Cost Effectiveness Analysis Of Gefitinib Plus Chemotherapy Versus Gefitinib Alone For Advanced Non-Small-Cell Lung Cancer With EGFR Mutations In China

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Objective: The aim of this study was to evaluate the cost-effectiveness of gefitinib plus chemotherapy (GCP) versus gefitinib alone for advanced non–small-cell lung (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations in China.

Methods: A decision-analytic Markov model was conducted to simulate the disease process of advanced NSCLC patients with EGFR mutations. Three distinct health states: progression-free survival (PFS), progressive disease (PD) and death were included. Clinical data were derived from the NEJ009 Study. The cost was evaluated from the perspective of the Chinese society. Quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICER) were calculated over a 10-year lifetime horizon. One-way sensitivity analysis and probabilistic sensitivity analysis were also

performed to explore the uncertainty of parameters in the study.

Results: The base case analysis demonstrated that gefitinib plus chemotherapy gained 2.44 QALYs at an average cost of $59,571.34, while the effectiveness and cost of gefitinib group were 1.82 QALYs and $52,492.75, respectively. The ICER for gefitinib plus chemotherapy was $11,499.98 per QALY gained. The ICER was lower than the accepted willingness-to-pay (WTP) threshold, which was three times gross domestic product (GDP) per capita of China ($31,498.70 per QALY). Variation of parameters did not reversal the cost-effectiveness of gefitinib plus chemotherapy through univariable and probabilistic sensitivity analyses.

Conclusion: Our results showed that gefitinib plus chemotherapy is a cost-effective treatment option compared with gefitinib for advanced NSCLC patients with EGFR mutations in China.

Keywords: cost-effectiveness, gefitinib, NSCLC, EGFR, Markov model

Introduction

According to the global cancer statistics in 2020, there were 2.207 million new cases of lung cancer and 1.79 million associated deaths worldwide, ranking first among all cancers in mortality.[1, 2] In China, lung cancer is a malignant tumor with the highest incidence and mortality. It was estimated that 816,000 new lung cancer cases and 715,000 deaths occurred in China in 2020, accounting for 23.8% of all the cancer deaths.[3] The costs of diagnosis and treatment of lung cancer bring huge economic burden to both the country and society. NSCLC was the most common histological

subtype, which accounted for approximately about 85% to 90% of all lung cancers.[2, 4, 5] The symptoms of NSCLC patients in the early stage are not typical, and most patients are advanced when they are newly diagnosed, so they can only receive palliative treatment. Approximately 35% to 40% of NSCLC patients are caused by epidermal growth factor receptor (EGFR) mutations in China,[6] and National Comprehensive Cancer Network (NCCN) guidelines recommend EGFR-TKIs for the first-line treatment of EGFR-mutated metastatic NSCLC.[7]

Although EGFR-TKIs have significantly improved the PFS and quality of life (QoL) of advanced NSCLC patients with EGFR mutations, most patients cannot escape the fate of drug resistance. About 30% of patients may lose the opportunity of follow-up treatment due to the rapid disease progression.[8] Compared with traditional chemotherapy, first-generation EGFR-TKIs did not bring significant extension of overall survival (OS) either in first-line use or sequential maintenance after chemotherapy. In order to overcome drug resistance and improve OS, the bottleneck of efficacy of single-drug therapy can be broken through the combination of EGFR-TKIs with chemotherapy via strategic adjustment. However, in the era without driver gene screening, 4 phase III randomized controlled studies (INTACT1, INTACT2, TRIBUTE and TALENT) showed that combined with EGFR-TKIs (gefitinib or erlotinib) could not improve OS in patients with advanced NSCLC on the basis of first-line chemotherapy.[9-12] The main reason for the negative results was that the EGFR mutations status in the treated population was not identified.

NEJ009 study is the first phase III clinical study comparing gefitinib alone with

gefitinib plus two platinum-containing drugs (pemetretrex and carboplatin) in first-line treatment of advanced NSCLC patients with EGFR mutations,[13] and the results have attracted wide attention since they were announced at the 2018 American Society of Clinical Oncology (ASCO). The study met its primary endpoint, with median OS significantly longer in the combination group than in the monotherapy group. In addition, the PFS of the combined treatment group reached 20.9 months, even surpassing the data of 18.9 months for third-generation EGFR-TKI osimertinib for the first-line treatment of NSCLC in the FLAURA study, [14] which broke a new record for first-line treatment of EGFR mutant patients.

Although the NEJ009 study demonstrated a significant PFS and OS benefit, the economics of both treatments are unknown to the patients and physicians. The purpose of this study was to evaluate the cost-effectiveness of gefitinib plus chemotherapy compared with gefitinib alone in the treatment of advanced NSCLC patients with EGFR mutations from Chinese societal perspective.

Methods

NEJ009 Study

The clinical data was based on the results of the NEJ009 study, an open-label, randomized phase III trial comparing gefitinib alone with gefitinib plus chemotherapy for NSCLC patients with EGFR mutations.[13] 345 eligible patients with newly diagnosed metastatic NSCLC with EGFR mutations were randomly assigned to gefitinib (gefitinib 250 mg orally per day) or GCP regimen (gefitinib 250 mg orally

per day combined with carboplatin area under the curve 5 and pemetrexed 500 mg/m^2 in a 3-week cycle for up to six cycles, followed by concurrent gefitinib and pemetrexed maintenance) until disease progression or the development of unacceptable toxic effects or death. The GCP group demonstrated a better median PFS than the gefitinib group (20.93 vs 11.17 months, HR 0.49, 95% CI 0.39 to 0.62, p<0.001), and median OS in the GCP group was also significantly longer than in the gefitinib group (50.9 vs 38.8 months, HR 0.722, 95% CI 0.55 to 0.95, p=0.021). The most frequently reported serious adverse events (SAEs, the rate of grade≥3) in the GCP group were neutropenia, anemia, and thrombocytopenia compared with liver toxicity in the gefitinib group.

Markov Model

A Markov model was constructed using TreeAge Pro software (TreeAge Pro 2019, Williamstown, MA, USA) to estimate the cost and quality-adjusted life years (QALYs) of GCP and gefitinib. The Markov model had three mutually exclusive health states including PFS, PD and death. It was assumed that all patients entered the model in the PFS state and could move to the other state or remain in the same state, and patients could only stay in the PD state or move to death after transferring to the PD state. The model diagram was shown in **Figure 1**. A cycle length of one month was set to capture relevant changes in the health states, with a half-cycle correction applied to adjust for the timing of events. According to the survival curve, time of follow-up and treatment in the NEJ009 Study, a total of 120 cycles of simulation, which was the equivalent of 10 years in the Markov model was adopted. A 3% annual

discount rate was used for costs and effectiveness.[15]

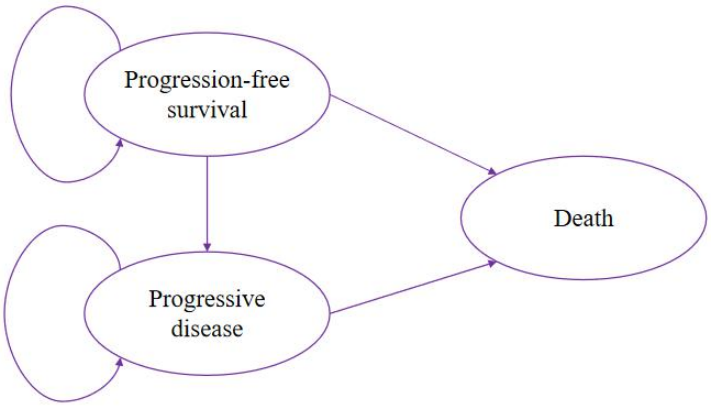

Figure 1 The Markov model simulated three health states: PFS, PD and death.

Survival Estimates and Utilities

Transition probabilities for the different health states were estimated from Kaplan-Meier survival curves which obtained from NEJ009 study. The Kaplan-Meier curves of PFS and OS for the two groups were read by GetData Graph Digitizer software (Version 2.26) to get the survival data. The Weibull distribution was fitted to the data for PFS and OS curves using R statistical software (version 4.0.5). The calculated scale parameter (λ) and shape parameter (γ), were presented in **Table 1**. The survival curve simulation results were shown in **Figure 2**. Formula $S(t)=\exp(-\lambda t^{\gamma})$ was used to calculate the survival probability at time t and we used formula $P(t)=1-\exp[\lambda(t-1)^{\gamma}-\lambda t^{\gamma}]$ to estimate the transition probability at a given cycle t.[16, 17] The transition probability from PFS to death state is derived from the natural death rate of Chinese population in 2020 (0.707%).[18] Health utility values were obtained from a recently published study.[19, 20] The utility values of the PFS state, PD state and death were 0.804, 0.321 and 0, respectively.

Table 1 Weibull Parameters of Model Estimated for Progression-free and Overall Survival Curves

Group		Parameter	Mean	SE	95% CI	
					Low	Up
GCP	PFS	scale (λ)	0.007645	0.002764	0.003763	0.015529
		shape (γ)	1.442737	0.101340	1.257181	1.655568
	OS	scale (λ)	0.001160	0.000705	0.000352	0.003819
		shape (γ)	1.622184	0.154090	1.346621	1.954137
Gefitinib	PFS	scale (λ)	0.019543	0.005265	0.011526	0.033136
		shape (γ)	1.391394	0.083233	1.237460	1.564476
	OS	scale (λ)	0.003684	0.001721	0.001475	0.009202
		shape (γ)	1.403482	0.120164	1.186665	1.659914

Abbreviations: GCP, gefitinib combined with carboplatin and pemetrexed; PFS, progression-free survival; OS, overall survival; SE, standard error; 95% CI, 95% confidence interval.

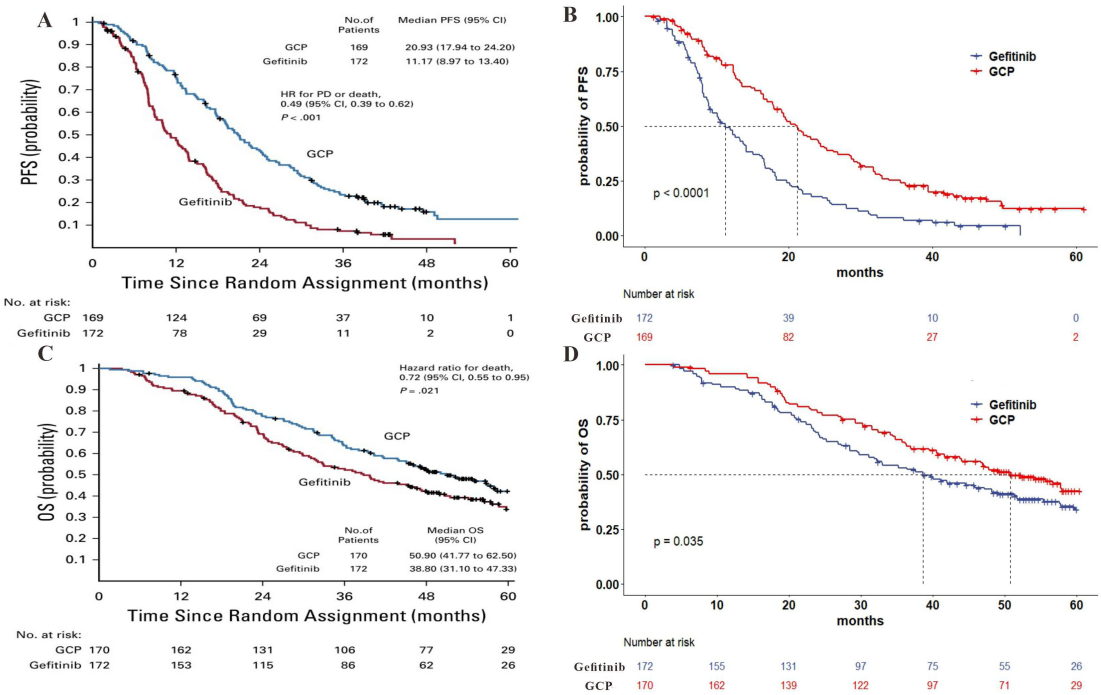

Figure 2 (A) Kaplan–Meier curve of the progression-free survival from the NEJ009

study. (B) Simulate progression-free survival curve for the GCP group and the Gefitinib group. (C) Kaplan–Meier curve of overall survival from the NEJ009 study. (D) Simulate overall survival curve for the GCP group and the Gefitinib group.

Cost Estimates and Outcomes

Costs were estimated from the perspective of Chinese society. The cost of this study only covered direct medical costs, which included drug costs of gefitinib and chemotherapies, follow-up costs, supportive care costs, SAEs treatment costs, and terminal care costs. To calculate the drug costs of chemotherapy per cycle, a base-case patient with a body surface area of 1.72 m^2 was assumed. The costs of follow-up included hospitalization expenses, the costs of outpatient-based physician visits, laboratory examination fees (inpatient and/or outpatient), and costs of computed tomography and magnetic resonance imaging. Once the disease progressed, patients were assumed to receive salvage chemotherapy.[21] SAEs management strategies were based on clinical practice and expert opinions, and SAEs related to costs were collected from the NEJ009 study as shown in **Table 2**. The costs of drugs and examinations were based on the 2020 fee standards of local hospitals in China. All costs were presented in US dollars, with an exchange rate of $1 = ￥6.9 (2020). Details of the cost information were provided in **Table 3**.

Incremental cost-effectiveness ratio (ICER) was calculated to evaluate the outcomes. The treatment is considered affordable and economical when the ICER value is less than the willingness-to-pay (WTP) threshold. The formula of ICER is as

follows:

$$\text{ICER} = \frac{\text{Cost (GCP)} - \text{Cost (Gefitinib)}}{\text{QALYs (GCP)} - \text{QALYs (Gefitinib)}}$$

The World Health Organization recommended that the increased cost was extremely cost-effectiveness when the ICER was less than GDP per capita (1 GDP), but could still count as cost-effectiveness if the ICER did not exceed three times GDP per capita (3 GDP).[15] Thus, we used $10,499.57 (1 GDP of China in 2020) per QALY and $31,498.70 (3 GDP of China in 2020) per QALY gained as the WTP threshold in different situations.[18]

Table 2 The Incidence and Expenditures of SAEs

Variables	GCP group	Gefitinib group	Expenditures of SAEs ($/per event)
Leukopenia	21.2	0.6	104.18
Neutropenia	31.2	0.6	67.26
Anemia	21.2	2.3	40.86
Thrombocytopenia	17.1	0.0	527.45
Liver dysfunction	12.4	22.2	85.28
Diarrhea	4.1	1.2	3.25
Vomiting	2.4	0.6	142
Stomatitis	0.6	0.0	4.66
Rash	4.1	2.9	1.47
Fatigue	4.1	0.0	105.36

Abbreviations: GCP, gefitinib combined with carboplatin and pemetrexed; SAEs, serious adverse events.

Variables	Base Case	Range	Distribution
Costs ($)			
Gefitinib (250mg)	23.13	18.5-27.76	Triangle
Pemetrexed (100 mg)	94.2	75.36-113.04	Triangle
Carboplatin (100 mg)	15.8	12.64-18.96	Triangle
Follow-up cost per cycle	178.57	142.86-214.28	Triangle
Cost of salvage therapy per cycle	1238.96	1486.75-991.17	Triangle
Terminal care	2583.37	2066.70-3100.04	Triangle
Cost of managing SAEs for GCP group per cycle[a]	7.67	6.14-9.2	Triangle
Cost of managing SAEs for Gefitinib group per cycle[a]	0.33	0.4-0.26	Triangle
Utility value			
PFS	0.804	0.643-0.965	Beta
PD	0.321	0.257-0.385	Beta
Body surface area (m^2)	1.72	1.38-2.06	Triangle
Discount rate (%)	3	0-8	Fixed

Table 3 Costs, utilities, and discount rates in the model

Notes: The costs of each SAE were calculated via multiplying the incidence of SAE by the expenditures of managing per SAE.

Abbreviations: GCP, gefitinib combined with carboplatin and pemetrexed; SAE, serious adverse event; PFS, progression-free survival; PD, progressive disease.

Sensitivity Analysis

One-way sensitivity and probabilistic sensitivity analyses were performed to

evaluate the effect of the model uncertainty on the cost-effectiveness of different treatment options. A one-way sensitivity analysis kept other parameters unchanged, and altered individual model parameters in the range of variation, and then verified the effect of individual model parameters on the results. The key parameters in the model were changed with a range of ±20% of their baseline value to examine their impact on the results. Results of the one-way sensitivity analysis were represented by a tornado diagram. The probabilistic sensitivity analysis was performed to assess the effects of uncertainty in all model parameters simultaneously using a second-order Monte Carlo simulation for 1000 times to obtain an acceptable cost-effectiveness curve with different hypothetical WTP thresholds. The beta distribution was applied to the utilities, and the triangle distribution was applied to the others.

Results

Base-Case Analysis

The results of a base-case analysis with a 10-year time horizon, as well as economic and health outcomes estimated by the model, are shown in **Table 4**. The total costs of the GCP group were $59,571.34, and the total costs of the gefitinib group were $52,492.75. The overall QALYs in the GCP group were higher than those in the gefitinib group (2.44 QALYs vs 1.82 QALYs). The GCP group generated a gain of 0.62 QALYs over gefitinib group, resulting in an ICER of $11,499.98/QALY gained, which was lower than the commonly accepted threshold for cost-effectiveness (3 GDP, $31,498.70 per QALY in China).

Table 4 The Cost and Outcome Results of the Cost-effectiveness Analysis

Parameters	**GCP group**	**Gefitinib group**
Costs ($)		
PFS state	25,452.68	14,078.91
PD state	34,118.67	38,413.85
Total Cost	59,571.34	52,492.75
Incremental costs ($)	7,078.59	/
Effectiveness (QALYs)		
PFS state	1.75	1.05
PD state	0.69	0.77
Total effectiveness	2.44	1.82
Incremental effectiveness (QALYs)	0.62	/
ICER ($/QALY)	11,499.98	/

Abbreviations: GCP, gefitinib combined with carboplatin and pemetrexed; PFS, progression-free survival; PD, progressive disease; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

Sensitivity Analysis

One-way deterministic sensitivity analysis of key variables revealed that the duration of PFS for GCP group, the duration of PFS for Gefitinib group, the utility of PFS, the cost of Gefitinib per 250 mg and cost of salvage therapy per cycle were the top five influential parameters in the model (**Figure 3**). The duration of PFS for GCP

group had the greatest influence on the results of the model. However, when the duration of PFS for GCP varied from 16.74 to 25.12, the ICER ranged from $19,875.78 per QALY to $5,918.34 per QALY, which was still lower than WTP (3 GDP). Furthermore, the top five influential parameters could gain ICER lower than 1 GDP within the range of variation. Other variables, such as body surface area (m^2), the utility of PD, and discount rate had a moderate or mild impact on the ICER results. The probabilistic sensitivity analysis showed that the probability of GCP being cost-effective reached to 100% when 3 GDP was set as the WTP threshold, (**Figure 4**), and 38.75% being extremely cost-effective when 1 GDP was WTP threshold. Correspondingly, the cost-effectiveness acceptability curve showed the probabilistic sensitivity analysis results of different WTP thresholds (**Figure 5**). If WTP threshold was $11,500/QALY, GCP treatment would have a 50% probability of being cost-effective.

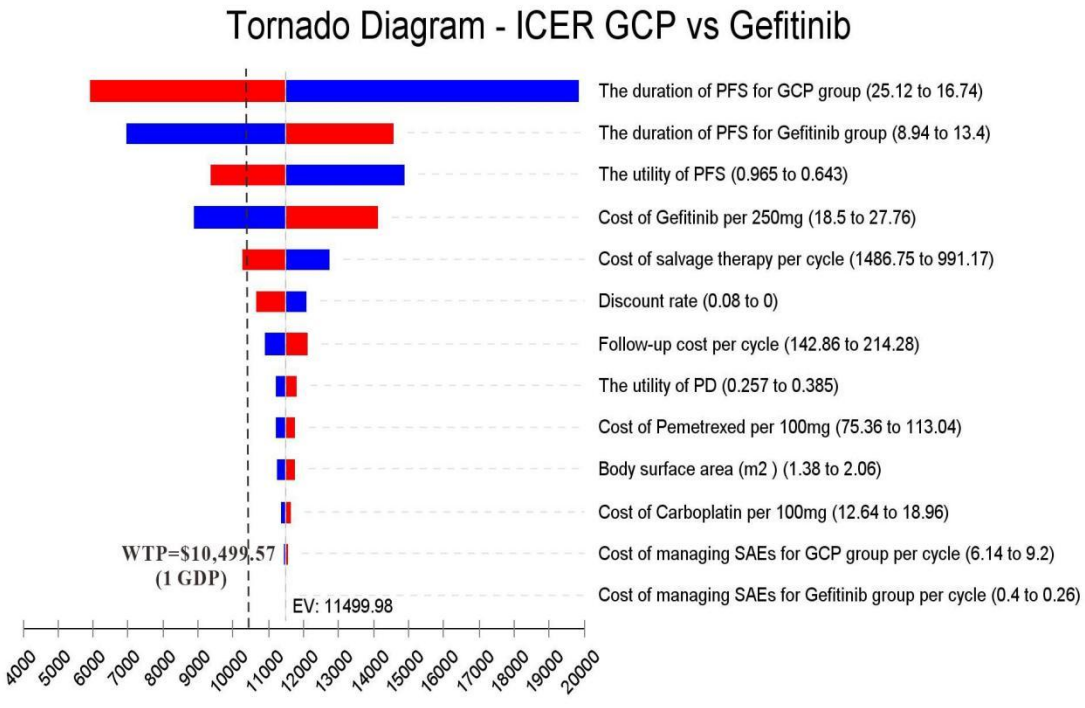

Figure 3 Tornado diagram of one-way sensitivity analysis. It summarized the results of one-way sensitivity analysis, which listed influential parameters in descending order according to their effect on the ICER over the variation of each parameter value.

Abbreviations: GCP, gefitinib combined with carboplatin and pemetrexed; PFS, progression-free survival; PD, progressive disease; SAEs, serious adverse events.

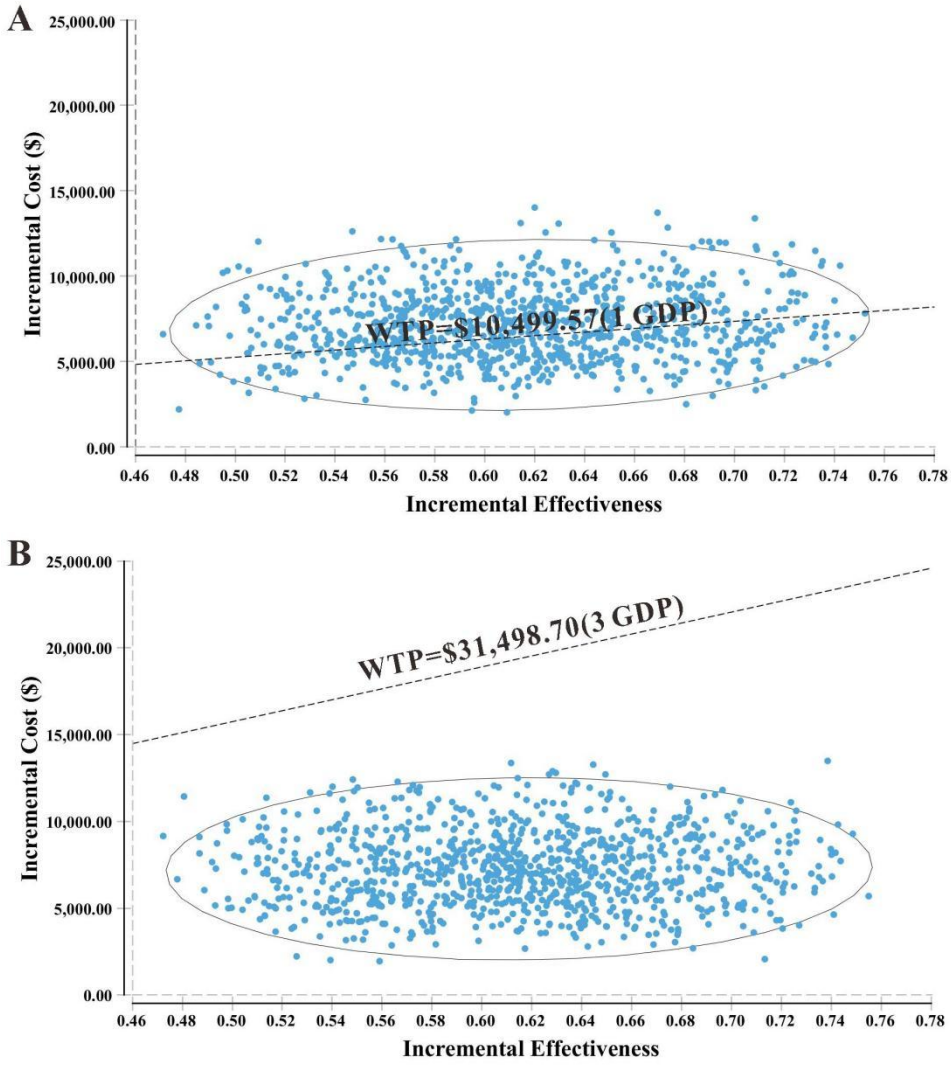

Figure 4 A probabilistic scatter plot of the ICER between the GCP and Gefitinib group. Each dot represents the ICER for 1 simulation. An ellipse means 95% confidence interval. Dots that are located below the ICER threshold represent cost-effective simulations. (A) A probabilistic scatter plot of under WTP=$10,499.57

(1 GDP). (B) A probabilistic scatter plot of under WTP=$31,498.70 (3 GDP).

Abbreviations: GCP, gefitinib combined with carboplatin and pemetrexed; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio.

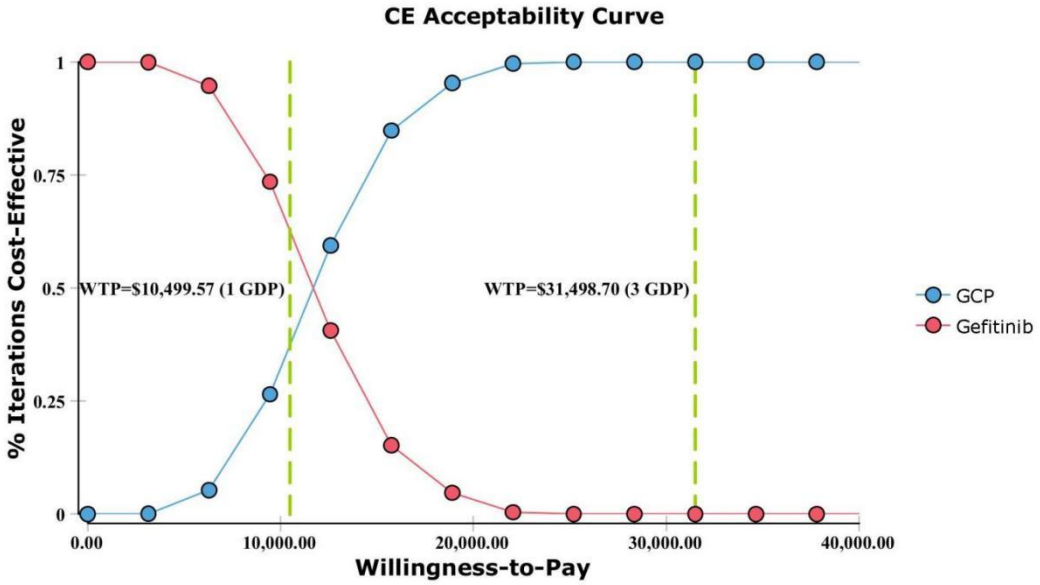

Figure 5 Cost-effectiveness acceptability curve.

Abbreviations: GCP, gefitinib combined with carboplatin and pemetrexed; WTP, willingness-to-pay; GDP, gross domestic product.

Discussion

In recent years, first-generation EGFR-TKIs such as gefitinib and erlotinib have been widely used in clinical practice and proved to be able to significantly improve patient survival.[22, 23] However, resistance mutations are inevitable due to the long term use of targeted drugs. Studies have found that the combination of gefitinib or erlotinib in advanced NSCLC patients with EGFR mutations can produce synergistic anti-proliferation and pro-apoptotic effects, [24-26] which can effectively inhibit the occurrence of targeted drug resistance. Besides, several studies of targeted drugs in

255 combination with chemotherapy have shown significant survival benefits. It has
256 become a new direction of targeted therapy to explore the combined application mode
257 of targeted drugs with chemotherapy to achieve the maximum survival benefit.
258 However, the cost-effectiveness of these regimens in advanced NSCLC patients with
259 EGFR mutations remains unknown. In this study, we investigated the
260 cost-effectiveness of gefitinib alone versus gefitinib plus chemotherapy for advanced
261 NSCLC patients with EGFR mutations based on NEJ009 study.

262 According to our analysis results, the addition of carboplatin plus pemetrexed to
263 gefitinib generated an ICER of $11,499.98/QALY, which was lower than the
264 commonly accepted WTP threshold of $31,498.70/QALY (3 GDP), indicating that the
265 GCP was cost-effective as the first-line treatment for advanced NSCLC patients with
266 EGFR mutations compared with gefitinib alone. The acceptability curve also
267 supported this finding, which showed that GCP was the preferred option at this WTP
268 threshold (3 GDP). It is worth noting that GCP had a 38.75% probability to be
269 extremely cost-effective at 1 GDP, which strongly suggested that GCP was not only
270 more effective, but also the added cost was well worth. The one-way sensitivity
271 analysis revealed that the duration of PFS for GCP group had the greatest influence on
272 the ICER. Generally, the cycle costs of chemotherapy in the model were influenced
273 by drug costs and duration of PFS, and the longer the PFS, the lower the
274 chemotherapy cost per cycle. The top five influential parameters were the main
275 tradeoffs when generalizing the results of clinical trials to real-world outcomes,
276 because they could gain ICER lower than 1 GDP in China.

To the best of our knowledge, there are few studies reporting the cost-effectiveness of EGFR-TKIs alone versus EGFR-TKIs plus chemotherapy for first-line treatment of NSCLC. Some cost-effective studies between EGFR-TKIs, including osimertinib, gefitinib, afatinib, and erlotinib have been performed by other researchers. In Japan, use of gefitinib and EGFR testing could be considered as a cost-effective first-line therapy with an ICER of $32,500/QALY, and Kimura et al demonstrated that gefitinib was more cost effective in comparison with afatinib and erlotinib regimens, although afatinib and erlotinib regimens were well-tolerated and could achieve sufficient effects.[27, 28] Cai et al showed 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 in China.[29] Different conditions, such as the model structure, time horizon, countries and regions, the measurement of costs and health utilities, may lead to inconsistent conclusions in similar clinical reports. Due to the superior efficacy and economy of gefitinib in EGFR-TKIs, it is meaningful and necessary to study the cost-effectiveness of gefitinib combined with chemotherapy.

It is worth noting that the second generation of EGFR-TKIs could not overcome the drug resistance of the first-generation, and simultaneously showed greater adverse reactions, resulting in its unsatisfactory clinical application.[30, 31] In orde to overcome drug resistance and improve survival time, NEJ009 was the first phase III clinical trial to evaluate the clinical efficacy of EGFR-TKI first-line platinum-containing two-drug combination chemotherapy in patients with EGFR-mutant advanced NSCLC. Although the third-generation EGFR-TKI osimertinib has received

299 marketing authorization for its significant survival benefit in EGFR-mutated NSCLC,
300 the price of osimertinib is 7.5-times of gefitinib and 5-times of afatinib in China. The
301 cost disadvantage caused by such a huge price difference might not be compensated
302 by its clinical output. From the economic point of view, the first-generation
303 EGFR-TKIs were still a more economical treatment option for EGFR-mutated
304 NSCLC in China.[32]

305 The study had some limitations that are worth discussing. First, basic information
306 was retrospectively collected from a phase III trial, and we used the Weibull
307 distribution to extrapolate the results beyond the follow-up duration of the RCTs,
308 which was not patient-level data in clinical practice. Second, the value of utilities of
309 health states were derived from previously published studies, which might not reflect
310 the health state of patients in China. Third, drug discounts and patient assistance
311 programs were not considered in this study, making the costs slightly higher than
312 those in the real-world in the long term. Finally, since it was difficult to accurately
313 estimate the impact of SAEs on utility values, in order to calculate the
314 cost-effectiveness for convenience, the negative effects of SAEs on utility were
315 excluded in our calculation, which may also decrease the accuracy of our analysis.

316 In conclusion, this is the first study to investigate the cost-effectiveness of
317 gefitinib plus chemotherapy for advanced NSCLC patients with EGFR mutations in
318 China. Gefitinib plus chemotherapy is cost-effective compared with gefitinib alone
319 from Chinese societal perspective. In addition to the efficacy and safety obtained from
320 the clinical trial, our study could also provide evidences to evaluate the economy of

gefitinib plus chemotherapy for the treatment of NSCLC from a pharmacoeconomic perspective. The results of our study are potentially significant for the decision-making of the patients, the government as well as the healthcare financial institutions.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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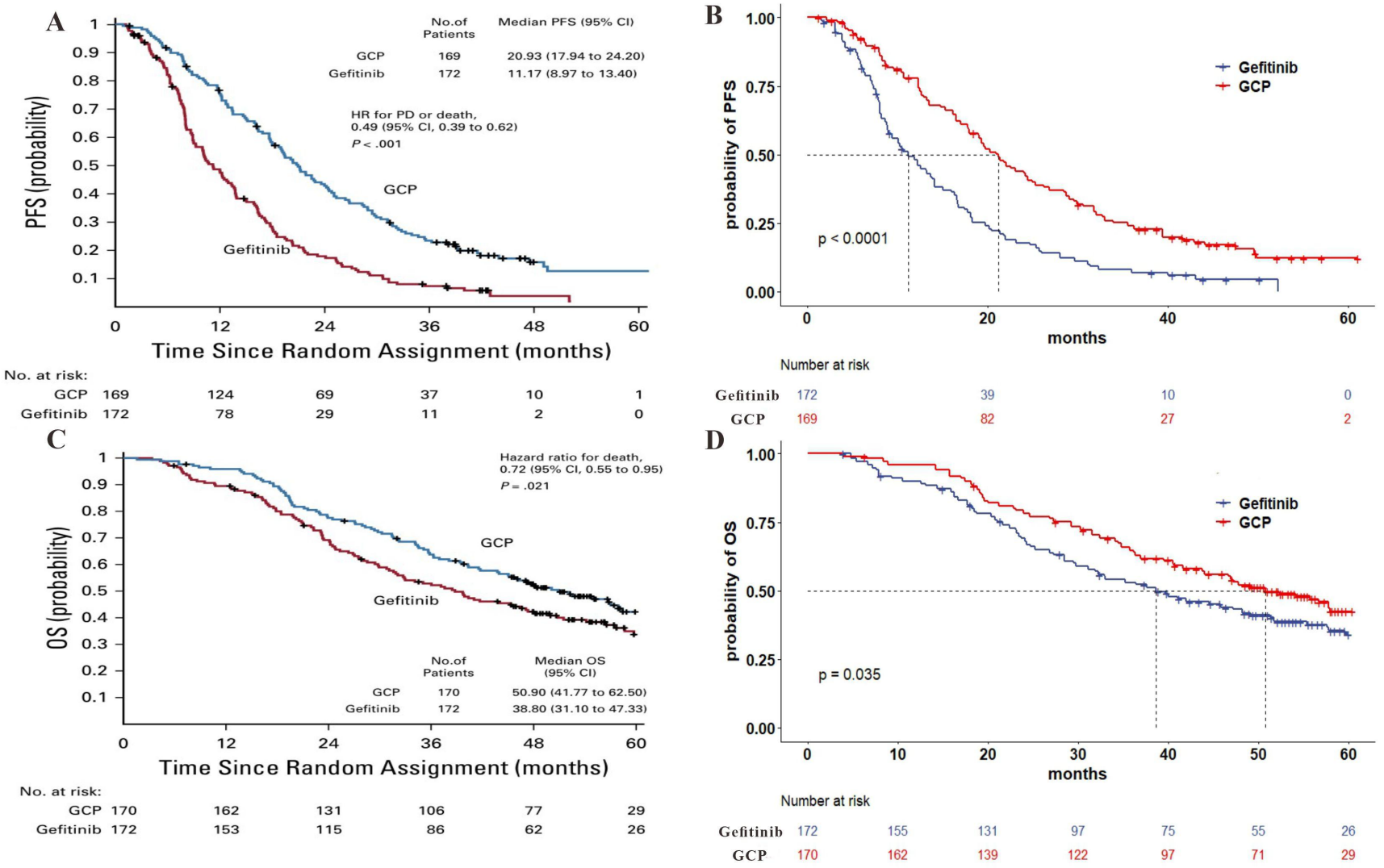
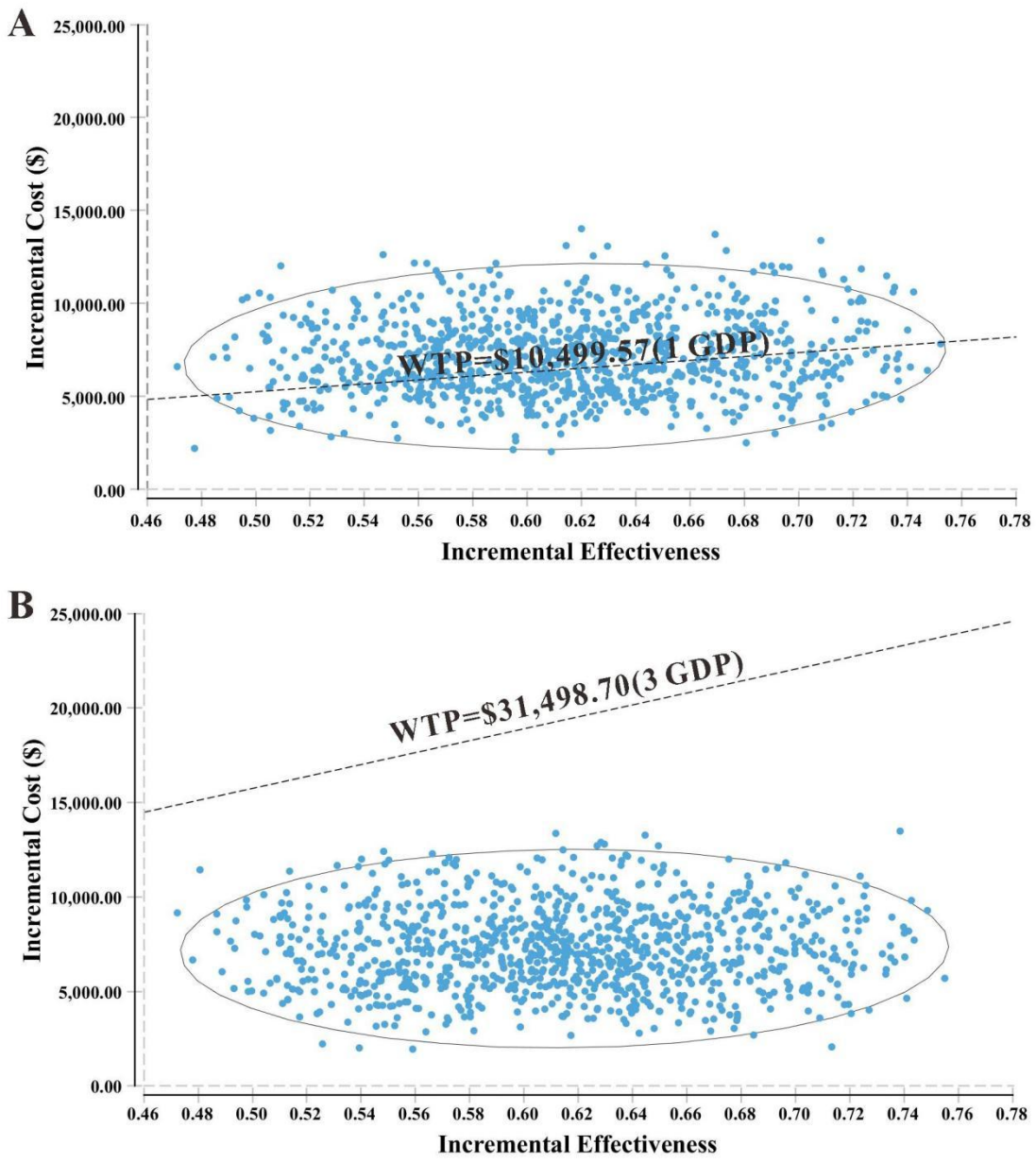

A
No.of Patients
Median PFS (95% CI)
GCP 169 20.93 (17.94 to 24.20)
Gefitinib 172 11.17 (8.97 to 13.40)
HR for PD or death, 0.49 (95% CI, 0.39 to 0.62)
P < .001
GCP
Gefitinib
PFS (probability)
Time Since Random Assignment (months)
No. at risk:
GCP 169 124 69 37 10 1
Gefitinib 172 78 29 11 2 0
B
Gefitinib
GCP
probability of PFS
p < 0.0001
months
Number at risk
Gefitinib 172 39 10 0
GCP 169 82 27 2
C
Hazard ratio for death, 0.72 (95% CI, 0.55 to 0.95)
P = .021
GCP
Gefitinib
OS (probability)
No.of Patients
Median OS (95% CI)
GCP 170 50.90 (41.77 to 62.50)
Gefitinib 172 38.80 (31.10 to 47.33)
Time Since Random Assignment (months)
No. at risk:
GCP 170 162 131 106 77 29
Gefitinib 172 153 115 86 62 26
D
Gefitinib
GCP
probability of OS
p = 0.035
months
Number at risk
Gefitinib 172 155 131 97 75 55 26
GCP 170 162 139 122 97 71 29


A
25,000.00
20,000.00
15,000.00
10,000.00
5,000.00
0.00
Incremental Cost ($)
WTP=$10,499.57(1 GDP)
0.46 0.48 0.50 0.52 0.54 0.56 0.58 0.60 0.62 0.64 0.66 0.68 0.70 0.72 0.74 0.76 0.78
Incremental Effectiveness
B
25,000.00
20,000.00
15,000.00
10,000.00
5,000.00
0.00
Incremental Cost ($)
WTP=$31,498.70(3 GDP)
0.46 0.48 0.50 0.52 0.54 0.56 0.58 0.60 0.62 0.64 0.66 0.68 0.70 0.72 0.74 0.76 0.78
Incremental Effectiveness