

BMJ Open Cost-effectiveness analysis of adding ramucirumab to the first-line erlotinib treatment for untreated EGFR-mutated metastatic non-small cell lung cancer in China

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ABSTRACT

Objective To investigate the cost-effectiveness of ramucirumab plus erlotinib compared with placebo plus erlotinib in the first-line setting for patients with EGFR-mutated metastatic non-small cell lung cancer (mNSCLC) from the Chinese healthcare system perspective.

Design A Markov model consisting of three health states using clinical survival data from the RELAY phase III randomised clinical trial, a lifetime horizon for costs and quality-adjusted life-years (QALYs) was constructed to analyse the cost-effectiveness of ramucirumab plus erlotinib. One-way and probabilistic sensitivity analyses were performed to evaluate the robustness of the model. Additional price reduction scenario analyses were performed.

Setting The Chinese healthcare system perspective.

Participants A hypothetical Chinese cohort of patients with confirmed previously documented ex19del or Leu858Arg mutation stage IV NSCLC, and without known epidermal growth factor receptor (EGFR) Thr790Met mutation and central nervous system metastases.

Interventions Ramucirumab plus erlotinib versus placebo plus erlotinib.

Primary outcome measure Costs, QALYs, incremental cost-effectiveness ratio (ICER).

Results In base-case analysis, ramucirumab plus erlotinib yield an additional 4.21 QALYs at a cost of \$540 590, resulting in an ICER of \$128 302/QALY. In price reduction scenario analysis, the ICER (\$65 227/QALY) was decreased significantly when the National Reimbursement Drug List (NRDL) negotiation was available for ramucirumab, and the ICER (\$131 554/QALY) was increased slightly when the NRDL negotiation was unavailable for erlotinib. Sensitivity analyses demonstrated our results to be most sensitive to the unit cost of ramucirumab (10 mg/kg), and more than 52.1% reduction in the price of ramucirumab resulted in the ICER under the willingness-to-pay threshold set for affluent regions (\$70 353/QALY).

Conclusions Ramucirumab plus erlotinib is unlikely to be cost-effective for patients with untreated EGFR-mutated mNSCLC in China. Reducing the price of ramucirumab through the National Healthcare Security Administration negotiation was found to be the most realistic action to improve cost-effectiveness.

Strengths and limitations for this study

- The trial-based Markov model can make a long-term projection based on the latest clinical trial data, which usually have short periods.
- The Markov model was able to simulate the treatment, survival and death of advanced non-small cell lung cancer, which makes up the limitation exist in commonly used meta-analytic techniques.
- We applied two willingness-to-pay thresholds in the model, reflecting the cost-effectiveness of ramucirumab plus erlotinib versus placebo plus erlotinib in both high-income and resource-constrained regions of China.
- The trial-based economic analysis should be interpreted with caution because the worldwide trial may not fully conform to the clinical pathway and treatment pattern in China.
- A potential for inherent bias in our Markov model was that several local data on costs and utilities were not available.

INTRODUCTION

Lung cancer remains the most prevalent malignancy,¹ as well as the leading cause of cancer-related deaths in China.² Non-small cell lung cancer (NSCLC) manifests the majority (nearly 85%) of primary lung cancers,^{3 4} and up to 46% of NSCLC cases diagnosed beyond early stages.⁵ Epidermal growth factor receptor (EGFR) mutations occur at frequencies of approximately 30%–50% in Asian patients with NSCLC, of which in-frame deletion within exon 19 (ex19del) accounts for 44% and the single point mutation in exon 21 (Leu858Arg) accounts for 41%.⁶

Historically, the most common form of personalised treatment for EGFR mutation-driven NSCLC has been the targeted therapy with small-molecule tyrosine

kinase inhibitors (TKIs), which are recommended as the first-line standard-of-care, because of their major improvement over traditional chemotherapy in long-term survival.^{7–10} Clinical evidence over the past few years has shown that the median progression-free survival (PFS) with TKIs for advanced disease ranges from about 1 year for first-generation TKIs (gefitinib and erlotinib), to 18.9 months for third-generation TKIs (osimertinib).^{7–9 11 12} However, EGFR TKIs are related to inevitable treatment resistance, which eventually leads to the loss of clinical benefits. Additionally, although great progress has been made in immune checkpoint inhibitors in recent years,¹³ their role in EGFR-mutated disease is poor,¹⁴ and treatment options for patients who have exhausted from these targeted therapies are generally limited.^{15 16} Thus, there is an ongoing unmet need for new treatment strategies, such as EGFR TKI-based combination therapy, to provide the best chance of long-time PFS, and therefore prolong remission and control tumour.

Increasing preclinical and clinical trials of first-line treatment of EGFR-mutated NSCLC has revealed better clinical outcomes for the dual blockade of the EGFR and vascular endothelial growth factor (VEGF) pathways, than for inhibition of the EGFR pathway alone.^{17–20} Ramucirumab, a fully human monoclonal IgG1 antibody, binds specifically to vascular endothelial growth factor receptor 2 (VEGFR-2) with high affinity.²¹ Therefore, ramucirumab has more extensive antitumor activity in contrast to other VEGF inhibitors. A very recent, phase III RELAY trial supported the potential of adding ramucirumab to the first-line erlotinib treatment. Compared with placebo plus erlotinib, ramucirumab plus erlotinib provided superior PFS in patients with untreated EGFR-mutated metastatic NSCLC (mNSCLC) (19.4 months vs 12.4 months; HR=0.59, 95% CI: 0.46–0.76, $p<0.0010$).²² Notably, a consistent PFS benefit was observed in patients with a baseline ex19del and Leu858Arg mutations. Although there has been a general uptrend in the incidence of several treatment-emergent adverse events for the combination strategy, the increase has been mainly limited to grade 1–2 events.

The significantly higher efficacy of ramucirumab plus erlotinib in comparison with placebo plus erlotinib has inspired us that the dual inhibition of EGFR and VEGF pathways appears to be a better alternative for patients with untreated EGFR-mutated mNSCLC.²² However, in mainland China, ramucirumab, the novel VEGFR-2 specific inhibitor with prohibitive price, has not been licensed. Instead, erlotinib has been approved for the first-line treatment of EGFR-mutated mNSCLC. The retail price of erlotinib in China was set by the National Healthcare Security Administration (NHSA) through National Reimbursement Drug List (NRDL) negotiation, which is 70% lower than its original price.²³ Cost-effectiveness analyses of an expensive new treatment strategy is necessary before it is widely used, especially in health resource-limited setting. In order to better determine the role of the dual blockade of the EGFR and VEGF pathways in

first-line metastatic EGFR-mutated NSCLC, we performed a cost-effectiveness analysis to compare ramucirumab plus erlotinib with placebo plus erlotinib, from the perspective of Chinese healthcare. Information on significant effectiveness incurred by ramucirumab could shed light on policy decision towards its listing in China.

MATERIAL AND METHODS

Analytical overview and model structure

A Markov model was constructed to evaluate the cost-effectiveness associated with the two first-line strategies for patients with mNSCLC: (1) ramucirumab 10 mg/kg every 2 weeks, plus oral erlotinib 150 mg/day; (2) intravenous placebo plus oral erlotinib. Our study is a trial-based economic assessment that used clinical data mainly from the RELAY phase III clinical trial. Therefore, a hypothetical cohort consistent with the RELAY trial population (patients with confirmed previously documented ex19del or Leu858Arg mutation stage IV NSCLC, and without known EGFR Thr790Met mutation and central nervous system (CNS) metastases, and the initial age for all patients was 65 years old) was created in the model to simulate the clinical efficacy reflected in the RELAY clinical trial. This model-based economic evaluation relied on a literature review, and it is exempt from the institutional research ethics board approval.

The course of mNSCLC was simulated by a Markov model, including three mutually exclusive health states (figure 1): PFS, progression survival (PS) and death. The Markov cycle length was 2 weeks, and the time horizon was lifetime. Half-cycle correction was adopted in the model. All hypothetical patients were in the PFS state initially, and randomly treated with first-line ramucirumab–erlotinib or placebo–erlotinib until Response Evaluation Criteria In Solid Tumors (RECIST) defined progression, or unacceptable toxicity. As reported in the RELAY trial, at the date cut-off, 29% (64 of 224) of patients in ramucirumab–erlotinib arm and 19% (43 of 225) in placebo–erlotinib arm were still under treatment. After RECIST-defined progression, we modelled patients as receiving type of subsequent line of therapy consistent with those detail in the RELAY trial. Subsequent line of therapy that included chemotherapy, EGFR-TKI targeted therapy and immunotherapy was allowed as long as there was continued benefit as judged by the investigator, when first subsequent line of therapy was failed, second subsequent line of therapy was administered at the discretion of the investigator. According to the RELAY trial, over half of patients received first subsequent line of therapy (54% in ramucirumab–erlotinib and 69% in placebo–erlotinib, respectively), and more patients were administered second subsequent line of therapy in ramucirumab–erlotinib arm than placebo–erlotinib arm (28% vs 34%, respectively).²² Patients who had not received subsequent therapy were treated with the best supportive care (BSC) based on current clinical guidelines in china.²⁴

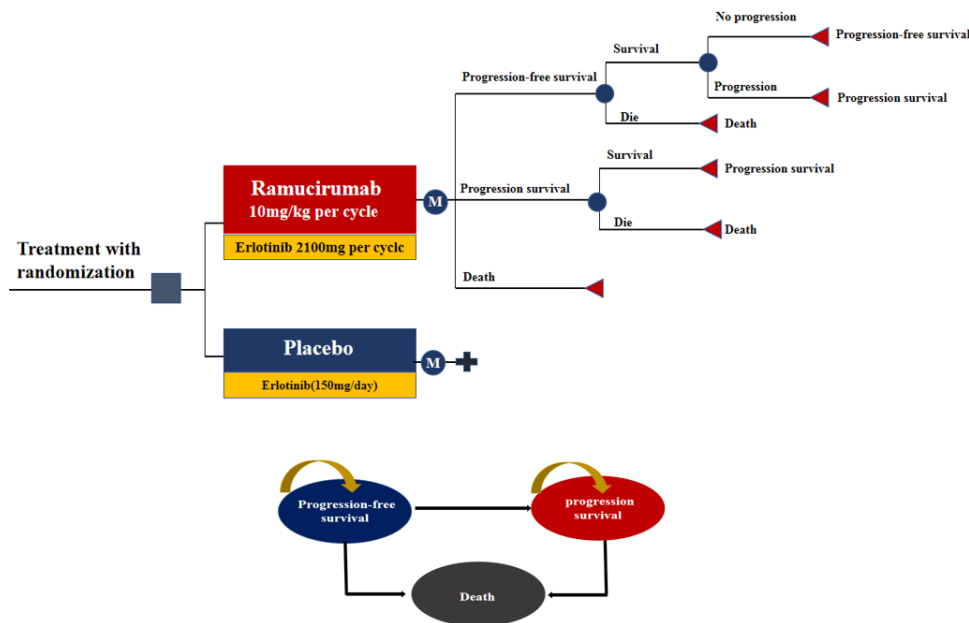


Figure 1 Schematics of the decision tree and the Markov state transition model. M, markov node.

The primary outcomes in the model were as follows: the total cost, life years (LYs), quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs). Cost and effectiveness were discounted at 3% annually. Due to the imbalance of economic development among different regions in china, we selected \$30 363/QALY as the willingness-to-pay (WTP) threshold value for general regions and \$70 353/QALY for affluent regions.²⁵

Model survival and progression risk estimates

The clinical effectiveness data associated with ramucirumab–erlotinib and placebo–erlotinib were available from the phase III RELAY trial, at the updated data cut-off (1 February 2018).²² GetData Graph Digitizer software package (V.2.26; <http://www.getdata-graph-digitizer.com/download.php>) was used to extract the PFS and overall survival (OS) data points from the investigator-assessed Kaplan-Meier (KM) curves, then four commonly used parametric survival models were fitted, including Weibull, exponential, log-logistic and log-normal distributions. The exponential survival distribution was chosen to independently fit the digitised KM plots of the two first-line treatments, as it provided the optimal fit based on statistical goodness-of-fit test (Bayesian information criterion (BIC) and Akaike’s information criterion (AIC)), visual fit and clinical rationality (see online supplemental appendix 1). The exponential distribution parameters, hazard rate (λ_{OS} and λ_{PFS}), was estimated by R software (V.3.3.1, <http://www.r-project.org>). Table 1 shows the final estimated exponential parameters. For the validation purpose, the predicted OS and PFS curves were compared with the investigated KM curves (see online supplemental appendix 1).

The time-dependency transition probabilities of death were calculated from the following formula:

$$tp(t_u) = \exp\{\lambda_{OS}(t - u) - \lambda_{OS}t\} \quad (\lambda > 0),$$

The transition probabilities of PFS at time t were calculated from the following formula:

$$tp(tp(t_u) = \frac{\exp\{\lambda_{PFS}(t - u) - \lambda_{PFS}t\}}{\exp\{\lambda_{OS}(t - u) - \lambda_{OS}t\}} \quad (\lambda > 0),$$

where t_u represents the arrival state after u Markov cycles, and t is calculated as integer multiple of Markov cycle length.²⁶

Utility estimates

QALYs in the model were estimated by weighting the patient’s life years with health utility value. Health utility values of PFS and PS states were derived from a previously published international study that capture utilities for mNSCLC in six countries, including China.²⁷ According to the study, utility decrements were found for treatment-related grade III/IV toxicities. Therefore, the current analysis calculated the utility value in PFS states based on the risk of adverse events reported in the RELAY trial, and the corresponding utility values were as follows: PFS (0.815), PFS plus diarrhoea (0.746), PFS plus hypertension (0.773), PFS plus rash (0.720), PFS plus nausea/vomiting (0.695), PFS plus fatigue (0.750) and PFS plus neutropenia (0.621).²⁷ Utility values used in the model are listed in table 1.

Cost estimates

The cost data were estimated from the perspective of Chinese healthcare, and only direct medical costs were considered in this model, including drug, management of serious adverse effects (SAEs) (grade III/IV adverse effects), routine follow-up in PFS state, subsequent therapy in PS state, BSC and terminal care cost (table 1). The unit cost for erlotinib (2100 mg per cycle) was based on the latest reimbursement price, negotiated by the NHSA with pharmaceutical companies in July 2017.²³ The unit cost of ramucirumab (10 mg/kg per cycle) was

**Table 1** Base cases, ranges and distributional assumptions of parameters

Parameter	Base-case	Range	Distribution	Source
Costs (\$)				
Ramucirumab (10 mg/kg per unit)	100.5	43.5–100.5	Fixed	Local charge
Erlotinib (2100 mg per unit)*	115.6	115.6–385.3	Fixed	Local charge
Routine follow-up per unit†	37.1	27.8–46.3	Lognormal	Wu <i>et al</i> ³¹
Subsequent therapy in PS state per unit‡	558.4	462.0–648.9	Lognormal	Zeng <i>et al</i> ³²
BSC per unit§	225.0	105.8–529.1	Lognormal	Wu <i>et al</i> ³¹
Terminal phase cost per unit¶	1751.9	1527.9–1977.7	Lognormal	Zeng <i>et al</i> ³²
Hypertension per event	12.9	11.6–14.2	Lognormal	Wu <i>et al</i> ²⁹
Diarrhoea per event	5.18	4.14–6.22	Lognormal	Lu <i>et al</i> ²⁸
Risk for SAEs				
Diarrhoea in ramucirumab arm	0.072	0.058–0.086	Beta	Nakagawa <i>et al</i> ²²
Diarrhoea in placebo arm	0.013	0.010–0.016	Beta	Nakagawa <i>et al</i> ²²
Hypertension in ramucirumab arm	0.235	0.188–0.282	Beta	Nakagawa <i>et al</i> ²²
Hypertension in placebo arm	0.053	0.042–0.064	Beta	Nakagawa <i>et al</i> ²²
Rash in ramucirumab arm	0.009	0.007–0.011	Beta	Nakagawa <i>et al</i> ²²
Rash in placebo arm	0.022	0.018–0.026	Beta	Nakagawa <i>et al</i> ²²
Vomiting in ramucirumab arm	0.009	0.007–0.011	Beta	Nakagawa <i>et al</i> ²²
Vomiting in placebo arm	0.004	0.003–0.005	Beta	Nakagawa <i>et al</i> ²²
Fatigue in ramucirumab arm	0.014	0.011–0.017	Beta	Nakagawa <i>et al</i> ²²
Fatigue in placebo arm	–	–	Beta	Nakagawa <i>et al</i> ²²
Neutropenia in ramucirumab arm	0.027	0.022–0.032	Beta	Nakagawa <i>et al</i> ²²
Neutropenia in placebo arm	0.009	0.007–0.011	Beta	Nakagawa <i>et al</i> ²²
Health utility values				
PFS state	0.815	0.652–0.978	Beta	Nafees <i>et al</i> ²⁷
PS state	0.321	0.257–0.385	Beta	Nafees <i>et al</i> ²⁷
PFS plus diarrhoea	0.746	0.597–0.895	Beta	Nafees <i>et al</i> ²⁷
PFS plus hypertension	0.773	0.618–0.928	Beta	Nafees <i>et al</i> ²⁷
PFS plus rash	0.720	0.576–0.846	Beta	Nafees <i>et al</i> ²⁷
PFS plus nausea/vomiting	0.695	0.556–0.834	Beta	Nafees <i>et al</i> ²⁷
PFS plus fatigue	0.750	0.600–0.900	Beta	Nafees <i>et al</i> ²⁷
PFS plus neutropenia	0.621	0.497–0.745	Beta	Nafees <i>et al</i> ²⁷
Distribution parameters				
Ramucirumab, OS, scale (exponential)	0.003728	–	Fixed	Estimated
Placebo, OS, scale (exponential)	0.004	–	Fixed	Estimated
Ramucirumab, PFS, scale (exponential)	0.02617	–	Fixed	Estimated
Placebo, PFS, scale (exponential)	0.01844	–	Fixed	Estimated
Discount rate (%)	3	0–8	Fixed	Guan <i>et al</i> ³³
Patient weight (kg)	65	52–78	Fixed	Lu <i>et al</i> ²⁸

*The price of erlotinib was set by the National Healthcare Security Administration (NHSA), for patients with EGFR (epidermal growth factor receptor) -mutated metastatic non-small cell lung cancer (mNSCLC) treated with erlotinib, 70% of the cost would be paid by China's basic medical insurance.

†The cost of routine follow-up included the cost of outpatient physician visit, laboratory tests and examinations.

‡According to RELAY trial, subsequent therapy referred to the treatment beyond the point of RECIST-defined progression, and included chemotherapy, EGFR-TKI targeted therapy and immunotherapy.

§BSC referred to the intervention of clinical symptoms caused by cancer, including anti-inflammatory treatment, analgesic treatment, antiemetic treatment, thoracic and abdominal puncture decompression, blood transfusion and nutritional support and so on.

¶The terminal phase cost referred to the cost of palliative end-of-life.

BSC, best supportive care; OS, overall survival; PFS, progression-free survival; PS, progression survival; RECIST, Response Evaluation Criteria In Solid Tumors; SAEs, serious adverse effects; TKI, tyrosine kinase inhibitor.

retrieved using the latest retail price driven from China-Hong Kong, as a result of the absence of ramucirumab in the Chinese mainland market. In calculating dosage amounts, a base-case patient with body weight of 65 kg (range: 52–78 kg) was assumed in the model.²⁸ In order to improve estimates accuracy of our model, the total costs of ramucirumab and erlotinib for each strategy were adjusted according to the median relative dose intensity reported in RELAY trial (see online supplemental appendix 2).

The costs of SAEs with $\geq 5\%$ difference in incidence between the two arms were considered in the model, including hypertension, diarrhoea, dermatitis acneiform. Based on the Chinese oncologists' common opinion, dermatitis acneiform does not require additional treatment. Therefore, the costs of dermatitis acneiform were excluded. The costs related to SAEs were calculated by multiplying the incidence of SAEs by the costs of managing SAEs per event. The incidence of SAEs was derived from previous study.^{29 30}

Other costs were obtained from published literature.^{31 32} All costs are reported in 2019 US dollars. Considering that costs related to Chinese healthcare are stable under central control by the government, the current analysis did not consider the inflation of the costs from different base years.

Sensitivity analysis

Considering the uncertainty bound to model parameters, a series of sensitivity analyses were performed to evaluate the robustness of the base-case results. In the one-way sensitivity analyses (OSA), all parameters varied over a priori defined range independently (shown in table 1), while the others were fixed to explore the sensitivity of the finding to plausible variations in specific parameters. The ranges of parameters were mainly come from published literature,^{29–33} or were assumed to vary within $\pm 20\%$ of the base-case value. In view of a series of negotiations on oncology drugs launched by China's NHSA, the average price reduction for new anticancer drugs was as high as 56.7%,²³ the cost ranges of ramucirumab (10 mg/kg per cycle) and erlotinib (2100 mg per cycle) were not assumed to vary within $\pm 20\%$ of the base-case value in the current analysis. For the cost range of ramucirumab (10 mg/kg per cycle), given a likely scenario that NHSA negotiations were available for ramucirumab, our analyses were conducted based on the price variation from \$43.5 (56.7% of reduction, the average price reduction through NRDL negotiation) to \$100.5 (the latest retail price). For the cost range of erlotinib (2100 mg per cycle), given a likely scenario that NRDL negotiation was unavailable for erlotinib, our analyses were conducted based on the price variation from \$115.6 (70% reduction, the latest reimbursement price set by NHSA) to \$385.3 (the latest retail price). The results of OSA were visualised by a tornado diagram.

The Monte Carlo simulation probabilistic sensitivity analyses (PSA) were performed by running 10 000

iterations, to test the influence of uncertainty in the model parameters on the ICERs for each strategy. Each iteration, we varied all parameters simultaneously, except for specific parameters such as ramucirumab cost (10 mg/kg per unit), erlotinib cost (2100 mg per unit), distribution parameters, discount rate and patient weight. The parameters were sampled from the set statistical distributions, including log-normal distributions for cost parameters, beta distributions for risks and utilities. Cost-effectiveness acceptability curves were created to illustrate the probabilities of each treatment strategy being cost-effective with respect to a given scenario, such as a wide range of WTP thresholds and different oncology drug prices. The base-case values, ranges and distributions of model parameters are listed in table 1.

Patient and public involvement

No patients or public were involved in the study.

RESULTS

Base-case results

The model showed that ramucirumab plus erlotinib in the first-line treatment for patients with untreated ex19del or Leu858Arg mutated mNSCLC result in substantial health benefits at incremental costs. The estimated mean PFS time and life expectancy for patients receiving ramucirumab plus erlotinib were 2.93 LYs and 9.04 LYs, respectively, which were 2.16 LYs and 7.85 LYs more than patients receiving placebo plus erlotinib. Adjusted for utilities, the ramucirumab plus erlotinib treatment added costs of \$540 590 (\$554 776 vs \$14 185) and yielded an addition QALYs of 4.21 (5.22 QALYs vs 1.01 QALYs), compared with the placebo plus erlotinib treatment. The ICER per LY gained and per QALY gained of the ramucirumab–erlotinib arm versus the placebo–erlotinib arm were \$54 015 and \$128 302, respectively (table 2).

The base-case results based on whether NRDL negotiation was available for erlotinib and ramucirumab were also reported in the current analysis (see online supplemental appendix 3).

One-way sensitivity analysis

The top five parameters with the greatest influence on the ICER for ramucirumab plus erlotinib strategy were (1) the unit cost of ramucirumab (10 mg/kg); (2) discount rate; (3) patient weight; (4) the utility of PS and (5) the cost of BSC (figure 2). More than 52.1% reduction in the price of ramucirumab resulted in the ICER under the WTP threshold set for affluent regions (\$70 353/QALY). Other parameters, such as utility values, and other direct medical costs had a moderate effect, and the risk of SAEs had a minor effect on the ICER. The result of OSA showed that all parameters varying over a plausible range, except the unit cost of ramucirumab (10 mg/kg), failed to make ICER lower than the WTP threshold selected for affluent regions, and none of these parameters showed a

Table 2 Summary of cost and outcome results in the base-case analysis

Item	Ramucirumab–erlotinib	Placebo–erlotinib	Difference
Mean LYs			
PFS state	2.93	0.77	2.16
PS state	9.04	1.19	7.85
Total	11.97	1.96	10.01
Mean QALYs			
PFS state	2.32	0.63	1.69
PS state	2.90	0.38	2.52
Total	5.22	1.01	4.21
Cost (\$)			
Drug costs in PFS state*	476 536	2187	479 349
Routine follow-up cost in PFS state	2801	728	2073
SAEs management costs in PFS state	3	15	–12
Subsequent therapy costs in PS state†	36 912	5841	31 071
BSC costs in PS state	38 050	4589	33 461
Terminal phase costs in dead state	474	826	–352
Total	554 776	14 186	540 590
ICER (\$)			
Per LY			54 015
Per QALY			128 302

*The costs of first-line ramucirumab plus erlotinib and placebo plus erlotinib were calculated based on clinical usage and dosage in RELAY trial, and then were adjusted according to median duration of therapy and median relative dose intensity.

†Subsequent therapy costs in PS state were estimated based on the proportion of patients in the first subsequent line of therapy and second subsequent line of therapy reported in RELAY trial.

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life-year; PFS, progression-free survival; PS, progression survival; QALY, quality-adjusted life-year; SAEs, serious adverse effects.

potential to reduce the ICER below the WTP threshold selected for general regions.

Probabilistic sensitivity analysis

The results of PSA are presented in figures 3 and 4. When the WTP threshold was 70 353/QALY, the proportions of simulations with cost-effectiveness for ramucirumab plus erlotinib strategy were 23.5%, while when the WTP threshold was \$30 363/QALY, the proportions dropped to 2.6% (figure 3). The acceptability curve also suggested that the proportions of simulations with cost-effectiveness for ramucirumab plus erlotinib were increased with the increasing WTPs, at a very high threshold (>\$480 000/QALY), more than 90% of simulations achieve cost-effectiveness. Figure 4 demonstrates that the likelihood of ramucirumab plus erlotinib being cost-effective increased with the decrease of the unit cost of ramucirumab, when the unit cost of ramucirumab decreased by 56.7%, the probabilities of ramucirumab plus erlotinib being cost-effective were 6.1% and 53.4% at the WTP threshold of \$30 353/QALY and the WTP threshold of \$70 353/QALY, respectively. Additionally, we provided more detailed results of PSA in online supplemental appendix 4.

DISCUSSION

To the best of our knowledge, the study is the first economic analysis of ramucirumab plus erlotinib versus placebo plus erlotinib for patients with previously untreated EGFR-mutated mNSCLC without known EGFR Thr790Met mutation and CNS metastases, and our results have reference significance for further promoting the NRDL negotiation in China. The main finding of the current analysis was that ramucirumab plus erlotinib could improve health outcomes (5.22 QALYs vs 1.01 QALYs) with a substantial augmentation of cost (\$554 776 vs \$14 185) compared with placebo plus erlotinib, resulting in an average ICER of \$128 302/QALY, which is higher than the two WTP thresholds selected for the current study. From the perspective of Chinese health-care, the ramucirumab plus erlotinib strategy was unlikely to be cost-effective.

The most influential parameter in our model was the unit cost of ramucirumab, which was mainly responsible for the unfavourable ICER of ramucirumab plus erlotinib versus placebo plus erlotinib. Fortunately for Chinese patients with cancer, a growing number of oncology drugs have been negotiated by NHSA to reduce the price since 2016.²³ When the NRDL negotiation

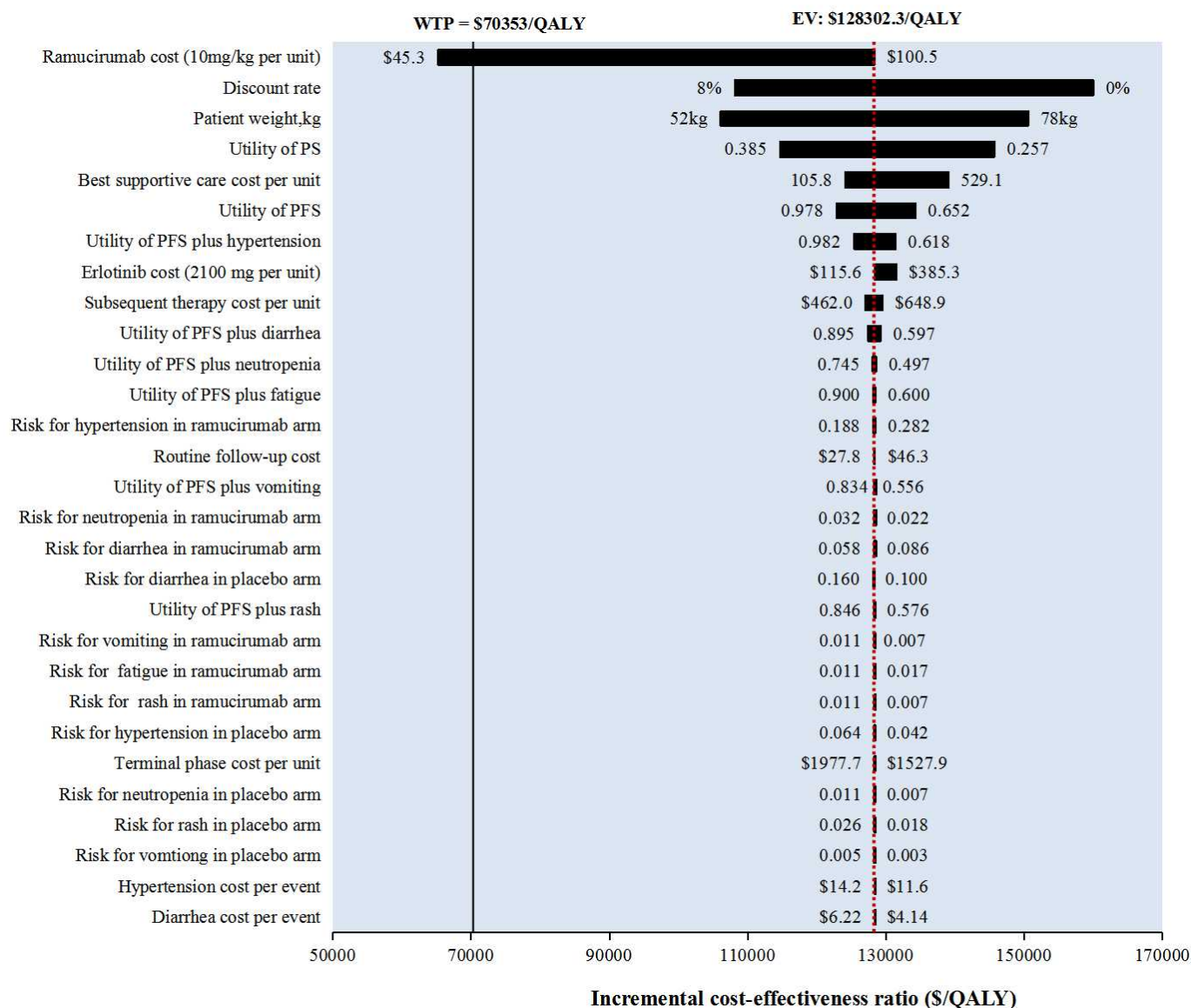


Figure 2 Tornado diagram of the one-way sensitivity analysis revealing variables' influence on the ICER. The red dotted line represents the ICER of \$128 302/QALY from the base-case results. The solid black line represents the WTP of \$70 353/QALY for affluent regions in China. ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; PS, progression survival; QALY, quality-adjusted life-year; WTP, willingness-to-pay threshold.

was available for ramucirumab, the ramucirumab plus erlotinib strategy might be a cost-effective therapeutic strategy alternative to erlotinib monotherapy, given that the ICER (\$65 227/QALY) was substantially lower than the WTP threshold selected for the affluent regions (\$70 353/QALY) in China. Thus, negotiating ramucirumab might be a feasible way to achieve favourable economic outcomes. From a more far-sighted perspective, NRDL negotiation will be the most attainable approach for integrating medical and health resource in China, through which patients with cancer can be provided with better treatment at lower cost.

In the current analysis, we also evaluated the impact of the price of erlotinib, another oncology drug, on economic outcomes. The OSA also pointed out that the ICERs were almost unaffected when the unit cost of erlotinib varied

across a plausible range. When the NRDL negotiation was unavailable for erlotinib, the base-case analysis showed that ramucirumab plus erlotinib strategy yielded an unfavourable ICER of \$131 554/QALY compared to placebo plus erlotinib strategy, which was slightly higher than our primary economic outcomes. One plausible explanation for this finding is that the dose and schedule of erlotinib in the two competing strategies were exactly the same.

The PSA found a higher likelihood that ramucirumab plus erlotinib would be cost-effective at a higher WTP threshold, which were generally coherent with our previous study.³⁴ Given the fact that the Chinese economy is highly unbalanced among 34 province-level administrative units, the per capita gross domestic product (GDP) extended from \$4727 in Gansu Province to \$29 510 in Shenzhen city in 2019. Therefore, in the current analysis,

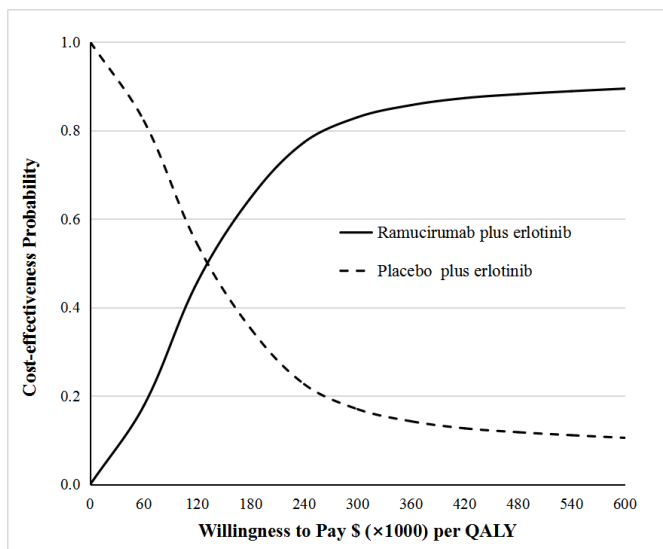


Figure 3 The cost-effectiveness acceptability curve. QALY, quality-adjusted life-year.

we set the WTP threshold for general regions (\$30 363, 3× national per-capita GDP in 2019) and affluent regions (\$70 353, 3× per-capita GDP of Beijing), respectively.

Although other dual inhibition of EGFR and VEGF pathways, such as bevacizumab plus erlotinib, has been recommended in EU and Japanese NSCLC treatment guidelines,¹⁶ we did not evaluate this therapy in comparison with ramucirumab plus erlotinib, because of the limitations of these published trials (small sample sizes, open-label designs and Japanese-only population). Most notably, bevacizumab plus erlotinib demonstrated superior PFS similar to ramucirumab plus erlotinib based on the results of the NEJ026.¹⁸ Considering that China has

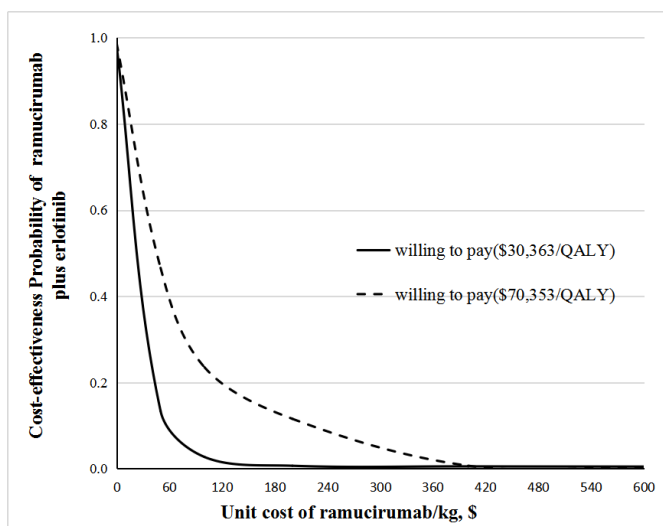


Figure 4 Probability of cost-effectiveness of ramucirumab plus erlotinib versus placebo plus erlotinib at different drug costs of ramucirumab. The dotted line represents the WTP threshold of \$70 353/QALY for affluent regions, while the solid line represents the WTP threshold of \$30 363/QALY for general regions. QALY, quality-adjusted life-year; WTP, willingness-to-pay.

the largest population of lung cancer in the world with limited resources, future phase III randomised trials are urgently needed to develop economic analyses of these innovative therapies.

However, this study has several limitations. First, just like all Markov models, our cost-effectiveness analysis was based solely on the phase III RELAY trial. Even more remarkable, this trial enrolled a predominantly Asian patient population (346 (77%) of 449), but the current analysis should be interpreted with caution because this worldwide trial may not fully conform to the clinical pathway and treatment pattern in China. Second, costs data from various sources present potential uncertainty. In our model, the drug costs data were estimated based on the Chinese market price, while other costs obtained directly from published literature, which reported medical costs associated with Chinese patients with cancer, however, all efforts were made to handle the uncertainty of costs parameters by performing a series of sensitivity analyses. Third, the utilities data were captured from a previously published international study, any biases in this study will be reflected in the model. Although the sensitivity analyses suggested only small impacts of utilities on our results, Chinese-specific health utility value remains an open question. Fourth, at the time of data cut-off, the OS data of ramucirumab plus erlotinib and placebo plus erlotinib remain immature. According to the statistical goodness-of-fit, an exponential survival model was used to extrapolate the long-term OS beyond the follow-up duration of the RELAY trial. Although there were slight numerical differences in costs and QALYs between lifetime and 64 Markov cycles, which was the survival follow-up time in the RELAY trial, the differences with regard to economic outcomes were not significant. Nevertheless, when mature OS data are available, the current findings could be verified.

Overall, from the perspective of Chinese healthcare system, ramucirumab plus erlotinib strategy for patients with previously untreated EGFR-mutated mNSCLC without known EGFR Thr790Met mutation and CNS metastases was unable to be cost-effective compare to placebo plus erlotinib strategy. When the NRDL negotiation was available for ramucirumab, the ramucirumab plus erlotinib strategy might be a cost-effective therapeutic strategy in affluent regions in China.

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