

Cost-effectiveness analysis of different sequences of osimertinib administration for epidermal growth factor receptor-mutated non-small-cell lung cancer

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Abstract. Osimertinib is a third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) that is clinically effective in patients with EGFR-mutated non-small-cell lung cancer (NSCLC). However, the use of this treatment is limited by its high cost. A cost-effectiveness analysis of different sequences of osimertinib administration in China and the United States was conducted in the present study. Markov models were established based on data from the FLAURA and AURA3 trials. First-line osimertinib was compared with both first-generation EGFR-TKIs and second-line osimertinib after the failure of first-generation EGFR-TKIs. The analysis also considered different payment modalities available in China. Additionally, one-way and probability sensitivity analyses, with a willingness-to-pay threshold (WTP) of three times the per capita gross domestic product [\$27,783/quality-adjusted life year (QALY) for China and \$100,000/QALY for the United States], were performed. The first-line osimertinib group displayed higher QALYs and costs than those of the first-generation EGFR-TKI group. The first generation EGFR-TKI group displayed an incremental cost-effectiveness ratio (ICER) of \$212,252/QALY in China and \$151,922/QALY in the United States. In addition, the ICERs were negative in the second-line osimertinib group, with higher QALYs and lower costs compared with those in

the first-line osimertinib group. Furthermore, osimertinib company donation was of benefit in China, with an average cost-effectiveness of \$836/QALY. The one-way sensitivity analysis highlighted the influence of utilities in different states. First-line osimertinib could be cost-effective either with higher WTP or a price reduction of 68% in China and 9% in the United States. Although first-line osimertinib therapy could have health benefits, it was not cost-effective compared with first-line first-generation EGFR-TKIs and second-line osimertinib therapy. However, paying via company donation may be a good choice in China.

Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide, with a 5-year survival rate in the range of 10-20% in most countries (1). Fortunately, the incidence and mortality rate of lung cancer have been steadily declining in recent years, due to the availability of new treatment strategies (2-3). However, non-small-cell lung cancer (NSCLC) is a common histological type that is still associated with poor prognosis (4-6).

Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy improves survival and quality of life for patients with sensitizing EGFR mutations (7). A meta-analysis of six trials demonstrated that EGFR-TKI therapy exhibited improved efficacy compared with chemotherapy, in terms of the objective response rate and progression-free survival (PFS), in patients with previously untreated EGFR-mutant NSCLC (8). Moreover, EGFR-TKIs are only associated with low-grade adverse effects such as diarrhea, skin rash and paronychia (9).

Gefitinib, erlotinib and icotinib are common first-generation EGFR-TKIs that are widely used in clinical practice (10). Osimertinib is a new oral, irreversible, third-generation EGFR-TKI, it was designed to inhibit EGFR mutation alleles and T790M resistance mutations, with higher anticancer activity and less toxicity than previous generations (10,11). In previous studies, osimertinib was highly effective and resulted in manageable adverse effects in patients with mutated EGFR-T790M NSCLC progression during or after first-line EGFR-TKI therapy (12-15). In 2015, the United States

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Abbreviations: CNS, central nervous system; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; FDA, Food and Drug Administration; ICER, incremental cost-effectiveness ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QALY, quality-adjusted life year; WTP, willingness-to-pay threshold

Key words: cost-effectiveness, osimertinib, NSCLC, EGFR-TKI, QALY

Food and Drug Administration (FDA) granted accelerated approval for osimertinib (16). This therapy was conventionally approved in 2017 for the treatment of locally advanced or metastatic EGFR-T790M mutation-positive NSCLC with progression during or after first-line EGFR-TKI therapy (16). This therapeutic use of osimertinib was also recommended by the European Medicines Agency and the China Food and Drug Administration (17,18).

EGFR-TKI therapy has long been the standard of care for patients with advanced EGFR-mutated NSCLC and therefore, emerging clinical trials are focusing on first-line osimertinib treatment (15,19-21). The AURA study first evaluated osimertinib as a first-line therapy and found that it prolonged PFS, compared with chemotherapy, in patients with advanced EGFR-mutated NSCLC (12). Thereafter, the FLAURA study demonstrated significant advantages of first-line osimertinib on PFS compared with first-generation EGFR-TKIs for patients with advanced EGFR-mutated NSCLC (20). In 2018, the FDA approved osimertinib as a first-line therapy for advanced EGFR-mutated NSCLC (16).

Osimertinib may provide greater benefits to patients as a first-line treatment than as a second-line treatment, especially in patients with a confirmed sensitizing EGFR mutation (21). Previously, second-line osimertinib has been used in patients with acquired resistance to previous generation EGFR-TKIs and those with the T790M mutation, which occurs in ~60% of patients (15). Additionally, improved selectivity of osimertinib for the mutated receptor is associated with fewer severe adverse events than those experienced with previous EGFR-TKIs, with a maximum severity of grade one or two (22). Moreover, brain metastasis is frequent in patients with EGFR mutations (9) and clinical trials have confirmed that osimertinib has greater central nervous system (CNS) penetration than other treatments (11,23,24). The significant efficacy of osimertinib may provide an alternative to whole-brain radiotherapy and associated adverse effects in patients with CNS metastasis (25).

Several economic analyses have estimated the cost-effectiveness of EGFR-TKIs including osimertinib, however, no study has compared different sequences of osimertinib administration (26-29). Therefore, the present study performed a cost-effectiveness analysis to assess the economic effects of first-line osimertinib vs. both second-line osimertinib after the failure of first-generation EGFR-TKIs and first-generation EGFR-TKIs. Analyses were carried out in the context of the Chinese health system and the United States payer system, including various forms of payment for EGFR-TKIs in China.

Materials and methods

Study basis. The present study was based on two international phase III clinical trials, namely the FLAURA trial and the AURA3 trial (15,20). Treeage Pro 2018.1 (Treeage Software, Inc.) was used to estimate the cost-effectiveness of different strategies and the net benefits of various drugs. An annual discount rate of 3% was used to calculate the values of costs and utilities, referring to previous economic studies (30,31).

Markov model structure. A number of Markov models were developed to evaluate the cost-effectiveness of the different treatment strategies (Fig. 1). The following three basic mutually

exclusive health states were included in Markov models for both the first-line osimertinib group and standard group (receiving first-generation EGFR-TKI): i) PFS, ii) progressive disease (PD); and iii) death. While second-line osimertinib groups contained the following four states: i) PFS1 (patients receiving first-generation EGFR-TKIs as first-line therapy before disease progression); ii) PFS2 (patients receiving osimertinib as second-line therapy after the first disease progression); iii) PD1 (patients receiving subsequent therapy after the second disease progression); and iv) death. The cycle length was three weeks with a 10-year time horizon. In both first-line osimertinib and standard groups, all patients were in the PFS state in the beginning and subsequently survived or died. Patients who survived either remained in the PFS state with no disease progression or transferred to a PD state with disease progression. Patients who transferred to a PD state either remained in a PD state or died. All patients in the second-line osimertinib groups began in the PFS1 state and either remained by surviving with no disease progression, transferred to a PFS2 state with disease progression or died. Patients in the PFS2 state remained in the PFS2 state, transferred to the PD1 state or died. Patients in the PD1 state remained or died. The cost-effectiveness analysis was conducted for both the Chinese health care system and the United States payer system.

Clinical data. In the FLAURA trial, 556 patients recruited from 29 countries with previously untreated EGFR mutation-positive (exon 19 deletion or L858R) advanced NSCLC were randomly assigned to receive osimertinib (80 mg; first-line osimertinib group) or a first-generation EGFR-TKI (gefitinib 250 mg or erlotinib 150 mg; standard group), once daily as the first-line treatment (20). In the AURA3 trial, 419 advanced NSCLC patients with disease progression after the failure of first-generation EGFR-TKI therapy and with T790M mutation received osimertinib (80 mg) once daily or subsequent therapy (chemotherapy, EGFR-TKI-containing therapy and radiotherapy; second-line osimertinib group) (15). Given the unavailability of the overall survival (OS) data and survival curve in this trial, OS data was derived from a review of 16 randomized controlled trials (32).

R version 3.5.3 (MathSoft) was used for statistical computing. Kaplan-Meier survival data were extracted from survival curves using GetData Graph Digitizer software 2.25 (Digital River GmbH). Weibull survival models were used to fit the survival curves. Weibull parameters, including scale and shape, were used to obtain time dependency transition probabilities with the following two formulas: $p=1-\text{Exp}(-rxt)$ and $pt=1-\text{Exp}[\text{scale} \times (t_0 - u)^{\text{shape_scale}} \times (t_0)^{\text{shape}}]$, where p is the probability at time t , r is the survival rate, u is the length of Markov cycle, t_0 is the current cycle number, pt is the transition probability.

Costs. Only direct medical costs were considered and these costs consisted of drug costs and costs of adverse events grade ≥ 3 , routine follow-up, supportive care and disease progression. The cost of routine follow-up included the costs of physician visits, computed tomography and other tests. While the cost of supportive care considered the costs of additional interventions such as nutrition support, palliative and psychological care. Due to the high price of anticancer drugs, the Chinese Government and pharmaceuticals companies have formulated specific

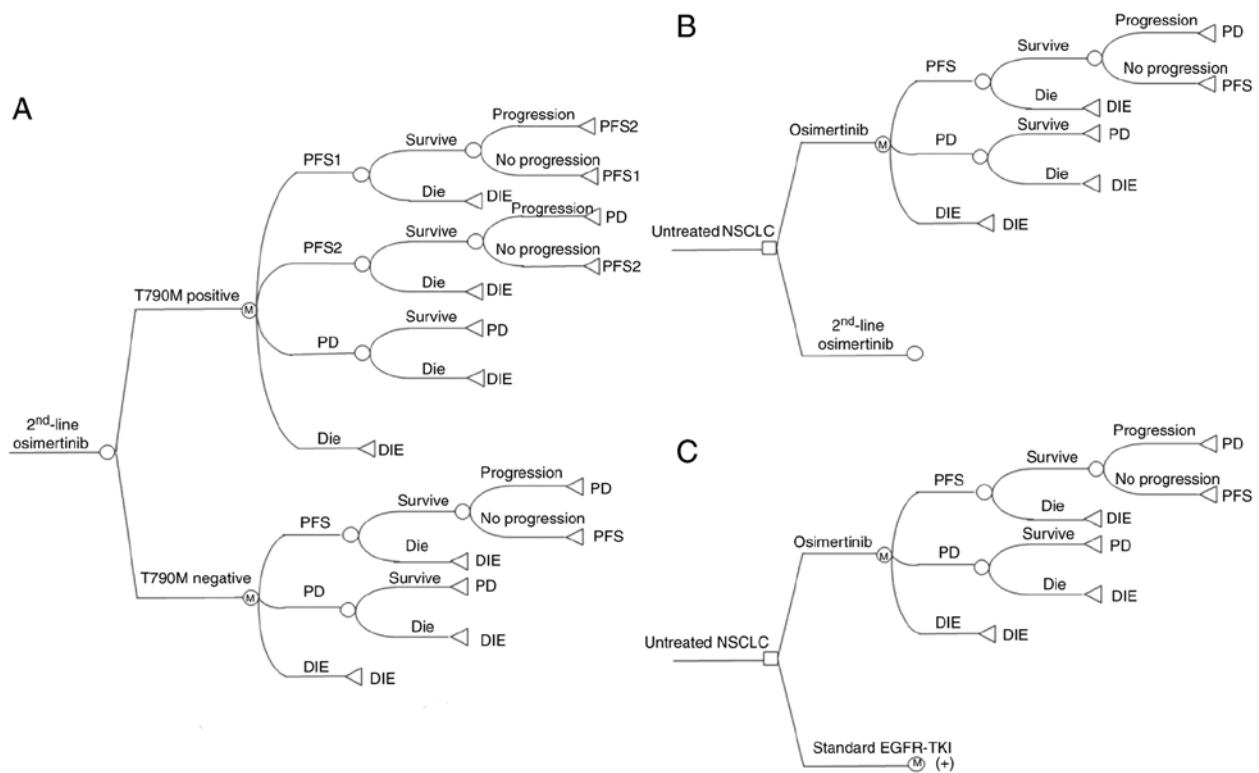


Figure 1. Structure of the Markov models. Markov model of (A) the second-line osimertinib group, (B) the first-line osimertinib group vs. second-line osimertinib group and (C) the first-line osimertinib group vs. standard group. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; PD, progressive disease; PFS, progression-free survival; PFS1, patients who received first-generation EGFR-TKIs as the first-line therapy; PFS2, patients who received osimertinib as the second-line therapy; PD1, patients receiving subsequent therapy after the second disease progression; NSCLC, non-small-cell lung cancer; circle, chance node; M, markov model; triangle, terminal node; square, decision node; (+), the same process as above.

health care policies and company donations. In 2017, erlotinib, gefitinib and icotinib were all included in the Chinese health insurance system, at a much lower cost than the market value. Patients taking gefitinib or icotinib can choose to purchase gefitinib for the first eight months and receive treatment free of charge from the ninth month, or purchase icotinib for the first 10 months and receive treatment free of charge from the eleventh month. Patients who used osimertinib purchased it the first four months of the first year and the first three months of the second year, after which pharmaceuticals companies covered the cost (33). Various methods of payment in China mentioned above were evaluated in the subgroup analysis. The costs of osimertinib and first-generation EGFR-TKIs were acquired from local hospitals in China and RXUSA in the United States (34). Other costs were indirectly extracted from published literature (26,35-41). Cost parameters were estimated in United States dollars (\$).

Health state utilities. Quality-adjusted life years (QALYs) were used to quantify the health condition of patients. Health state utilities represented patients' preferences for health states on a scale of 0-1 and were obtained from a comprehensive international study that described utilities for various populations in different states and on different treatment strategies, thus, utilities for the Chinese population and the United States population were applied respectively (42). The utilities of the stable disease state were distinguished among different drugs (43). Only the utilities of adverse events with morbidities >50% were extracted.

Base case and subgroup analyses. To measure the cost-effectiveness (CE) between different groups, the primary endpoints included the incremental efficacy, incremental cost and incremental cost-effectiveness ratio (ICER). Secondary endpoints included the average CE ratio and net benefit [willing-to-pay threshold (WTP) benefit-costs] for each group, to further evaluate the average benefit of the treatment strategies.

For the base case analysis, analyses assessed the cost-effectiveness of the first-line osimertinib group vs. standard group, as well as the first-line osimertinib group vs. second-line osimertinib after the failure of first-generation EGFR-TKIs group. Adjustments to utilities were made in accordance with the proportions available in the clinical trials for different groups. As Chinese and American patients in the FLAURA trial received erlotinib and gefitinib, respectively, as the first-line treatment, the corresponding costs were used as representation when performing the analysis in each context.

In the subgroup analysis, Markov models were used for several first-line EGFR-TKI therapy groups, considering different methods of payment in China (Fig 1C). The analysis also included icotinib, a common EGFR-TKI that is only used in China (44). The results of a randomized, double-blind phase III trial indicated that icotinib was not inferior to gefitinib in terms of PFS (45). Thus, it was assumed that the utilities and transition probabilities of icotinib were the same as those of gefitinib for patients who received icotinib (125 mg) thrice daily. With respect to irreversible second-generation EGFR-TKIs, clinical trials have confirmed that afatinib significantly improves outcomes compared with those of gefitinib

Table I. Clinical data.

Parameter	First-line osimertinib	First-generation EGFR-TKIs	Second-line osimertinib
Median PFS (months)	18.9 (15.2-21.4)	10.2 (9.6-11.1)	10.1 (8.3-12.3)
Objective response rate (%)	80 (75-85)	76 (70-81)	71 (65-76)
Adverse events grade ≥ 3 (%)	34	45	23
Rash or acne (%)	58	78	34
Diarrhea (%)	58	57	41

Values presented are the mean and 95% confidence intervals. EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors; PFS, progression-free survival.

Table II. Unit costs.

Parameter	United States		China		Health insurance (\$/cycle)	Specification
	Cost (\$/cycle)	Specification	Cost (\$/cycle)	Company donation		
Osimertinib	13,075.00	80 mg	5,632.42	4 months, first year; 3 months, second year	-	80 mg
Erlotinib	-	-	646.07	-	193.82	150 mg
Gefitinib	7,105.34	250 mg	781.25	8 months	234.35	250 mg
Icotinib	-	-	662.64	10 months	198.79	125 mg
Adverse events grade ≥ 3	9,540.45	-	245.87	-	-	-
Disease progression	6,882.08	-	846.94	-	-	-
Routine follow-up	437.00	-	51.50	-	-	-
Supportive care	2,414.00	-	337.50	-	-	-

Costs are shown in United States dollars (\$). Specifications indicate the dosage. -, no data available.

and has modest activity in patients who are resistant to treatment with reversible EGFR-TKIs (46,47). These drugs were not considered due to a lack of available data. In the subgroup analysis, the osimertinib-company donation group was compared with the erlotinib-health insurance, gefitinib-health insurance, gefitinib-company donation, icotinib-health insurance and icotinib-company donation groups. Considering the medical insurance system in the United States, the payment and reimbursement rate differed among different insurance companies, therefore the subgroup analysis was not carried out for the United States due to a lack of available data.

Sensitivity analysis. One-way and probabilistic sensitivity analyses were performed to assess uncertainties and the robustness of the cost-effectiveness analysis. The ranges were set as $\pm 20\%$ for utilities and $\pm 30\%$ for costs. The one-way sensitivity analysis estimated the effect of each parameter on the ICER and results are expressed in the form of a tornado diagram. For the probabilistic sensitivity analysis, Monte Carlo simulation was performed with 1,000 iterations and each parameter was fitted to a specific distribution, namely, a β distribution for utilities and lognormal distribution for costs (48,49). The WTP was set at three times the per capita gross domestic product, which was \$27,783/QALY for China

Table III. Health state utilities.

Health state	Utility value	
	United states	China
Response	0.883	0.815
Response + diarrhea	-0.279	-0.069
Response + rash	-0.123	-0.095
Stable with gefitinib	0.800	0.800
Stable with erlotinib	0.810	0.810
Stable with osimertinib	0.840	0.840
Stable + diarrhea	-0.323	-0.072
Stable + rash	-0.151	-0.099
Progressive disease	0.166	0.321

Response, treatment was effective in the assigned group; stable, patients remained stable disease to the treatments in the assigned group.

and \$100,000/QALY for the United States (50,51). The results are presented as cost-effectiveness acceptability curves.

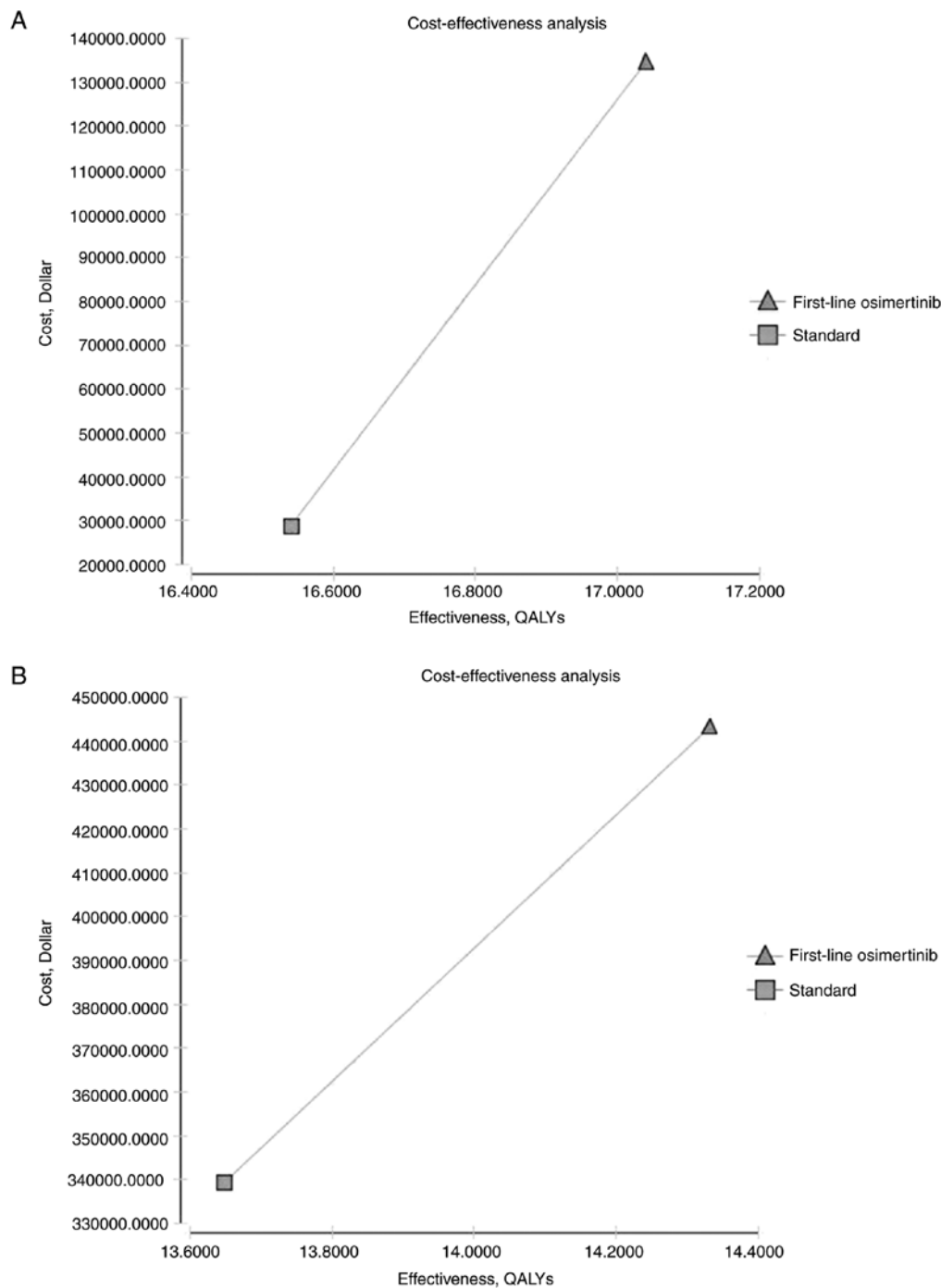


Figure 2. Cost-effectiveness analyses. Cost-effectiveness analysis of (A) the first-line osimertinib group and standard group in China and (B) the first-line osimertinib group and standard group in the United States. QALYs, quality-adjusted life years.

Results

Clinical data. The median PFS of the first-line osimertinib group was 18.9 months, which was significantly longer than that of the standard group (10.2 months; first-generation EGFR-TKIs as the first-line treatment, log-rank test, $P < 0.001$), and the median PFS of the second-line osimertinib group was 10.1 months. Clinical data are shown in Table I, while costs are summarized in Table II. Health state utilities of patients who were responsive to the treatments were set as 0.883 in the United States while 0.815 in China. Other utilities are displayed in Table III. The ranges of parameters were displayed in Table IV.

Base case analysis. Compared with the standard group, first-line osimertinib was associated with higher cumulative QALYs and costs. The ICER was \$212,252/QALY in China and \$151,922/QALY in the United States. The standard groups were superior to the first-line osimertinib groups in terms of both average CE and net benefit (Table V).

Compared with first-line osimertinib, second-line osimertinib was associated with higher cumulative QALYs and low costs. The ICER between first-line and second-line osimertinib was -\$63,329/QALY in China and -\$47,650/QALY in the United States. Second-line osimertinib was also advantageous in terms of average CE and net benefit. These results

Table IV. Parameter ranges.

A, Utilities in China			
Health state	Base case	Low	High
First-line osimertinib group	0.724	0.579	0.869
Second-line osimertinib group	0.761	0.609	0.913
Standard group	0.698	0.558	0.837
Erlotinib group	0.699	0.559	0.839
Gefitinib group	0.697	0.557	0.836
Icotinib group	0.697	0.557	0.836
Progressive disease state	0.321	0.257	0.385
B, Utilities in the United States			
Health state	Base case	Low	High
First-line osimertinib group	0.633	0.506	0.759
Second-line osimertinib group	0.706	0.565	0.848
Standard group	0.598	0.478	0.717
Progressive disease state	0.166	0.133	0.199
C, Costs in different groups in China (\$/cycle)			
Health state	Base case	Low	High
First-line osimertinib group	6,105.01	4,273.51	7,936.52
Second-line osimertinib group	6,077.97	4,254.58	7,901.36
Standard group	1,145.71	802.00	1,489.42
Osimertinib-company donation group	6,105.01	4,273.51	7,936.52
Erlotinib-health insurance group	693.46	485.42	901.50
Gefitinib-health insurance group	733.99	513.79	954.19
Gefitinib-company donation group	1,280.89	896.62	1,665.16
Icotinib-health insurance group	698.42	488.90	907.96
Icotinib-company donation group	1,162.28	813.60	1,510.96
Progressive disease state	846.94	592.86	1,101.02
D, Costs in different groups in the United States (\$/cycle)			
Health state	Base case	Low	High
First-line osimertinib group	19,169.75	13,418.83	24,920.68
Second-line osimertinib group	18,120.30	12,684.21	23,556.39
Standard group	14,249.54	9,974.68	18,524.41
Progressive disease state	6,882.08	4,817.46	8,946.70
Costs are shown in United States dollars (\$).			

are shown in Table V and the CE analysis results are shown in Fig. 2.

Subgroup analysis. In the subgroup analysis, the osimertinib-company donation group had the highest QALYs and the lowest costs, while the gefitinib-health insurance group had the

highest costs and the lowest QALYs. The osimertinib-company donation group displayed improved QALYs and lower costs, with negative ICERs, compared with the first-generation EGFR-TKIs group. The average CE and net benefit analyses highlighted the benefits of the osimertinib-company donation group. Among different methods of paying for first-generation EGFR-TKIs

Table V. Results of cost-effectiveness analysis.

A, China							
Treatment	QALY	Cost (\$)	Average CE (\$/QALYs)	Net benefit (\$)	IncrEff	IncrCost (\$)	ICER (\$/QALYs)
First-line osimertinib group	17.040	134,551.58	7,896	338,859	-	-	-
Second-line osimertinib group	18.529	40,259.66	2,173	474,518	-1.489	94,291.91	-63,329
Standard group	16.541	28,695.91	1,735	430,859	0.499	105,855.67	212,252
Osimertinib-company donation	17.040	14,247.24	836	459,164	-	-	-
Erlotinib-health insurance	16.575	18,969.21	1,144	441,533	0.465	-4,721.97	-10,163
Gefitinib-health insurance	16.523	19,840.90	1,201	439,227	0.516	-5,593.66	-10,835
Gefitinib-company donation	16.523	14,800.64	896	444,267	0.516	-553.41	-1,072
Icotinib-health insurance	16.523	19,076.09	1,154	439,992	0.516	-4,828.85	-9,354
Icotinib-company donation	16.523	14,800.64	896	444,267	0.516	-553.41	-1,072

B, United States							
Treatment	QALY	Cost (\$)	Average CE (\$/QALYs)	Net benefit (\$)	IncrEff	IncrCost (\$)	ICER (\$/QALYs)
First-line osimertinib group	14.332	443,198.08	30,924	990,002	-	-	-
Second-line osimertinib group	15.568	384,279.76	24,683	1,172,569	-1.236	58,918.32	-47650
Standard group	13.649	339,417.88	24,868	1,025,471	0.683	103,780.20	151,922

Costs are shown in United States dollars (\$). QALY, quality of life year; CE, cost-effectiveness; IncrEff, incremental efficacy; IncrCost, incremental cost; ICER, incremental cost-effectiveness ratio; -, no data available; standard group, patients receiving first-generation EGFR-TKI as first-line therapy.

in China, gefitinib-company donation and icotinib-company donation displayed the greatest profit maximization, followed by erlotinib-health insurance, icotinib-health insurance and gefitinib-health insurance (Table V).

Sensitivity analysis. The results of the one-way sensitivity and base case analyses showed that the utilities of the PFS state in the standard group were the most influential parameter, whereas the utilities of the PFS state in the osimertinib-company donation group played the most important role in subgroup analyses (Fig. S1). A probabilistic sensitivity analysis with Monte Carlo simulations revealed comparisons between the first-line osimertinib groups and standard groups at a WTP threshold of \$27,783/QALYs in China and \$100,000/QALYs in the United States showed that neither of the first-line osimertinib groups were cost-effective. CE acceptability curves (Fig. S2), indicating CE tendencies based on different levels of WTP, showed that first-line osimertinib would be cost-effective if the WTP was increased to \$420,000 in China and \$130,000 in the United States.

Discussion

In the present study, a CE analysis was conducted for different sequences of osimertinib administration in two different countries. The first comparison made was between the CE of first-line osimertinib and first-generation EGFR-TKIs (standard group), as the first-line therapy. The osimertinib

group had slightly higher QALYs but at a much higher cost. The ICER exceeded the WTP threshold in both countries and first-generation EGFR-TKIs showed improved average CE and net benefit. Accordingly, first-line osimertinib did not offer any economical benefit. This finding was primarily a result of the high cost of osimertinib due to patent protection (52). The manufacturing company could consider lowering the price of osimertinib in order to enhance its CE. Given a WTP threshold of \$27,783 in China and \$100,000 in the United States, price reductions of 68 and 9% with costs fixed to \$1,781 and \$12,029 per cycle, respectively, would allow osimertinib to be cost-effective as a first-line therapy compared to first-generation EGFR-TKIs.

Subsequently, the cost-effectiveness of the first-line vs. second-line osimertinib group was estimated. The results showed that second-line osimertinib was associated with higher QALYs, improved net benefit, lower costs, improved average CE and negative ICERs in both countries. Clinical data extracted from the clinical trials showed that the rates of adverse events were higher in patients with NSCLC receiving first-line osimertinib than in those receiving second-line osimertinib (including adverse events grade ≥ 3 and other common adverse effects), accounting for the observation of lower QALYs in the first-line osimertinib group. However, considering that first-line osimertinib may significantly prolong the PFS period in patients with EGFR-T790M-negative NSCLC and provide greater benefit in patients with advanced

EGFR-mutated NSCLC, clinical decisions regarding treatment sequences of osimertinib administration should consider multiple factors (47).

Finally, several subgroup analyses were performed to contrast the various payment methods available in China. The results demonstrated that osimertinib-company donation was the most cost-effective choice. Furthermore, although the price and donation policies of gefitinib and icotinib are different, they had similar cost-effectiveness. Of note, paying via company donation was only applied to self-paying and underinsured patients in China (33). In general, the efficacy of various EGFR-TKIs depends on a given patient's clinical situation and tumor characteristics (47). As these features were similar among patients in the included cohorts and economic benefit primarily depended on different levels of costs (53,54), these results can serve as a clinical decision-making reference for the Chinese Government, physicians and patients.

Two previous cost-effectiveness analyses showed that osimertinib treatment was not cost-effective compared to the standard chemotherapy in patients with T790M mutation-positive NSCLC as a second-line therapy in China and the United States (26). However, osimertinib treatment as a second line therapy may be a potential economically preferable option for payers in the United Kingdom (27). Recent studies demonstrated that no economic benefit was found when first-line osimertinib was compared with first-generation EGFR-TKIs, or second-line osimertinib was compared with first-generation EGFR-TKIs in China and the United States (28,29), which are consistent with the results described in the present study.

In the one-way sensitivity analysis, utilities were the most influential parameters. Utilities were adjusted in accordance with practical rates from the clinical trials. Although the utilities were extracted from published literature, it was a recent international study that had utilities available for various populations that was chosen (42). Previous research showed that health state utilities depended on patient preferences and are closely associated with their ethnicity, culture and education level. Patients from Asian countries generally reported higher health state utilities than those from other countries (42). In the present study, utilities specific to Chinese and American populations were used to ensure the accuracy of the results. This approach may also explain observed differences in QALYs between countries.

The advantages of the present study are as follows. Firstly, to the best of our knowledge, this is the first cost-effectiveness analysis to compare the economic benefits of different treatment sequences of osimertinib. Additionally, it is the first study to compare osimertinib with different EGFR-TKI drugs obtained via various payment methods in China. Secondly, the clinical trials used in the present study were conducted across 29 countries, including China and the United States. The present study simulated the clinical trials in the administration of drugs, which contributed to the reliability and stability of the results. Thirdly, the utilities were extracted from a recent comprehensive international study with the same measuring protocols (42). Finally, the utilities and costs of different drugs and various alternative payment options were considered in order to simulate real medical decisions made in daily clinical work.

The present study also had some limitations. First, the OS data from the clinical trials was unavailability and OS

data derived from other published literature was also used. Authentic mortality probabilities should be recalculated when the OS data is available. Secondly, the most common adverse events were taken into account for the estimation of health state utilities, while only grade ≥ 3 adverse effects were evaluated. Thirdly, a high level of crossover between the groups may have affected the results. Finally, health economic evaluations are limited by region disparity. Therefore, the results may only be applicable to countries with similar economic development.

In conclusion, administering the new third-generation EGFR-TKI osimertinib as the first-line therapy could result in more health benefits (47,55). However, it was not cost-effective compared with the first-generation EGFR-TKIs for previously untreated EGFR-mutated advanced NSCLC, or with the second-line osimertinib for patients with mutated-T790M advanced NSCLC and progressive disease after first-generation EGFR-TKI therapy, in the context of the Chinese health system and the United States payer system. First-line therapy with osimertinib may be a good choice compared to first-generation EGFR-TKIs, using the company donation policy in China.

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Availability of data and materials

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

Authors' contributions

WqL performed the data analyses and wrote the manuscript. LQ contributed significantly to analysis and manuscript preparation. WL helped perform the analysis and contributed to constructive discussions. XC contributed to the collection of cost and utility data and revised the work critically for important intellectual content. HH was a major contributor to the design of the Markov model and to writing the manuscript. HT contributed analysis tools and the design of the study. YZ analyzed and interpreted the patient data from the clinical trials. XW helped analyze the data. JC contributed to the conception and design of the study. All authors approved the final version of the manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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