurable mCRC according to the Response Evaluation Criteria in Solid Tumors (version 1.1) and were randomly assigned to receive cetuximab or bevacizumab. The second-line treatment (Table 1) and first-line treatment AE risks (Table 2) were also derived from FIRE-3 data.

Model Survival and Progression Risk Estimates

The estimates of OS for the bevacizumab and cetuximab groups were based on the results of FIRE-3. First, the GetData Graph Digitizer (version 2.25) was used to extract the data points from the OS Kaplan-Meier curves announced by Heinemann et al,[13] and these data points were then fit into the parametric survival models. Because Weibull distributions are flexible and are widely used in cancer survival analyses, the Weibull survival curves were matched to the number of patients in the 3 states over time. Next, the shape parameter (γ) and the scale parameter (λ) were estimated from this fit to Kaplan-Meier curves using the R software package (http://www.r-project.org) using the method of Hoyle et al[24] (Table 3), and the mean OS time was denoted as $S(t)$. The cause-specific mortality M at cycle t due to the following formula:

$$M = \frac{S(t) - S(t-1)}{S(t)}$$

where

$$S(t) = (-\lambda t^{\gamma})(\lambda > 0; \gamma > 0)$$

Using the same approach, the time-dependency transition probabilities from PFS to PD state were estimated.

Table 2. Baseline Costs, Utility, and Adverse-Event Risks in 2 Groups of Patients With Metastatic Colorectal Cancer in China.

Parameters	Median	Range	Distribution
Costs, $			
Irinotecan per 40 mg[a,b]	83.3	66.64-99.96	Lognormal
Leucovorin per 100 mg[a,b]	3.59	2.87-4.31	Lognormal
Fluorouracil per 250 mg[a,b]	4.97	3.98-5.96	Lognormal
Bevacizumab per 100 mg[a,b]	649.62	519.70-779.54	Lognormal
Cetuximab per 100 mg[a,b]	618.76	495.00-742.51	Lognormal
Laboratory evaluations per cycle[a,b]	69.25	55.4-83.1	Lognormal
CT per cycle[b,c]	147.88	87.66-208.10	Gamma
Expenditures on main adverse events (grade 3 or 4), $			
Hematotoxicity[a]	531.54[19]	198.77-864.29	Lognormal
Diarrhea[a]	44.36[19]	28.54-54.68	Lognormal
Risk for main adverse events in Bmab (grade 3 or 4)			
Hematotoxicity[a]	0.2102[10]	0.1682-0.2522	Beta
Diarrhea[a]	0.1356[10]	0.1085-0.1672	Beta
Risk for main adverse events in Cmab (grade 3 or 4)			
Hematotoxicity[a]	0.2458[10]	0.1966-0.2950	Beta
Diarrhea[a]	0.1145 [10]	0.0916-0.1374	Beta
Utility			
PFS state in 2 groups[a]	0.73[20,21]	0.58-0.88	Beta
PD state in 2 groups[a]	0.59[20,21]	0.47-0.70	Beta

Abbreviations: Bmab, bevacizumab; Cmab, cetuximab; CT, computed tomography; PD, progression disease; PFS, progression-free survival.
[a]The range was assumed to be varied ±20%.
[b]Local charge. The cost of drugs were estimated from the price of different brands and the percentage use of each brand in China.[22,23]
[c]The range was assumed to be varied ±50%.

Utility Estimates

To estimate the total QALYs, the survival time was adjusted by health-related quality of life. Mean utility values of 0.73 and

Table 3. Weibull Parameters for PFS and OS for the 2 Strategies.

	Shape (γ), Mean (SE)	Scale (λ), Mean (SE)	Adjusted R^2
PFS			
Bmab group	1.632477 (0.066126)	0.013767 (0.002455)	0.9839925
Cmab group	1.568734 (0.003341)	0.015248 (0.084307)	0.9883756
OS			
Bmab group	1.6672275 (0.0159772)	0.0027702 (0.0001572)	0.9984568
Cmab group	1.4913639 (0.0217298)	0.0033325 (0.0002731)	0.9946561

Abbreviations: Bmab, bevacizumab; Cmab, cetuximab; OS, overall survival; PFS, progress-free survival; SE, standard error.

0.59, respectively, for patients in PFS and PD states presented in Table 2 were obtained from the previously published literatures, in which the utility values were assessed based on EQ-5D questionnaire.[20,21]

Cost Inputs

Direct medical costs related to the practice were measured, including treatment drugs, routine follow-up treatment cost for patients, and treatment of major AEs. In the first-line setting, the intravenous drug costs for each 2-week cycle of FOLFIRI were based on FIRE-3 data obtained from patients who received the following doses: irinotecan, 180 mg/m^2; leucovorin, 400 mg/m^2; and fluorouracil, 400 mg/m^2 bolus; and 2400 mg/m^2 continuously over 46 hours. When bevacizumab was added, the cost was based on dosing at 5 mg/kg. When cetuximab was added, the dose was 400 mg/m^2 during the first week and then 250 mg/m^2 weekly. A typical body surface area of 1.72 m^2 and weight of 60 kg were used to estimate the dosage of the anticancer drugs, based on the mean values in China.[25] The second-line treatments included FOLFOX (oxaliplatin, leucovorin, and fluorouracil) plus bevacizumab, FOLFIRI plus bevacizumab, bevacizumab plus fluorouracil, cetuximab, cetuximab plus FOLFOX, cetuximab plus irinotecan, and fluorouracil and FOLFOX; details on these treatments are presented in Table 1. The cost of oxaliplatin, irinotecan, leucovorin, fluorouracil, bevacizumab, and cetuximab was estimated using local prices (Table 2).[22,23]

Based on expert opinion, only grade 3/4 AEs were considered to estimate the costs of treatment-associated toxicity. The incidence rates of AEs in the model were derived from the FIRE-3 trial data. The costs of AEs were based on the published literature,[19] in which a CEA of chemotherapy regimens associated with cancer was also performed in China.

The costs of follow-up included a computed tomography (CT; baseline estimate; every 6 weeks in first 3 months; every 10 weeks after 3 months; every 3 months after progression) and laboratory evaluations (every 2 weeks); information on these costs was obtained from the Xiangya Hospital (Table 2). In accordance with China's Guidelines for Pharmacoeconomic Evaluations,[18] the discount rate in this model was assumed to be 3% per year for both costs and outcomes, and the willingness-to-pay (WTP) threshold was set at a value of \$24 081 (3 × per capita gross domestic product [GDP]). The GDP data were obtained from the China Statistics Press data on national accounts in 2016.[26] Costs in this study were calculated in US dollars (USD, \$), corresponding to the 2016 consumer index and assuming an average exchange rate of \$1 to 6.6423 Chinese Yuan (RMB, ¥).[27]

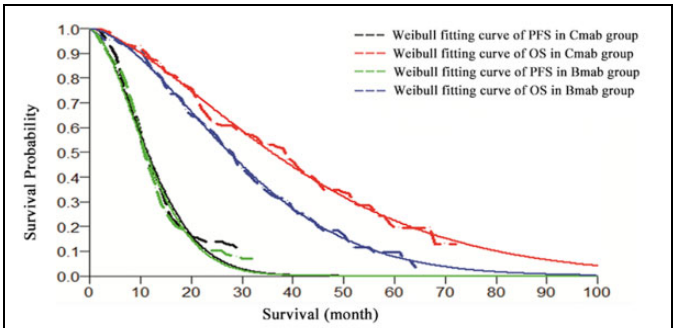
Sensitivity Analysis

A series of sensitivity analyses were performed to vary each parameter at a specific time over its range to examine the effect of these parameters on the ICER. One-way sensitivity analyses were performed including 16 variables, and a tornado diagram was created based on the ICERs. In addition, a probabilistic sensitivity analysis used 1000 Monte Carlo repetitions, randomly varying all parameters simultaneously during each repetition. The values, range, and distribution of each parameter (based on the related literature and from the local charge) are presented in Table 2.

Results

Baseline Results

The Weibull model-derived survival curves did not differ significantly from the results of the clinical trials. The survival probabilities at specific time calculated from our model satisfactorily matched those from the clinical trial. The median PFS and OS data for the different strategies varied from 0.02 to 0.14 between the model outcomes and the trial data (Figure 2). Over the 10-year time horizon, 99.97% of patients in the bevacizumab arm and 98.51% in the cetuximab arm died. The effectiveness and costs were compared in this model for FOLFIRI plus bevacizumab and FOLFIRI plus cetuximab. We evaluated the baseline results over a 1-, 2-, 5-, and 10-year time horizon; the details are summarized in Table 4. Over the 10-year time horizon, the bevacizumab treatment provided 1.58 QALYs (2.46 LYs) at a cost of \$92549.31, whereas cetuximab provided 2.05 QALYs (3.23 LYs) at a cost of \$94987.31. The ICERs for the cetuximab group compared with bevacizumab was \$5187.23/QALY and \$3166.23/LY. The FOLFIRI plus cetuximab treatment yielded better outcomes, regardless of the time horizon.



Treatment	Model	Clinical trial (FIRE-3)	Difference
Median progression-free survival, mo			
Cetuximab group	10.56	10.7	0.14
Bevacizumab group	10.68	10.7	0.02
Median overall survival, mo			
Cetuximab group	38.25	38.3	0.05
Bevacizumab group	27.9	28.0	0.10

Figure 2. Weibull fitting curves of progression-free survival (PFS) and overall survival (OS) in the 2 treatment groups. The median PFS and OS calculated from our model and observed in the FIRE-3 trial. Cmab group, FOLFIRI plus cetuximab; Bmab group, FOLFIRI plus bevacizumab.

Sensitivity Analysis

The results of 1-way sensitivity analyses are presented in the tornado diagram (Figure 3). The variables with the greatest influence on the ICER were the cost of cetuximab (ranging from $495.00 to $742.51, with the ICER increasing from $-2214.73/QALY to $12555.47/QALY). However, changes in this range will not cause the ICER to exceed the WTP value. The other 3 most influential variables included the cost of bevacizumab, the discount rate, and the utility of the PD state. All of these variables did not led to an ICER surpass the WTP threshold of $24 081/QALY. None of other parameters significantly altered the ICER.

The ICER scatterplot (Figure 4) shows the results of the probabilistic sensitivity analysis with a WTP threshold of $24 081; the scatter points represent the incremental cost and effectiveness values obtained from the Monte Carlo simulation (1000 repetitions). These results demonstrated a 92.8% probability that cetuximab is cost effective at WTP values of $24 081/QALY.

The acceptability curve (Figure 5) shows that the relative cost-effectiveness changed with numerical changes in the WTP threshold. When the WTP was $24 081 for each QALY gained, the probability was nearly 90% that the cetuximab treatment was cost-effective. When the threshold was less than $5000, the likelihood of the cetuximab group achieving cost-effectiveness was less than 50%.

Discussion

In the past decade, abundant evidence has demonstrated that pairing chemotherapy with targeted therapies such as anti-EGFR and antiangiogenesis agents (for instance, cetuximab or bevacizumab) yields good clinical benefits at a favorable cost.[28-31] The clinical data and other research studies strongly support the addition of cetuximab to FOLFIRI chemotherapy in patients with RAS WT mCRC.[10-12] Although bevacizumab in combination with FOLFIRI or FOLFOX is recommended as the first-line treatment, second-line and maintenance treatments are not specific for RAS WT mCRC.[32-34] Although the FIRE-3 study did not consider a specific cohort of patients with RAS WT and BRAF-mutated mCRC, further exploration via post hoc statistical modeling in this study showed that the BRAF mutation status was an independent adverse prognostic factor. Right-sided tumors are more frequently characterized by a host of adverse prognostic factors, including BRAF mutation positivity, microsatellite instability, hypermutation, serrated pathway signature positivity, and mucinous histology. Moreover, some studies have suggested that patients with left-sided mCRC have a better prognosis, a prolonged survival time, and more treatment options compared to those with right-sided mCRC.[4-7,35]

The best treatment decisions are driven by multiple factors, including drug costs, anticipated toxicities, and practice patterns, in addition to therapeutic effects. Recently, several studies in other countries have evaluated the cost-effectiveness of routine RAS screening in patients with mCRC[36-38] and

Table 4. Baseline Analysis Results of Bmab + FOLFIRI and Cmab + FOLFIRI in China.

Parameters	Bmab + FOLFIRI	Cmab + FOLFIRI
1-year horizon		
Lys	0.93	0.94
QALYs	0.65	0.66
Total cost, $	37950.37	37929.27
ICER for Cmab group, $/LY	–	−2354.83
ICER for Cmab group, $/QALY	–	−2110
2-year horizon		
Lys	1.62	1.70
QALYs	1.09	1.13
Total cost, $	61046.09	56,058.95
ICER for Cmab group, $/LY	–	−68472.48
ICER for Cmab group, $/QALY	–	−124678.5
5-year horizon		
Lys	2.39	2.88
QALYs	1.54	1.84
Total cost, $	89854.14	86143.90
ICER for Cmab group, $/LY	–	−7523.76
ICER for Cmab group, $/QALY	–	−12367.47
10-year horizon		
Lys	2.46	3.23
QALYs	1.58	2.05
Total cost, $	92549.31	94987.31
ICER for Cmab group, $/LY	–	3166.23
ICER for Cmab group, $/QALY	–	5187.23
WTP, $/QALY	–	24081

Abbreviations: FOLFIRI, irinotecan, leucovorin, and fluorouracil; FOLFOX, oxaliplatin, leucovorin, and fluorouracil; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

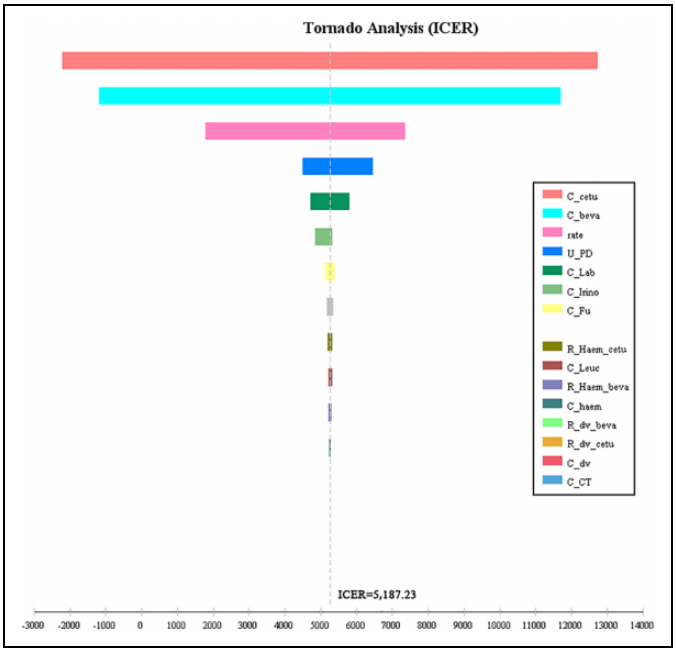


Figure 3. Tornado diagram for the 1-way sensitivity analysis of the FOLFIRI plus cetuximab and FOLFIRI plus bevacizumab treatment groups.

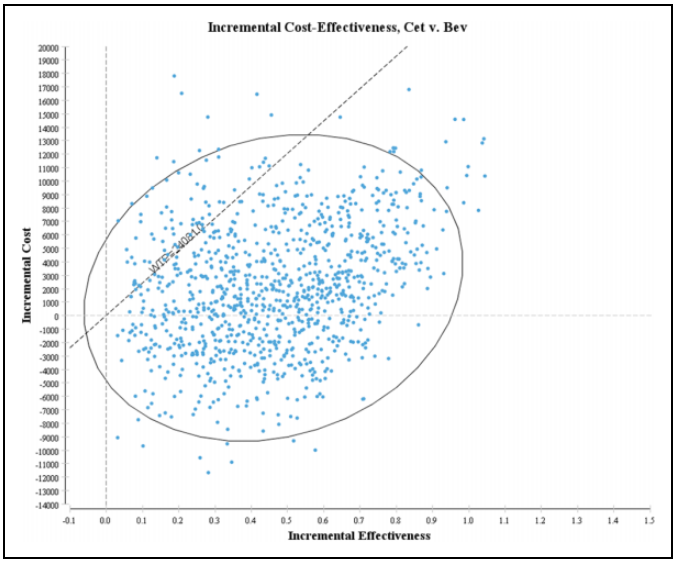


Figure 4. The results of the Monte Carlo probabilistic sensitivity analysis for the FOLFIRI plus cetuximab and FOLFIRI plus bevacizumab treatment groups.

first-line cetuximab or bevacizumab relative to chemotherapy for mCRC (Table 5).[15,16,39] A study performed in the United States by Shankaran et al showed that cetuximab has an ICER of $107 630/QALY ($86 487/LY) compared with bevacizumab in KRAS WT patients. Studies performed in Canada by Ewara et al[16] and Lawrence et al[39] compared 3 treatments: bevacizumab, cetuximab, or panitumumab plus chemotherapy in patients with KRAS WT mCRC; the results showed that

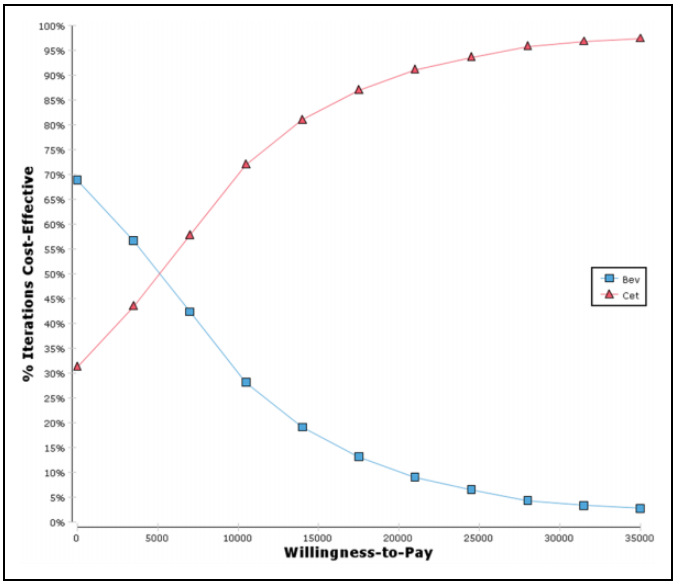


Figure 5. Acceptability curves for the choice of 2 treatment strategies at different willingness-to-pay (WTP) thresholds in Chinese patients with metastatic colorectal cancer (mCRC).

bevacizumab plus chemotherapy outperformed the other 2 first-line treatment strategies. However, no available studies have compared the cost-effectiveness of these 2 biologic agents in view of the primary tumor location and from a Chinese perspective.

Our analysis is the first Markov model-based study to evaluate the health and economic outcomes of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as a first-line treatment in patients with left-sided mCRC with final RAS WT in China. In line with the FIRE-3 trial data, the results suggest that cetuximab may be a better choice than bevacizumab, given that the former can increase both LYs and QALYs.

In our Markov model, differences in product costs resulted in higher lifetime costs for cetuximab compared with bevacizumab. However, on the basis of a comprehensive analysis incorporating both the increased costs and the clinical benefits, patients treated with cetuximab therapy obtained greater mean clinical benefits, as demonstrated by an ICER of $5187.23/QALY, than those on bevacizumab; this value is well below the WTP threshold of $24 081 among Chinese people. That is, there are valuable clinical benefits from cetuximab treatment despite the increased costs. To compare the 2 therapeutic regimens, we also generated tornado diagrams using TreeAge Pro software. The results showed that the costs of cetuximab and bevacizumab impacted utmost on the ICER. However, the cost variation of these 2 drugs does not led to an ICER entrancing the WTP threshold of $24 081 (Figure 3). Next, we performed a probabilistic sensitivity analysis to verify the accuracy of the baseline results. As shown in Figure 4, this analysis further demonstrated the superior cost-effectiveness of cetuximab.

According to the cost-effectiveness acceptability frontier curves, the WTP calculated from the average GDP of China influenced the final results. In China, regional differences

Table 5. Several Cost-Effectiveness Analyses of Routine RAS Screening and Cetuximab or Bevacizumab Treatment in Patients With Metastatic Colorectal Cancer.

Regimen	Country	ICER	Cost-Effectiveness	Reference
RAS testing + Cmab and FOLFIRI RAS testing + Bmab and FOLFIRI KRAS testing + Cmab and FOLFIRI KRAS testing + Bmab and FOLFIRI	China	The ICER of RAS-Cmab group compared with KRAS-Cmab group was $1186.22/QALM, $6475.86/QALM in RAS-Bmab group and $9962.0/QALM with KRAS-Bmab.	RAS testing + Cmab and FOLFIRI is a cost-effective strategy	[36]
RAS testing + Cmab/Bmab and FOLFIRI KRAS testing + Cmab/Bmab and FOLFIRI	China	$88394.09/QALY	RAS testing is more cost-effective	[37]
Early KRAS testing in high-risk patients with CRC	Italy	Euro6000-13 000/QALY	Early KRAS testing is a cost-effective strategy	[38]
Bevacizumab + FOLFIRI Cetuximab + FOLFIRI	The United States	$107 630/QALY	Cetuximab treatment is cost-effective	[15]
Bevacizumab + FOLFIRI Cetuximab + FOLFIRI Panitumumab + FOLFIRI	Canada	Compared with bevacizumab plus FOLFIRI, panitumumab plus FOLFIRI resulted in loss of 0.033 QALYs at an incremental cost of $23 359; cetuximab plus FOLFIRI resulted in loss of 0.008 QALYs at an incremental cost of $3159.	Bevacizumab plus FOLFIRI is cost-effective	[16]
Bevacizumab + chemotherapy Cetuximab + chemotherapy Panitumumab + chemotherapy	Canada	Compared with bevacizumab + FBC, panitumumab + chemotherapy is dominated and cetuximab + chemotherapy has an ICER of $3.8 million per QALY.	Bevacizumab plus chemotherapy is cost-effective	[17]

Abbreviations: FOLFIRI, irinotecan, leucovorin, and fluorouracil; FOLFOX, oxaliplatin, leucovorin, and fluorouracil; QALM, quality-adjusted life-month; QALY, quality-adjusted life-year.

contribute to differences in the GDP. For instance, treatment with cetuximab in the Guizhou province, which has a low GDP, does not increase the cost-effectiveness of cetuximab. Thus, the treatment solutions that increase cost-effectiveness should be considered in order to reduce the economic disparity.

In China, many of the patients who accepted these 2 drugs were supported by Chinese charity funding to decrease the treatment expenses. We have taken the impact of Chinese charity funding into account by modulating the price of these 2 drugs. However, our study was limited by the different influences of health insurance policies among different areas throughout China. It is challenging to assess the costs in greater detail while considering both health insurance policies and charity funding in the various regions of China. Although cetuximab has better cost-effectiveness compared to bevacizumab, patients in China will need to spend much more money on cetuximab plus chemotherapy than chemotherapy alone, which would directly contribute to a reduction of the willingness of patients to choose this regimen. In summary, reducing the price of cetuximab would improve its cost-effectiveness, resulting in increased charity funding and an even more comprehensive health-care policy in China.

The findings from FIRE-3 should also be considered in light of the CALGB/SWOG 80405 results that seem to be divergent. Analysis of the RAS WT population of CALGB/SWOG 80405 suggested comparable OS between the 2 groups containing bevacizumab and cetuximab treatment.[12] Although it is important to acknowledge and reconcile the conflicting results of studies comparing biologics in first-line mCRC treatment, the FIRE-3 findings cannot be discounted based on those from CALGB/SWOG 80405. On the one hand, a retrospective analysis of FIRE-3, which took the impact of extended RAS testing and primary location into consideration, concluded that the OS benefit was even greater for the left-sided RAS WT cohort. On the other hand, a recent meta-analysis assessing data from 3 studies (FIRE-3, PEAK, and CALGB 80405) reported no difference in PFS (HR 0.92, 95% confidence interval [CI], 0.71-1.18; $P = .50$); however, in the OS analysis, data strongly favored first-line treatment containing cetuximab rather than bevacizumab drugs (HR 0.77, 95% CI, 0.63-0.97; $P = .016$).[40] Therefore, we still can come to the conclusion safely that for patients with left-sided RAS WT mCRC, first-line treatment with FOLFIRI plus cetuximab is a better option.

Our analysis has several limitations. First, an inevitable limitation was the use of a Weibull distribution to infer consequences beyond the lifetime horizon of the FIRE-3 trial. Second, bias was induced by the Markov model, which was simulated over a lifetime horizon instead of only a 6-year trial. Third, regional differences in economy and health-care policy lead to different final cost of treatments in China. Fourth, different therapies after the first-line treatment were estimated according to the information published for the FIRE-3 trial, which may differ in Chinese clinical practice. Fifth, the patients enrolled in the FIRE-3 trial were from Europe, while our research was estimated from the Chinese health-care system. We recognized racial differences in the efficacy of some drugs. However, the drugs used in the FIRE-3 trial are also commonly used in patients with mCRC in China. And there was no clear data suggesting that the efficacy of cetuximab or bevacizumab was related to race for patients with left-sided RAS WT mCRC. Lastly, the FIRE-3 study did not consider a specific cohort of patients with RAS WT and BRAF-mutated mCRC; however, further exploration via post hoc statistical modeling in this study showed that the BRAF mutation status was an independent adverse prognostic factor.[11] Right-sided tumors are more frequently characterized by a host of adverse prognostic factors, including BRAF mutation positivity, microsatellite instability, hypermutation, serrated pathway signature positivity, and mucinous histology. The BRAF status could modify the proposed CEA.

Our results suggest that for patients in China with left-sided RAS WT mCRC, first-line treatment with FOLFIRI plus cetuximab is a better option than FOLFIRI plus bevacizumab.

Authors' Note

Jiaqi Han and Desheng Xiao contributed equally to this study. This study was based on model techniques and a literature review; written consent was not required according to the ethics committee of the Xiangya Hospital of Central South University (Changsha, People's Republic of China).

Declaration of Conflicting Interests

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