Cost-effectiveness of Osimertinib as First-line Treatment and Sequential Therapy for EGFR Mutation-positive Non-small Cell Lung Cancer in China

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ABSTRACT

Purpose: This study aimed to evaluate the cost-effectiveness of osimertinib with gefitinib or erlotinib as first-line and sequential therapy for epidermal growth factor receptor (EGFR) mutation–positive non–small cell lung cancer (NSCLC) in China.

Methods: The Markov model was used, and the study included 3 health states over a 10-year period. Transition probabilities and safety data were collected from the FLAURA (AZD9291 versus gefitinib or erlotinib in patients with locally advanced or metastatic Non-small Cell Lung Cancer) trial. Cost and utility values were derived from local charges and literature. Sensitivity analyses were performed to observe model stability.

Findings: : The strategy with gefitinib or erlotinib first-line therapy and second-line gene-guided osimertinib therapy (GE-T790M) resulted in a gain of 0.31 quality-adjusted life year (QALY) at a cost of $15,200.95 per patient compared with the gefitinib or erlotinib first-line therapy and second-line chemotherapy (GE-chemotherapy). The incremental QALY and incremental cost values for first-line osimertinib therapy compared with GE-chemotherapy was 0.96 and $69,420.76, respectively. Compared with the GE-T790M strategy (0.96 QALY and $29,223.33), first-line osimertinib was estimated to be more effective (1.61 QALYs) and more costly ($83,443.14). Relative to the GE-chemotherapy strategy, the incremental cost-effectiveness ratios were $47,873.96 and $71,954.08 per QALY gained with GE-T790M and the osimertinib first-line strategy. The incremental cost-effectiveness ratio for first-line osimertinib versus GE-T790M was estimated to be $83,766.61. The results were found to be robust for univariate and multivariable sensitivity analyses.

Implications: Gefitinib or erlotinib first-line and chemotherapy second-line strategies were the most cost-effective first-line treatments for EGFR mutations in patients with NSCLC. Gefitinib or erlotinib first-line and gene-guided osimertinib second-line strategies were more cost-effective than osimertinib first-line treatment for patients who preferred osimertinib administration in China. (*Clin Ther.* 2019;41:280–290)

Key Words: cost-effectiveness, first-line treatment, NSCLC, osimertinib.

INTRODUCTION

Lung cancer has the highest morbidity and mortality in China[1]; the majority of cases are non–small cell lung cancer (NSCLC). Most patients are diagnosed at a

Accepted for publication December 9, 2018
https://doi.org/10.1016/j.clinthera.2018.12.007
0149-2918/$ - see front matter

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late stage when surgery is no longer advisable.[2] The latest generation of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) limits both EGFR-sensitizing mutations and T790M mutations; the representative drug is osimertinib. According to the latest clinical guidelines, first-line treatment with osimertinib is recommended for patients with locally advanced or metastatic EGFR mutation−positive NSCLC.[3,4] The US Food and Drug Administration approved osimertinib for the first-line treatment of patients with EGFR exon 19 deletions or exon 21 L858R mutations NSCLC. The US Food and Drug Administration and their guidelines have also recommended gefitinib and erlotinib for the first-line treatment of patients with EGFR-sensitizing mutations.

The AURA (AZD9291 first time In patients ascending dose study) study (Phase I clinical trial) showed that the median survival for patients with sensitizing EGFR mutations subjected to first-line therapy with osimertinib was 20.5 months. The first-line treatment with osimertinib has excellent safety and efficacy for patients with advanced EGFR-positive NSCLC.[5] The FLAURA (AZD9291 versus gefitinib or erlotinib in patients with locally advanced or metastatic Non-small Cell Lung Cancer) trial was the first prospective, global, randomized trial that assessed osimertinib compared with either erlotinib or gefitinib as first-line therapy in patients with locally advanced or metastatic NSCLC and EGFR mutations. In this trial, the median progression-free survival (PFS) was 19.1 months in the osimertinib-treated group and 10.9 months in the standard treatment group (gefitinib or erlotinib); osimertinib significantly reduced disease risk or death risk by 54%. Moreover, in patients with brain metastases, osimertinib also exhibited excellent results, with a median PFS of 15.2 months, compared with 9.2 months for the standard treatment group. Osimertinib can significantly prolong the duration of response compared with standard treatment (median, 17.2 vs 8.5 months). The frequency of adverse events of grade 3 or higher was lower with osimertinib than that with erlotinib or gefitinib.[6]

NSCLC is a disease with a very serious disease burden, and the cost of EGFR-TKI treatment accounts for a large proportion of the economic burden for the patient and society.[7] In the final 3 months of life, the average cost of care for patients with advanced NSCLC is $16,955, which far exceeds the range that most Chinese families can afford, although some of this cost is covered by medical insurance.[8] Decision-makers, patients, and physicians are interested in financial considerations regarding this first-line therapy choice because EGFR-TKI is expensive. Chinese decision-makers face the question of whether osimertinib should be covered by insurance.

According to economic analyses, osimertinib first-line treatment for EGFR-mutated NSCLC does not have a performance−price ratio in the United States or Brazil.[9] Another study showed that, compared with standard chemotherapy, osimertinib second-line treatment for T790-mutated patients who have undergone first-line TKI-resistance therapy is not cost-effective in the United States and China.[10] However, another study revealed that osimertinib treatment may be cost-effective compared with platinum-based dual chemotherapy after treatment failure in patients with EGFR-T790M mutation NSCLC in the United Kingdom.[11]

In the present study, the FLAURA data were used to assess the cost-effectiveness of EGFR-TKI first-line therapy and support drug subsidy decisions from the perspective of the Chinese medical system. To the best of our knowledge, this analysis is the first to evaluate the cost-effectiveness of osimertinib compared with gefitinib/erlotinib in the treatment of Chinese first-line and sequential therapy for advanced or metastatic EGFR mutation−positive NSCLC.

MATERIALS AND METHODS

Model Structure

The decision and Markov models were established to evaluate the overall costs and health outcomes of patients under each therapy option. The population included patients at least 18 years of age who had locally advanced or metastatic NSCLC. Local or central tests confirming the EGFR exon 19 deletion or L858R mutations alone or co-occurring with other EGFR mutations were performed.[6] Three treatment strategies were considered: (1) osimertinib as the first-line chemotherapy; (2) gefitinib or erlotinib as the first-line therapy and second-line osimertinib therapy if T790M mutation−positive after failure of therapy (GE-T790M); and (3) gefitinib or erlotinib as the first- and second-line chemotherapy after failure of therapy (GE-chemotherapy). The disease development process of the study subjects was divided into 3

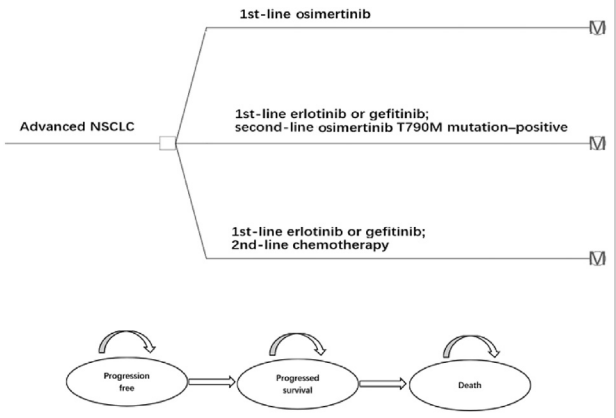

Figure 1. Schematics of the decision tree and the Markov state transition model. NSCLC = non–small cell lung cancer.

disease states: PFS, progressed survival (PS), and death (Figure 1). We hypothesized that all patients entered the PFS health state in the initial stage of the model and were assigned in the original health state or transition to the PS health state according to the transition probability. The patients who entered the state of PS can only stay in the state of PS or progress to the state of death.

The chemotherapy cycle of treatment for patients with NSCLC takes 21 days. The cycle length of the Markov model was set to 21 days to facilitate the calculation of parameters. According to the opinions and experiences of expert clinicians, patients with locally advanced or metastatic EGFR-mutant NSCLC rarely survive for >10 years. After 10-year operation of our model, all patients in the 3 groups died. Thus, the simulation period was 10 years to reflect the disease progression. Cost of treatment and utility scores were derived from literature and local drug prices. The average exchange rate of Chinese Yuan renminbi for the entire year of 2017 is 6.7518 yuan per US dollar.[12] The incremental cost-effectiveness ratio (ICER) is the cost per additional quality-adjusted life year (QALY) gained. This study used the following formula to calculate the ICER:

$$\text{ICET} = \frac{(\text{cost[strategy A]} - \text{cost[strategy B]})}{(\text{effectiveness[strategy A]} - \text{effectveness[strategy B]})}$$

The study used TreeAge software 2015 (TreeAge Software, Inc, Williamstown, Massachusetts) to program the decision and Markov models, as well as to analyze the data.

Clinical Data

The transition probabilities of disease progression or death were derived from published literature. Separate PFS and overall survival (OS) data were extracted from the FLAURA trial (Table I).[6,13,14] PFS and OS curves of each treatment were read by using

Table I. Key model input parameters.

Input Parameter	Value (Range)	Source (References)
Weibull survival model of PFS of osimertinib	Scale = 0.0089881; shape = 1.5005341; r^2 = 0.9876568	6
Weibull survival model of PFS of control	Scale = 0.0217580; shape = 1.4609727; r^2 = 0.9963140	6
Weibull survival model of OS of osimertinib	Scale = 0.0038858; shape = 1.3594015; r^2 = 0.9801747	6
Weibull survival model of OS of control	Scale = 0.0091946; shape = 1.2232394; r^2 = 0.9801747	6
Probability of second-line chemotherapy survival after progression	0.086 (0.08–0.093)	14
T790M mutation detection rate	0.63 (0.56–0.79)	13

PFS = progression-free survival; OS = overall survival.

GetData Graph Digitizer software (Version 2.26, getdata-graph-digitizer.com). Although the clinical trial observation time was comparatively short, the world of model research is lifelong. The parametric survival model can predict the survival rate according to a given time. The Weibull function was used to simulate the PFS and OS curves of the sample group to determine the transition probability of each Markov state. The calculated scale (λ) and shape (γ) parameters, as well as adjusted r^2 values of the Weibull function, are presented in Table I. Formula $S(t) = P(T \geq t) = \exp(-\lambda t^{\gamma})$ was used to calculate the survival probability at time t. Formula $P(t) = 1 - \exp[\lambda(t-1)^{\gamma} - \lambda t^{\gamma}]$ was used to calculate the transition probability at a given cycle t.[15] The probabilities of patient first-line therapy with gefitinib and erlotinib are assumed to be 66.06% and 33.94%, respectively, according to the FLAURA trial; the prevalence of mutations of T790M is 63% in patients with advanced NSCLC.[13] The incidence of adverse events grade 3 or higher in the osimertinib group (34%) was lower than that in the gefitinib or erlotinib group (45%). The probability of serious adverse events from the chemotherapy strategy was 63.70%.[14]

Cost and Utility

Only direct medical costs, including the cost of drugs, chemotherapy, supportive care, detection of T790M, routine follow-up, and management of adverse events, were considered in the Markov model (Table II).[10,14,16–18] Costs for osimertinib, erlotinib, and gefitinib were considered every day during the patient's treatment process. The osimertinib, erlotinib, and gefitinib dosage amounts were referenced to the guidelines of the Chinese Society of Clinical Oncology Primary Lung Cancer.[3,4] The recommended dosage of osimertinib is an 80-mg tablet once a day until disease progression. The continuous medication of the patients is self-funded for 4 months, and they can then take advantage of 8 months of drug assistance in the first phase after the approval of the charity project. The patients are then continuously medicated for 3 months by self-funding in the second phase, after which they can request drug assistance until the disease progresses.

Erlotinib and gefitinib were administered at doses of 150 and 250 mg, respectively, once a day until disease progression. The cost of testing for the T790M mutation per patient identified and administered with second-line osimertinib after treatment failure with first-line gefitinib and erlotinib was added to the treatment costs. When the disease progresses, the patients will receive salvage chemotherapy and supportive care. According to published research, regardless of the first-line treatment, 56.6% (26%–72%) of patients are hypothesized to receive salvage treatment.[14] The cost of chemotherapy used the following formula: 56.6% × (cost of salvage chemotherapy per cycle + cost of serious adverse

Table II. Base-case cost estimates and utilities.

Input Parameter	Value (Range)	Source (Reference)
Cost of osimertinib per day, US $	251.78 (125.89–251.78)	Local charge
Cost of erlotinib per day, US $	28.88 (11.55–28.88)	Local charge
Cost of gefitinib per day, US $	34.92 (13.97–34.92)	Local charge
Cost of EGFR mutation testing, US $	441 (368–515)	10
Cost of SAEs per unit, US $	362 (272–453)	10
Cost of follow-up per cycle, US $	59.2 (44.4–74)	10
Cost of supportive care per cycle, US $	359 (169–845)	10
Cost of salvage chemotherapy per cycle, US $	2352.7 (1921.1–4383.3)	16, 17
Utility of PFS	0.82 (0.78–0.86)	14, 17, 18
Utility of PS	0.58 (0.5–0.66)	14, 17, 18

EGFR = epidermal growth factor receptor; PFS = progression-free survival; PS = progressed survival; SAEs = serious adverse events (grade 3 or higher).

events) + (1−56.6%) × cost of supportive care per cycle + cost of follow-up per cycle.

The model included all adverse events of grade 3 or 4 reported in the FLAURA trial. The costs of treatment for serious adverse events were calculated according to the following formula: cost of serious adverse event per cycle × cumulative probability of serious adverse event in the related therapeutic schedules.[19] The health utility values of the 3 states were derived from previously published literature. The utility measurement is a method to determine the degree of preference of a certain state of the patient's health. Utility values ranged from 0 to 1, where 0 means death and 1 means complete health.[20] The model input data for cost and utility are shown in Table II.

Model Outcomes

The Markov cohort model was developed to estimate QALYs and long-term costs of treating NSCLC patients with TKIs. The primary study end point was ICERs at different points in time. No general agreement was made on a cost-effectiveness ratio threshold for Chinese patients with NSCLC. The World Health Organization recommended that the increased cost is acceptable when the ICER is < 3 times the gross domestic product per capita, and the increased cost is not worthwhile when the ICER is > 3 times the gross domestic product per capita. Thus, we used US $26,508 per QALY gained as the cost-effectiveness threshold.[11,21–24]

Sensitivity Analyses

One-way sensitivity and probabilistic sensitivity analyses assessed the effect of the model uncertainty on the cost-effectiveness of different treatment options. A one-way sensitivity analysis keeps other parameters unchanged, alters individual model parameters in the range of variation, and then verifies the effect of individual model parameters on the results. The key parameters in the model were changed within 95% CIs or within ±25% or ±50% of the baseline value. Results of the one-way sensitivity analysis are represented by a tornado diagram. To make a more reasonable and comprehensive response parameter uncertainty impact on the model results, the study added all uncertain model parameters in the model for analysis. The probabilistic sensitivity analysis used a second-order Monte Carlo simulation for 1000 times to obtain an acceptable cost-effectiveness curve. The cost parameter used triangular distributions, and probability and utility parameters used beta distribution.

RESULTS

Base Case Analysis

The simulated PFS and OS curves were consistent with those of the original data, and thus the fitting effect is reasonable and acceptable. The survival curve simulation results are shown in Figure 2. Compared with GE-chemotherapy, the treatment strategy with GE-T790M resulted in an increased 0.31 QALY (0.96 vs 0.65 QALY) per patient, with an additional cost of $15,200.95 ($29,223.33 vs $14,022.38). The corresponding incremental QALY and incremental cost values for first-line osimertinib treatment compared with GE-chemotherapy were 0.96 and $69,420.76, respectively. Relative to the GE-chemotherapy strategy, the ICERs were $47,873.96 and $71,954.08 per QALY gained with GE-T790M and osimertinib first-line strategy (Table III). The strategy of the osimertinib first-line treatment was estimated to be more effective (1.61 QALYs) but at a high cost ($83,443.14) compared with that of GE-T790M (0.96 QALY and $29,223.33). The ICER for osimertinib first-line treatment against GE-T790M was estimated to be $83,766.61.

Sensitivity Analysis

In the comparison between the osimertinib first-line and GE-chemotherapy strategies, a one-way sensitivity analysis was used to test the responsiveness of the model and the robustness of our results and then summed into a tornado diagram by using TreeAge software. Figure 3 shows that the cost of salvage chemotherapy exhibited the highest impact on the results, followed by the price of osimertinib, probability of receiving salvage chemotherapy, health utility with PS, cost of support care, price of gefitinib, health utility with PFS, price of erlotinib, cost of serious adverse events, and cost of follow-up. The changes in the individual parameters slightly altered the overall value associated with therapy, but they did not change the conclusions regarding the relative cost-effectiveness of the osimertinib first-line and GE-chemotherapy strategies.

To reflect the influence of all model input parameters on the research results, the probability sensitivity analysis of 1000 cases was conducted by

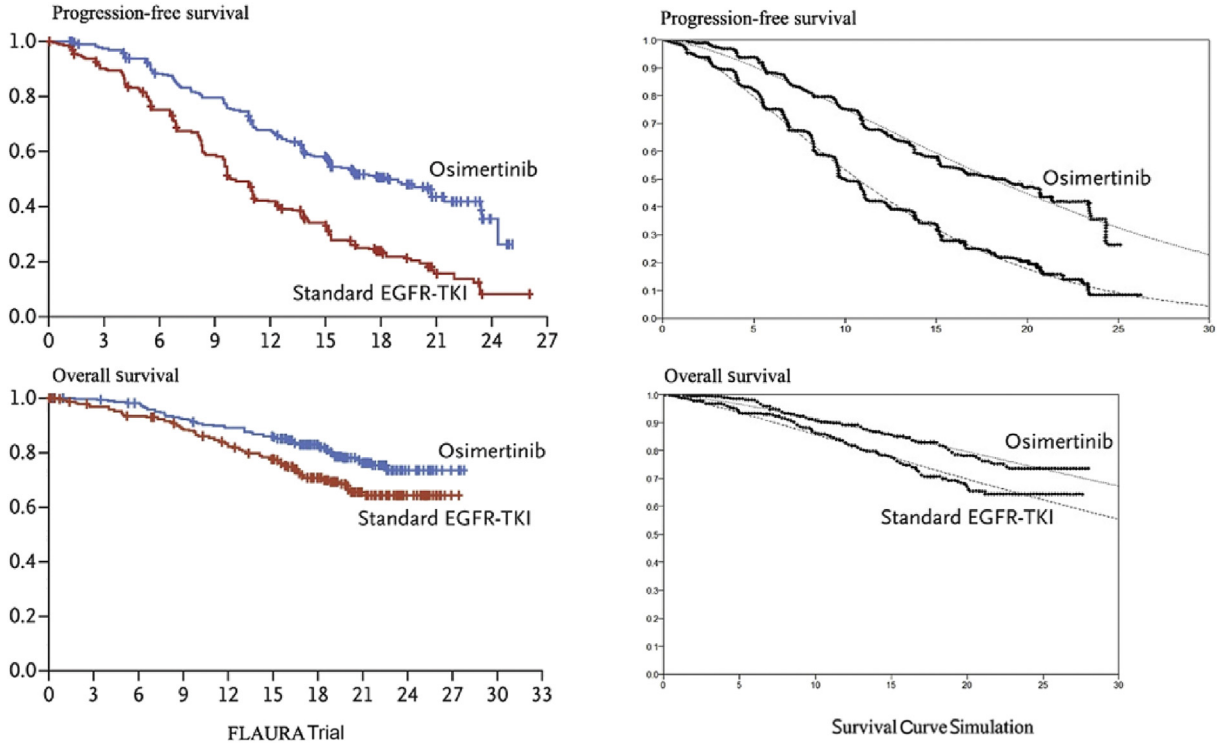

Figure 2. Progression-free survival and overall survival. EGFR-TKI = epidermal growth factor receptor–tyrosine kinase inhibitor. FLAURA = AZD9291 Versus Gefitinib or Erlotinib in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer.

Table III. Summary of cost and outcome results from a base-case analysis.

Strategy	Costs, US $	QALYs	△Costs, US $	△QALYs	ICER, US $/QALY
GE-chemotherapy	14,022.38	0.65	/	/	/
GE-T790M	29,223.33	0.96	15,200.95*	0.31*	47,873.96*
Osimertinib first-line therapy	83,443.14	1.61	69,420.76*	0.96*	71,954.08*
			54,219.81†	0.65†	83,766.61†

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; / = No comparison.
* Compared with gefitinib or erlotinib as the first-line and second-line chemotherapy after failure of therapy (GE-chemotherapy).
† Compared with gefitinib or erlotinib first-line therapy and second-line gene-guided osimertinib therapy (GE-T790M).

setting different distributions for each parameter. According to the results of the probability sensitivity analysis, the GE-chemotherapy treatment was extremely cost-effective compared with the osimertinib first-line therapy. Figure 4 shows the scatter plot with the slash as the willingness-to-pay (WTP) threshold line ($26,508/QALY). The ellipse represents the 95% CI of ICERs. The figure further shows that the ICER is concentrated in the effect-dominant quadrant and is located above the WTP

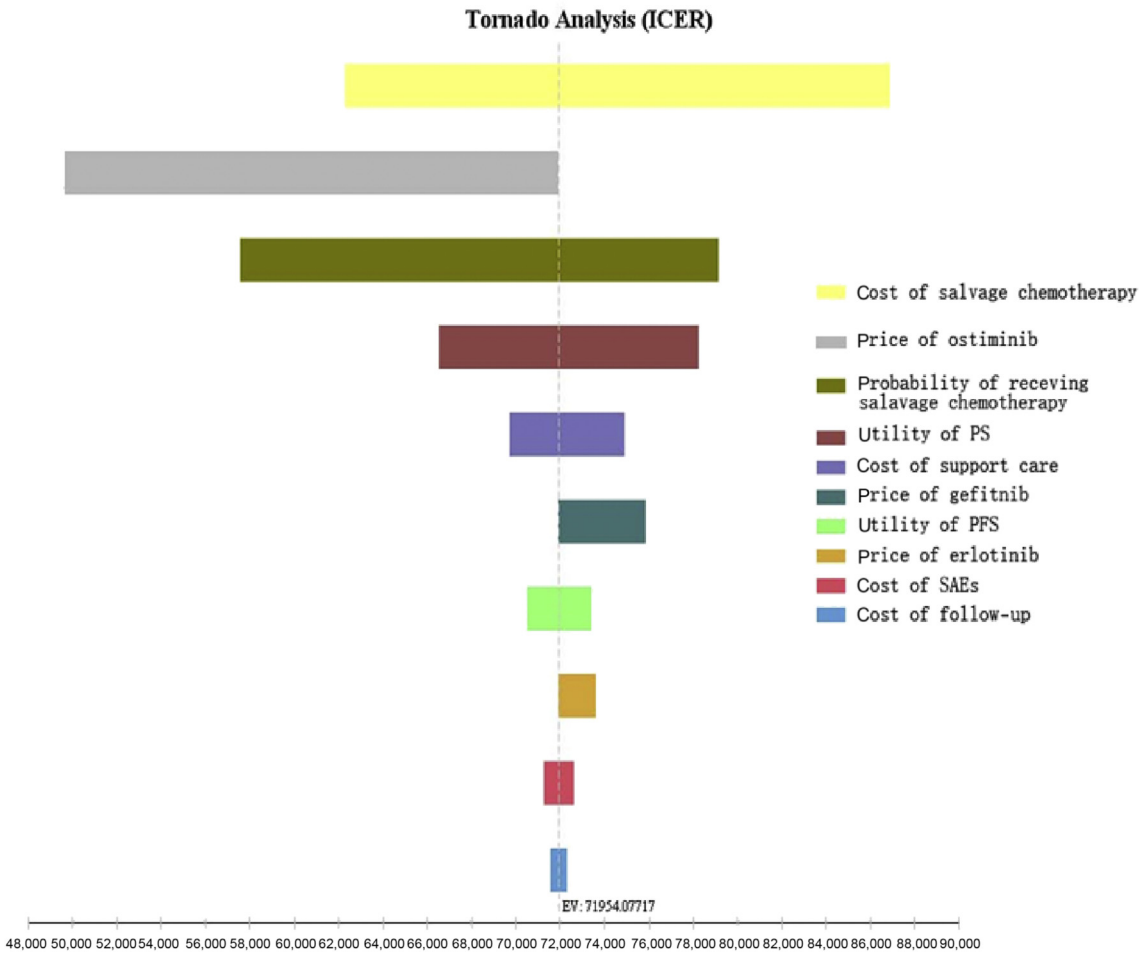

Figure 3. One-way sensitivity analysis. ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; PS = progressed survival; SAEs = serious adverse events.

threshold line. The scatter plot shows that the ICER of 1000 simulations is greater than the WTP threshold.

Cost-effectiveness acceptability curves (Figure 5) show that the GE-T790M therapy and osimertinib in the first-line therapy exhibited an increased probability of cost-effectiveness as the WTP threshold increased (up to $120,000). With a WTP of $48,000 and $60,000, the probability of GE-T790M being most cost-effective was 51.9% and 99.3%, respectively.

DISCUSSION

To the best of our knowledge, the present study is the first to investigate both the overall health and economic effects of osimertinib compared with gefitinib or erlotinib in the first-line treatment and sequential therapy of EGFR mutation in patients with NSCLC based on the Phase III, randomized, double-blind FLAURA trial[6] in China. The mathematical model was designed to assess the cost and QALYs of osimertinib compared with either erlotinib or gefitinib as first-line and sequential therapies in Chinese patients who were diagnosed with NSCLC and EGFR mutations. Preliminary results of the study found that ~0.96 QALY was gained for patients treated with osimertinib in the first line and an ICER of $71,954.08 for patients treated with GE-chemotherapy. The ICERs of the osimertinib first-line or GE-T790M strategy versus GE-chemotherapy was far beyond the threshold ($26,508/QALY) by

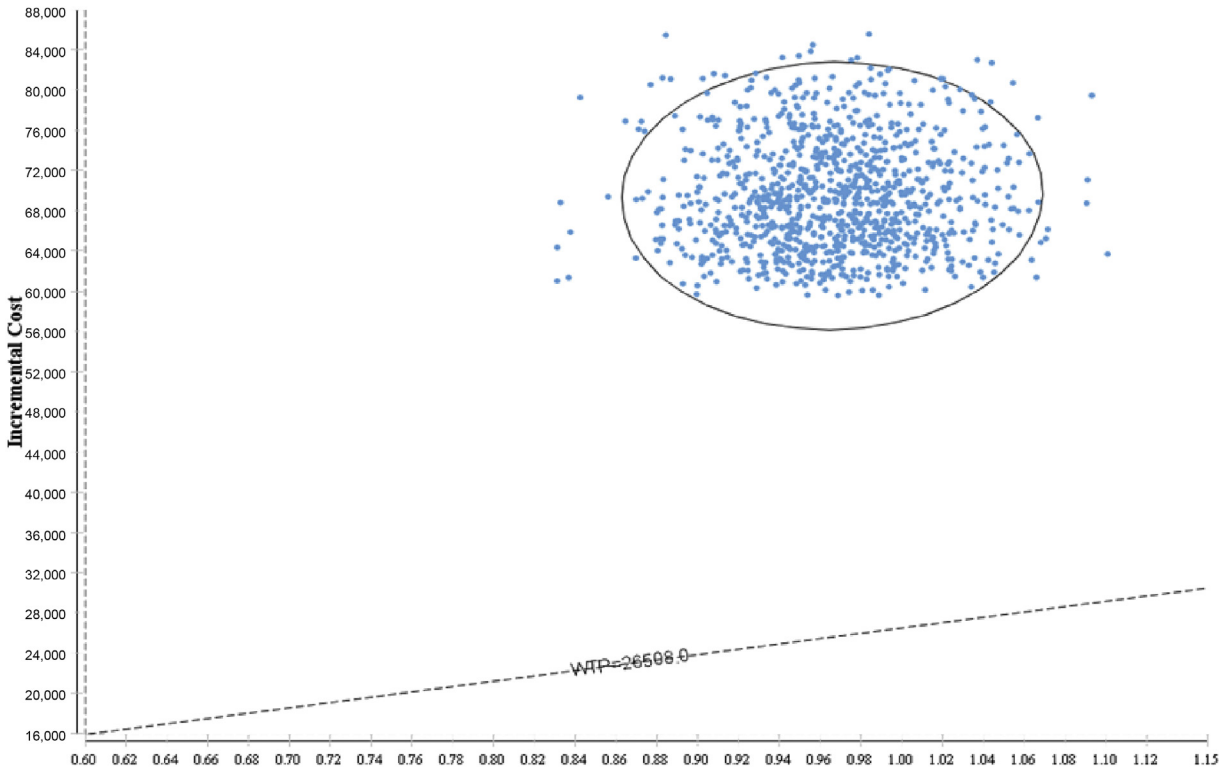

Figure 4. Probabilistic sensitivity analyses of gefitinib or erlotinib first-line therapy and second-line gene-guided osimertinib therapy (GE-T790M).

incremental cost-effectiveness analysis. We also compared the osimertinib first-line strategy with GE-T790M, and the results indicate that compared with osimertinib first-line treatment in 10 years, the ICER in GE-T790M would be expected to be less than $83,766.61. The uncertainty factor of the model exists at each evaluation stage. However, the results of the analysis are basically stably supported by sensitivity analyses (including one-way sensitivity and probabilistic sensitivity analyses). The cost-effectiveness of GE chemotherapy was relatively stable across different scenarios. Furthermore, one-way sensitivity analysis determines the cost of salvage chemotherapy and the cost of osimertinib, which are the top 2 sensitive parameters.

These findings therefore suggest that, at the time of the analysis, gefitinib or erlotinib in the first- and second-line chemotherapy after failure of therapy is the most cost-effective treatment for patients with NSCLC. Also, gefitinib and erlotinib as the first-line therapy and second-line osimertinib therapy if T790M mutation–positive therapy failed is a more cost-effective treatment for Chinese patients who prefer administration of osimertinib. A recently published study only compared osimertinib second-line therapy versus chemotherapy second-line after first-line TKI resistance therapy in patients with EGFR-T790M mutation.[10] In the Chinese population and in those with central nervous system metastasis, relative to the chemotherapy second-line strategy, the ICERs were $48,081 and $53,244 per QALY gained with osimertinib second-line strategy. The osimertinib second-line treatment strategy was found to be expensive. The results of this study are consistent with our findings.

The present study has certain limitations. First, due to the lack of health status values for disease status in the Chinese population, the utility value of this study can only be obtained from foreign literature when comparing QALYs. However, each country or region

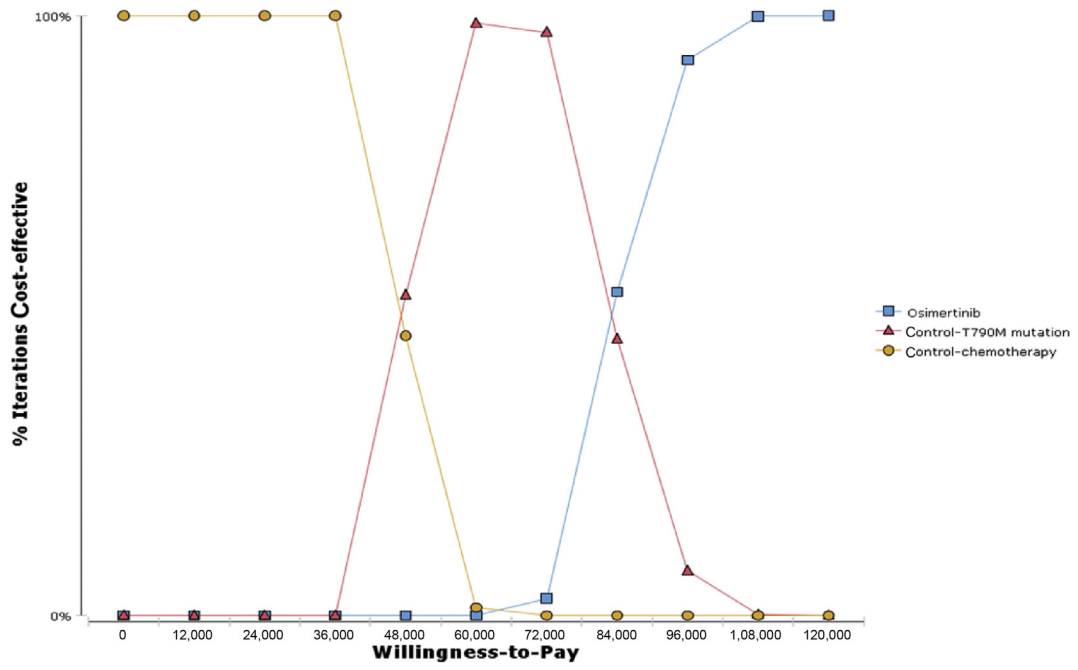

Figure 5. Cost-effectiveness acceptability curves.

has different preferences for each state because of its ethnic and cultural background. The model is a simulation of disease outcomes; referring to published literature,[10,11] we did not consider the effect of adverse drug reactions on the utility. Second, the triangular distribution of cost parameters may lead to bias in the output of the model. Third, the present model did not include two-line TKI treatment after failure of osimertinib therapy, and it assumed that patients who experienced failure of osimertinib first-line treatment will proceed to chemotherapy or supportive care. Fourth, only published international multicenter clinical trial results are currently available, and the effectiveness data can only be obtained from clinical trials that include 29 countries; thus, it may not represent the actual Chinese population.[6] Fifth, the study assumed the probability of people subjected to first-line treatment with gefitinib or erlotinib according to the FLAURA trial. Sixth, starting May 1, 2018, the import tariff on drugs, including anticancer drugs (such as gefitinib, erlotinib, and osimertinib) will be reduced to zero; thus, all the anticancer drugs actually imported in China will achieve zero tariff, which is expected to have a certain impact on the decline in cancer drug prices. No reduction in the price of drugs occurred at the time of research; thus, the study did not consider the effects of this policy. Seventh, the proportion of gefitinib or erlotinib in the first line of study was derived from clinical trials. Eighth, at present, no cancer-related incremental cost-effectiveness threshold value is suitable for China's national condition. Based on the recommendation in the "China Guidelines for Pharmacoeconomic Evaluations,"[24] the study uses the threshold of pharmacoeconomic research recommended by the World Trade Organization; that is, triple gross domestic product per capita. This threshold is also commonly used by Chinese researchers. Furthermore, we did not consider more personalized aspects for treatment decisions. For example, different chemotherapy regimens may be available after the disease progresses, but choices of chemotherapy drugs were not discussed.

Nonetheless, the individual variables in the model did not affect the final result. The sensitivity analysis

indicated that the probability, utility, and cost data would be unlikely to affect the final results.

CONCLUSIONS

From the perspective of the Chinese health care system, gefitinib or erlotinib as first- and second-line chemotherapy is an economical and effective strategy for the treatment of EGFR mutation in patients with NSCLC. For patients newly diagnosed with advanced NSCLC who prefer administration of osimertinib, gefitinib, or erlotinib in the first line of treatment, the second-line gene-guided osimertinib therapy is an alternative economical and effective strategy. These results may be used to provide guidance for NSCLC treatment decisions by physicians and health care requests in China.

ACKNOWLEDGMENTS

This study was supported by Fujian Provincial Department of Science & Technology (grant no. 2017Y0035) of the People's Republic of China and the National Natural Science Foundation of China (grant no. 71804025).

Ms. Cai and Ms. Zhang were responsible for data analysis and write/revise manuscript; Prof. Liu, Dr. Zheng, Ms. Li, and Ms. Yang served as clinical consultants/advisors; Ms. Chen and Md. Weng were responsible for study concept and design.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article. The funding agencies had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

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