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Regorafenib versus Cetuximab plus Irinotecan in Third-line Metastatic Colorectal Cancer in Iran: A Model-based Cost-utility Analysis

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Abstract
Background: Metastatic colorectal cancer (mCRC) constitutes a significant health burden globally, accompanied by elevated mortality rates. This study aimed to assess the cost-effectiveness of Regorafenib, an orally administered multi-kinase inhibitor, compared to the combination of Cetuximab and Irinotecan (CetIri) as third-line therapy for mCRC in Iran.
Method: A model-based cost-utility analysis was conducted employing a semi-Markov model for a hypothetical cohort of 1,000 patients, integrating time-dependent transition probabilities. From the perspective of the Iranian healthcare payer, the analysis included direct medical costs, such as therapy, monitoring, and adverse effect-related expenses, sourced from national databases in Iran. A yearly discount rate of 5% was applied to both costs and outcomes. Data analysis utilized Microsoft Excel, R version 4.1.3, and TreeAge Pro Healthcare version 2022 software, with the significance threshold set at 0.05.
Results: The base-case analysis revealed that Regorafenib offers a cost saving of $12,154 and an incremental gain of 0.1 Quality-adjusted life years (QALYs) per patient over a 19-month horizon compared with the CetIri regimen. Probabilistic sensitivity analysis showed a greater than 99% probability of Regorafenib being cost-effective.
Conclusion: Consistent with existing evidence, the findings advocate Regorafenib as a cost-effective alternative to CetIri for third-line treatment of mCRC in Iran, considering the specific healthcare system context. Given the foundational assumptions, caution is advised when extrapolating these results to other regions.
Keywords: Economic evaluation, Survival analysis, Chemotherapy, Angiogenesis inhibitors, Quality-adjusted life years

Introduction

Colorectal cancer (CRC) stands as the third most frequently diagnosed cancer and the second leading cause of cancer-related deaths worldwide. Furthermore, an increasing trend in CRC incidence and mortality in individuals under 50 years of age has been noted in recent decades.[1] Metastasis is common in CRC patients, with estimates indicating that 26.4% of patients initially diagnosed with localized or regional colon cancer and 29.5% of rectal cancer cases eventually develop metastatic disease.[2] Chemotherapy remains the primary therapeutic approach, significantly improving overall survival (OS). Moreover, metastatic CRC (mCRC) can be treated using various medication regimens, including fluorouracil, irinotecan, oxaliplatin, cetuximab, bevacizumab, and panitumumab.[3,4]

Regorafenib, an orally administered multi-kinase inhibitor, targets angiogenic, stromal, and oncogenic receptor tyrosine kinases.[5] Approved by the United States Food and Drug Administration (FDA) in 2012, Regorafenib has become a standard-of-care (SOC) option for refractory mCRC in patients who have received prior standard treatments.[6] Despite the demonstrated improvement in OS with Regorafenib in previous clinical trials, grade 3 to 4 adverse events (AEs), such as hand-foot skin reaction (HFSR), fatigue, diarrhea, hypertension, and rash, are more frequently reported with its use.[7–9]

Given Regorafenib's safety and efficacy profiles, this study aims to conduct a cost-utility analysis (CUA) comparing Regorafenib with the CetIri regimen as the third-line optimal therapy for mCRC in Iran. Additionally, the intention is to simulate disease progression using time-dependent transition probabilities (TDTPs) derived directly from randomized controlled trials (RCTs).

Methods

Health economic analysis plan

This pharmacoeconomic study was meticulously designed, executed, and reported, adhering to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist. Detailed information on the study's methodology is available upon request from the corresponding author via B-fatemi@farabi.tums.ac.ir.

Study population

A hypothetical cohort of 1,000 mCRC patients receiving third-line therapy was utilized to simulate patient transitions and outcomes within the model. Given the simulation-based approach of this study, patient consent and institutional review board (IRB) approval were not requisite.

Setting and location

The model's input parameters, particularly costs and natural mortality rates, were tailored to reflect Iran's healthcare setting.

Comparators

The study compared the Regorafenib oral tablet with the Cetuximab plus Irinotecan (CetIri) regimen.

Perspective

Analysis was conducted from the perspective of the Iranian healthcare payer, considering the data availability within the context of Iran's healthcare system.

Time horizon

The study's time horizon spanned 1.9 years, equivalent to the patients' cohort's lifetime, considering that 99% of the patients were expected to have passed away within this timeframe. This duration is thus considered a lifetime horizon for this analysis (Supplementary file 2).

Discount rate

Costs and Utilities were discounted annually at 5.8% and 5%, respectively.

Selection of outcomes

As a Cost-Utility Analysis (CUA), the primary outcome of interest was health-

related quality of life (HRQOL), quantified in terms of quality-adjusted life years (QALYs).

Measurement of outcomes

QALYs for each patient were calculated by multiplying the number of years lived in a given health status by the quality of life (QOL) weight assigned to that status, where the weight (w) ranges from zero to 1, indicating the health-related quality of life weight for a specific health status.[10]

$$QALYs\ lived\ by\ individual\ in\ a\ year = 1 \times w$$

Valuation of outcomes

Outcomes were assessed by aggregating the QALYs garnered throughout the study model.

Measurement and valuation of resources and costs

Data from Iranian national databases and cost resources, including the 2021 Medical Services Fact Book[11] and the 2020 Pharmaceutical Statistics Fact Book,[12] were utilized to estimate medical costs. This encompassed all direct medical costs associated with therapies, monitoring, and adverse effects.

Currency price date and conversation

All costs were reported in 2021 rates of the United States dollar (US$), adjusted using a purchasing power parity (PPP) conversion factor of 1 US$ = 46,072.46 Iranian Rials (IRR).[13]

Rationale and description of the model

A semi-Markov model, incorporating time-dependent transition probabilities (TDTPs), was developed to assess the cost-effectiveness of Regorafenib in comparison to the Cetuximab plus Irinotecan (CetIri) regimen. The model delineates three health states: I) progression-free (PF), II) post-progression (PP), and III) death, reflecting the natural disease course and patient progression as observed in referenced randomized controlled trials (RCTs) (Figure 1). Initially, all patients are modeled to enter the PF state, from which they may either remain stable, progress, or die. Literature and clinical guidelines recommend administering Regorafenib daily for three weeks, followed by a one-week hiatus.[4,14,15] Accordingly, the treatment cycle duration was set at four weeks. Analyses were performed using Microsoft Excel, R version 4.1.3, and TreeAge Pro Healthcare version 2022 software, with a significance level 0.05.

Analytics and assumptions

TDTPs were derived using WebPlotDigitizer to extract data points from OS and PFS curves in RCTs. The Hoyle and Henley method,[9] facilitated the calculation of Weibull distribution parameters for survival curves. TDTPs were computed as follows:

$$Probability\ \text{of}\ death = (OSt1 - OSt2)/OSt1$$

$$Probability\ \text{of}\ progress = ((PFSt1 - PFSt2)/PFSt1)\text{-Probability of death}$$

$$survival_t = \exp\left(-\left(\frac{1}{\exp(intercept)^{\frac{1}{\exp(scale)}}}\right) \times t^{\left(\frac{1}{\exp(scale)}\right)}\right)$$

From the payer's perspective, only direct medical costs were included. Costs were estimated using national database figures.

The CUA's primary outcome, the incremental cost-effectiveness ratio (ICER), was evaluated against Iran's willingness-to-pay (WTP) threshold, ranging from one to three times the 2021 gross domestic product (GDP) per capita, PPP ($16,484 to $49,452), according to World Bank statistics.[16]

Characterizing heterogeneity

Despite efforts to control for heterogeneity among mCRC patients receiving third-line therapy, the absence of a head-to-head study introduces a potential variability risk.[8,17]

Characterizing the distributional effect

Key variables were modeled as random variables to assess distributional impacts, with all TDTPs based on Weibull

distributions and adjusted by a random variable coefficient (mean = 1, standard deviation (SD) = 0.25) at each stage (Table 1).

Characterizing uncertainty

The primary bias risk stems from patient heterogeneity, an issue unaddressed due to the lack of direct RCT comparisons. Deterministic and probabilistic sensitivity analyses were performed to mitigate this uncertainty and validate the model's robustness. The former involved varying input parameters by ±25% of their baseline values, while the latter entailed Monte Carlo simulations with 1,000 samples.

Patient and public engagement in the study's design was deemed inapplicable.

Results

Study parameters

Transition probabilities

TDTPs were determined based on the Weibull distribution of OS and PFS Kaplan-Meier curves from referenced RCTs.[8,17] Shape and scale parameters for plotting the Weibull distribution were calculated using the Hoyle-Henley method.[18] The mean OS for the Regorafenib and CetIri groups were 8.07 and 5.52 months, respectively. The mean PFS times were 3.2 months for Regorafenib and 4.7 months for CetIri (Supplementary file 1).

Health-related quality of life

HRQOL data were adapted from studies in other countries due to the absence of local evidence.[19] Estimated HRQOL weights for patients in the PF and PP states were 0.73 (SD = 0.25) and 0.59 (SD = 0.31), respectively.

Costs

Direct medical costs are detailed in Table 2. The Regorafenib regimen is as per international mCRC guidelines.[20], involves 160 mg daily for 21 days, followed by a 7-day rest, totaling 84 oral tablets per 28-day cycle. Conversely, patients in the CetIri group received 18 cetuximab ampoules and 8 irinotecan ampoules per cycle.[17] The medication costs per cycle for the Regorafenib and CetIri groups were $1,468 and $3,597, respectively.

In the case of disease progression, patients were assumed to receive the FOLFOX regimen. To calculate the cost of the FOLFOX regimen, the cost of oxaliplatin, fluorouracil, and calcium folinate was included (Oxaliplatin 85 mg/m^2, fluorouracil 2,400 mg/m^2, and calcium folinate 400 mg/m^2).[21] All doses were calculated based on the Iranian population's mean weight and height. Based on the CORRECT trial, the most common AEs with Grade 3 or higher grades associated with Regorafenib were HFSR, diarrhea, and oral mucositis.[8] Based on expert opinion, HFSR was presumed to be controlled with 0.05% clobetasol cream and urea 10% cream. Diarrhea also was supposed to be managed by a 28-day course of loperamide. Also, a course of treatment with diphenhydramine compound gargling was assumed to manage oral mucositis. Regarding the management of AEs for the CetIri regimen, the cost of emollient cream for acne-like rashes, 4 mg ondansetron for nausea, and diphenhydramine compound for oral mucositis were inputted into the model. Other direct medical costs related to chemotherapy, including injections, follow-up visits, pre-medications, and lab tests, were also considered (Table 2).

Willingness-To-Pay (WTP)

One to three times the 2021 Iran GDP/Capita (PPP) (16,484 to 49,452 US$) was determined as the WTP threshold.[16]

Summary of main results

The base-case model showed that Regorafenib is associated with both a lower cost and higher effect, suggesting that Regorafenib is the dominant alternative compared to the CetIri regimen in the treatment of mCRC in Iran (**Error! Reference source not found.**). in such a way that the lifetime treatment of mCRC patients

with Regorafenib compared to the CetIri regimen is associated with a $12,154 cost saving and about 0.1 increase in QALYs (Table *3*).

Effect of uncertainty

Tornado analysis showed the model's outcome is robust against ± 25% changes in critical variables, with Regorafenib remaining cost-effective in all scenarios (Figure 3). Monte Carlo simulations with 1,000 samples affirmed Regorafenib's cost-effectiveness at a WTP threshold of $16,484, with over 99% probability compared to the CetIri regimen. Probabilistic sensitivity analysis (PSA) also highlighted a 78% and 99% probability of Regorafenib being dominant and cost-effective, respectively. Increasing the WTP threshold to three times the GDP per capita ($49,452) did not alter Regorafenib's status as the cost-effective option (Figure 4).

Discussion

The results of the CUA estimated that regorafenib could lead to cost savings of 12,154 US$ while increasing QALYs by 0.1 over a 25-month time horizon. So, the base-case model demonstrated that regorafenib is a dominant alternative compared to the CetIri regimen in the optimal third-line therapy for patients with mCRC in Iran. The resulting ICER, with a PSA of 1000 samples and thresholds of one, two, and three times Iran's GDP per capita, confirmed that regorafenib remained a cost-effective alternative with more than 99% probability.

Deterministic and probabilistic sensitivity analyses were performed to assess the robustness of the findings and test the impact of varying key parameters.

These analyses further confirmed the stability of the cost-effectiveness findings observed in the base-case model. Variations in drug costs, utility values, and treatment duration did not significantly alter the overall findings. This finding indicated that regorafenib's cost-effectiveness is robust and not heavily reliant on specific input values, thereby enhancing the reliability and generalizability of the results.

The present study's findings are consistent with previous research, which predicted cost savings and increased QALYs in the regorafenib group compared to the CetIri regimen in other countries, such as China.[19] Previous cost-utility analyses in Spain have also concluded that regorafenib is a cost-effective alternative for third-line therapy in mCRC.[22]

The papers indicate that the cost-effectiveness of regorafenib in treating third-line mCRC differs depending on the setting and perspective. According to Goldstein et al. (2015), regorafenib may provide minimal additional benefit at a high cost per quality-adjusted life-year (QALY) from the US payer perspective.[23] Zhu et al. (2018) concluded that regorafenib monotherapy was more effective and cost-saving than cetuximab plus irinotecan in the Chinese setting.[19] However, A cost-effectiveness study in 2021 concluded that fruquintinib was a cost-effective choice compared to regorafenib from the Chinese healthcare perspective.[24]

While considering the findings of this study, it is essential to acknowledge its limitations. Since the study utilized a simulated model based on a hypothetical cohort, the inputs were not derived from real-world clinical data. Furthermore, the probabilities and assumptions used in the model were obtained from RCTs conducted in countries other than Iran, which may have different geographical and genetic circumstances. Therefore, caution should be exercised when generalizing these findings. Moreover, the study's analysis was performed from the perspective of the Iranian healthcare payer, incorporating local pricing and resource utilization patterns. Consequently, the results may not directly apply to other healthcare systems with different cost structures and

reimbursement mechanisms. Thus, careful consideration is needed when extrapolating these findings to other countries or regions.

Conclusion

This study unequivocally establishes Regorafenib as a superior alternative to the Cetuximab plus Irinotecan (CetIri) regimen in managing mCRC in Iran. The cost-effectiveness of Regorafenib and its ability to enhance QALYs for patients are illustrated through a comprehensive CUA. These outcomes align with existing literature, underscoring the clinical value of Regorafenib in the therapeutic landscape of mCRC.

Notwithstanding, caution is warranted when applying these results beyond the Iranian healthcare context, given the variability in medical infrastructure, economic conditions, and patient demographics across different regions. Hence, while the findings advocate for Regorafenib's preferential use in Iran, the generalizability of these results to other healthcare settings may be limited.

Looking ahead, there is a pressing need for further empirical research to corroborate the conclusions. Future studies should incorporate real-world data to paint a more nuanced picture of Regorafenib's effectiveness and cost-efficiency, considering the specificities of local healthcare environments. Such research endeavors will guide healthcare policy and clinical decision-making, ensuring that patients with mCRC receive the most effective and economical treatment options.

This study contributes to the burgeoning body of literature advocating for Regorafenib and highlights the importance of contextually informed healthcare policies and practices. Moving forward, researchers and healthcare practitioners are responsible for persisting in exploring and validating the optimal strategies for managing mCRC, thereby enhancing patient outcomes across diverse healthcare landscapes.

Conflict of Interest

None declared.

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Table 1. Random variables in the model

Variable name	Distribution type
Costs	Gamma
Quality of life in the progression state	Beta
Quality of life in the progression-free state	Beta
The mean height of the Iranian adult population	Normal
The mean weight of the Iranian adult population	Normal
TDTPs	Weibull
Random variable coefficient of TDTPs	Normal

TDTPs: *Time-dependent transition probabilities*

Table 2. Cost parameter variables

Cost variable	Cost per unit (USD)
Atropine injection, 0.5 mg/1mL	0.44
Angiocath	0.66
Complete blood count test	1.15
Chemotherapy	53.86
Clobetasol 0.05% topical cream	1.15
Creatinine test	0.49
Cetuximab, the brand of Merck	168.89
Dexamethasone injection 8 mg/2mL	0.49
Diphenhydramine injection 5 mg/1mL	4.82
Fluorouracil injection parenteral 50 mg/1 mL 5 mL	2.53
Infusion set	0.75
Irinotecan, injection parenteral 20 mg/1 mL	40.05
Lab administration	1.02
Loperamide 2 mg oral tablet	0.03
Leucovorin injection	8.56
Mucositis	1.97
Sodium chloride infusion 1 L	4.03
Nausea and vomiting	2.07
Ondansetron injection 8 mg/4 mL	0.92
Oxaliplatin	60.42
Skin rash	14.76
Regorafenib 40 mg oral tablet	17.36
Subcutaneous medication	6.56
Syringe, 20 mL	0.66
Syringe, 5 mL	0.16
Syringe, 10 mL	0.07
Urea 10% topical cream	3.33
Oncologist visit	2.03

mg: Milligram; mL: Milliliter; L: Liter; USD: United States dollar

Table 3. Base-case model results

Strategy	Cost	Incremental cost	Eff	Incremental Eff	ICER	NMB
Regorafenib	5,827		0.40			796
CetIri	17,981	12,154	0.31	-0.09	-129,739	-12,902

CetIri: Cetuximab plus irinotecan regimen; Eff: Effectiveness; ICER: Incremental cost-effectiveness ratio; NMB: Net monetary benefit

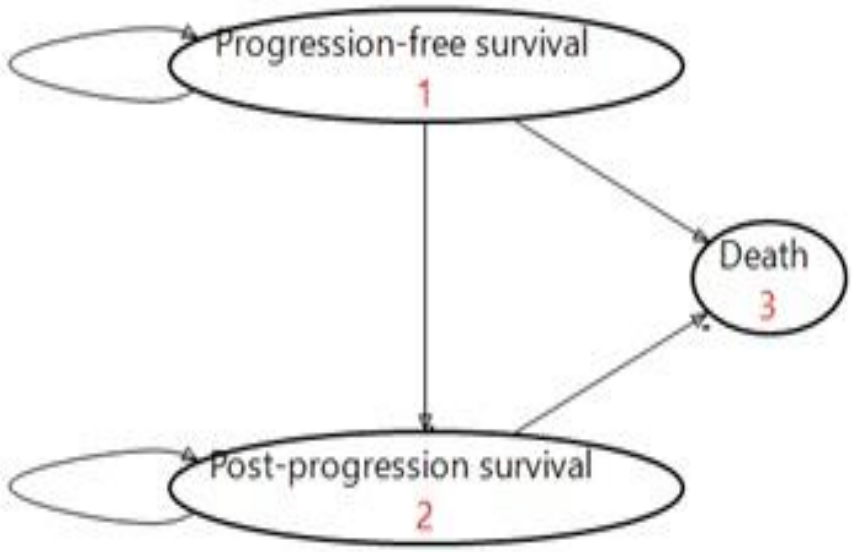

Figure 1. Markov Model illustrates three health states: progression-free survival, post-progression survival, and death, with transitions indicated by arrows.

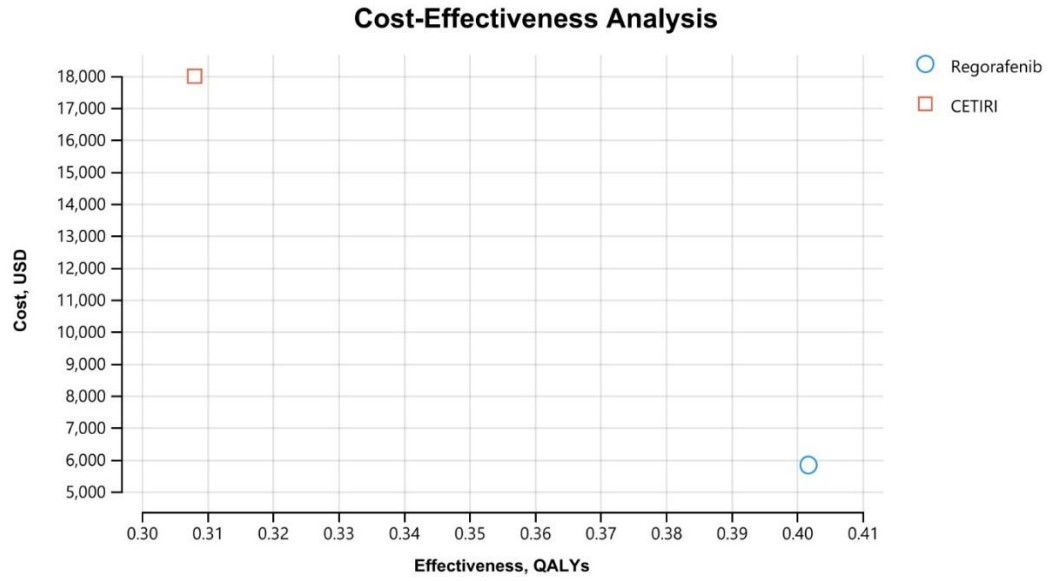

Figure 2. This figure shows the cost-effectiveness analysis plot comparing Regorafenib vs. Cetuximab plus Irinotecan regimen, highlighting the superior cost-effectiveness of Regorafenib.
CETIRI: Cetuximab plus irinotecan regimen; QALYs: Quality-adjusted life years; USD: United States dollar

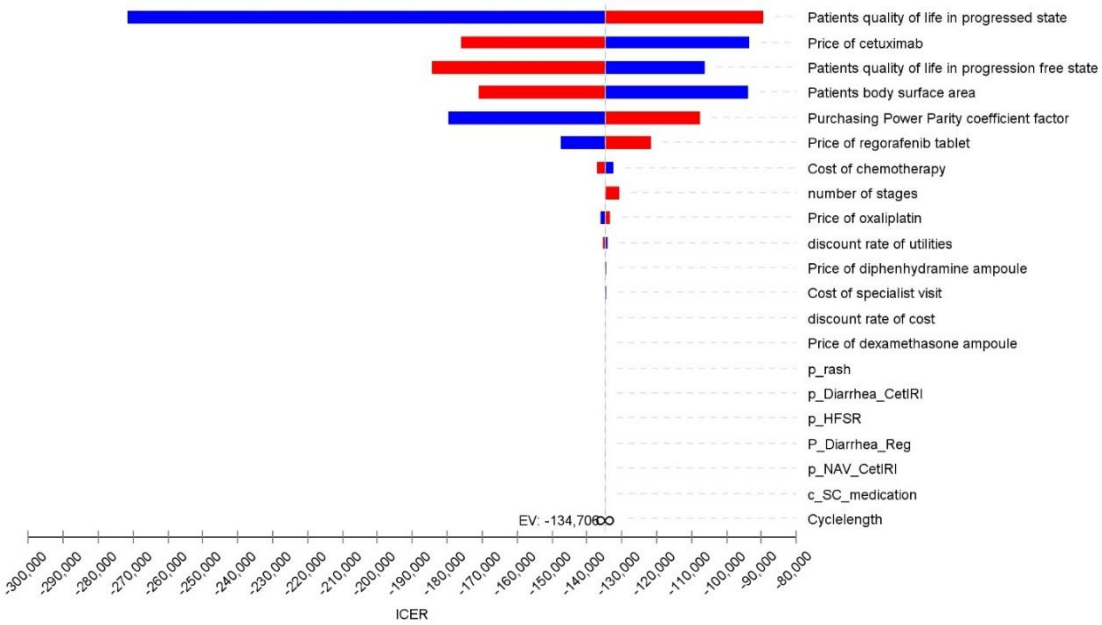

Figure 3. This figure shows the deterministic sensitivity analysis using a Tornado diagram to depict the impact of parameter value changes on the model, with essential variables ranked at the top.

C: Cost; CetIri: Cetuximab plus irinotecan regimen; EV: Estimated value; ICER: Incremental cost-effectiveness ratio; P: Price; SC: Subcutaneous

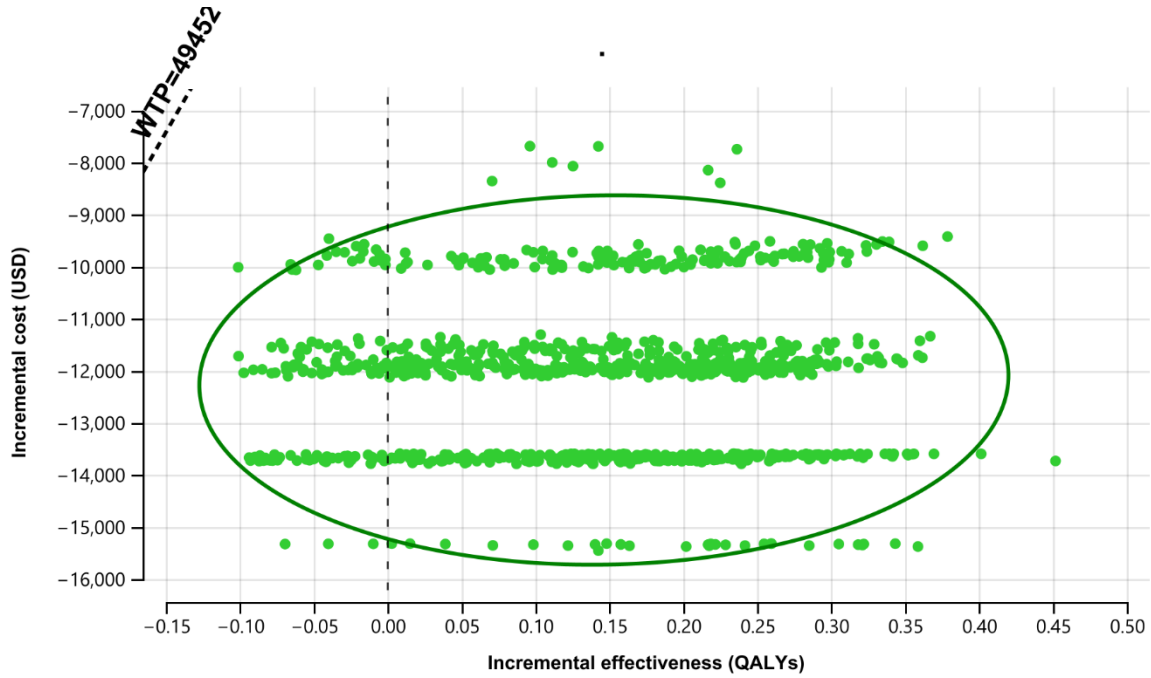

Figure 4. Incremental cost-effectiveness scatter plot from probabilistic sensitivity analysis with 1000 resamples, compared against the WTP threshold. Points under the WTP threshold denote acceptable cost-effectiveness, with a circle indicating the 95% confidence interval.

WTP: Willingness to pay; QALYs: Quality-adjusted life years; USD: United States dollar