Cost-effectiveness of Osimertinib as a Second-line Treatment in Patients With *EGFR*-mutated Advanced Non−Small Cell Lung Cancer in China

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ABSTRACT

Purpose: To assess the cost-effectiveness of osimertinib used as a second-line treatment after failure of epidermal growth factor receptor tyrosine kinase inhibitor therapy for advanced non−small cell lung cancer (NSCLC) in China.

Methods: From the perspective of China's health care system, a Markov model was used for estimating the costs and health outcomes of osimertinib and 4 platinum-based chemotherapies, including pemetrexed + platinum (PP), gemcitabine + platinum (GP), docetaxel + platinum (DP), and paclitaxel + platinum (TP). Two scenarios were considered, one in all confirmed patients with T790M-positive disease (scenario 1) and the other in all patients whose disease progressed after epidermal growth factor receptor tyrosine kinase inhibitor therapy, which consisted of patients with T790M-positive or T790M-negative NSCLC (scenario 2). Clinical data for transition probabilities and treatment effects were obtained from published clinical trials. Health care resource utilization and costs were derived from local administrative databases and published literature. Deterministic and probabilistic sensitivity analyses were conducted to assess the uncertainty of the results.

Findings: In the base-case analysis, compared with the 4 platinum-based chemotherapies, osimertinib yielded an additional 0.671 to 0.846 quality-adjusted life-year (QALY), with incremental costs of 15,943 to 20,299 USD in scenario 1, and an additional 0.376 to 0.808 QALY with incremental costs of 9710 to 15,407 USD in scenario 2. In the probabilistic sensitivity analysis, the probabilities that osimertinib would be cost-effective were 57.7% in scenario 1 and 58.4% in scenario 2 if the willingness-to-pay threshold were 30,000 USD/QALY, and probabilities would be more than 75 % in both scenarios if the willingness-to-pay threshold were 50,000 USD/QALY.

Implications: Osimertinib is likely to be cost-effective when used as a second-line treatment of advanced NSCLC in China based on the latest reimbursement price of osimertinib through National Reimbursement Drug List negotiation. (*Clin Ther.* 2019;41:2308−2320)

Key words: China, cost-effectiveness analysis, non−small cell lung cancer, osimertinib, platinum-based chemotherapy.

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in China, with >781,000 new cases and 626,000 deaths each year.[1] Around 85% of cases of lung cancer are non−small cell lung cancer (NSCLC).[2] Epidermal growth factor receptor gene (*EGFR*) mutations, found in 10%−15% of Western patients and up to 50% of Asian patients, play an important role in tumor development. EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib,

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and icotinib, are the standard first-line therapy for *EGFR* mutation−positive NSCLC. However, in the majority of patients, disease progresses after 9−13 months of treatment,[3] and about 60% of these patients are found to have an *EGFR* T790M mutation.[4,5]

Osimertinib is a third-generation EGFR-TKI that is selective for both *EGFR* and T790M resistance mutations. A randomized, international, Phase III trial, AURA3 (Osimertinib or Platinum Pemetrexed in *EGFR* T790M-positive Lung Cancer),[3] was conducted to compare the efficacy and tolerability of osimertinib and pemetrexed + platinum (PP) in patients with centrally confirmed T790M-positive advanced NSCLC after the failure of first-line EGFR-TKI therapy, and found that the median progression-free survival (PFS) time was significantly longer with osimertinib than with PP (10.1 vs 4.4 months; hazard ratio [HR] = 0.30; 95% CI, 0.23−0.41; $P < 0.001$). The objective response rate was significantly greater with osimertinib than with PP (odds ratio = 5.39; 95% CI, 3.47−8.48; $P < 0.001$). Likely due to the greater PFS and objective response with osimertinib over standard chemotherapy in patients with advanced *EGFR* T790M−positive NSCLC after the failure of EGFR-TKI therapy, the Chinese Food and Drug Administration approved osimertinib for use as a second-line treatment in these patients in 2017.

Despite the clinical benefit of osimertinib in prolonging PFS compared with PP, osimertinib was also associated with higher costs. Two studies have assessed the cost-effectiveness of osimertinib versus PP used as second-line treatment of advanced NSCLC in patients in whom first-line EGFR-TKI therapies have failed,[6,7] and reported that osimertinib might be considered a cost-effective treatment from the perspective of the public payer in the United Kingdom, but was unlikely to be so in the United States and China. However, those 2 studies were limited by the inclusion of PP as the only comparator.

Other platinum-based chemotherapies are commonly used in China, including gemcitabine + platinum (GP), docetaxel + platinum (DP), and paclitaxel + platinum (TP). In clinical comparisons, efficacy and tolerability were different between PP and these platinum-based chemotherapies.[8,9] The costs of these chemotherapies vary substantially in China, ranging from $634 per 3 weeks with gemcitabine to $1562 per 3 weeks with pemetrexed. Previously published cost-effectiveness analyses of osimertinib in the Chinese setting did not use data on overall survival (OS) with osimertinib, and assumed same postprogression survival (ie, the duration from disease progression to death) for osimertinib and PP.[7] This assumption might underestimate the postprogression survival benefit of osimertinib. Moreover, the latest reimbursement price of osimertinib was set by the National Healthcare Security Administration in October 2018 through National Reimbursement Drug List negotiation. This reimbursement price of osimertinib, including the portion paid by basic medical insurance and out-of-pocket payment by patients, was discounted by 71% compared with its original price, and this reimbursement price would be applied to all provinces in China for 2 years.[10] An update and comprehensive economic evaluation of osimertinib is necessary for decision makers.

Our study therefore aimed to compare the cost-effectiveness of osimertinib with that of 4 commonly used platinum-based chemotherapies used as second-line treatments of advanced NSCLC after the failure of EGFR-TKI therapy in China.

MATERIALS AND METHODS

Overview

We developed a Markov model to analyze the cost-effectiveness of osimertinib versus PP, GP, DP, and TP as second-line treatments, from the perspective of China's health care system. A hypothetical cohort of patients with advanced NSCLC, a mean age of 65 years, and a World Health Organization (WHO) performance status of 0−2 was modeled. In consideration of potentially different health care resource utilization and clinical benefit associated with this patient population, we constructed 2 scenarios. *Scenario 1* considered patients who were confirmed T790M positive. The treatment group received osimertinib, while the comparator groups received 1 of 4 platinum-based chemotherapies (Figure 1A). In *scenario 2*, patients were those with progression after first-line EGFR-TKI therapy and with T790M-positive or -negative NSCLC. Patients in the treatment group first underwent genetic testing. Patients with T790M-positive disease received osimertinib, while patients with T790M-negative disease received PP chemotherapy. Patients in the comparator groups received 1 of 4 platinum-based chemotherapies directly, without genetic testing (Figure 1B).

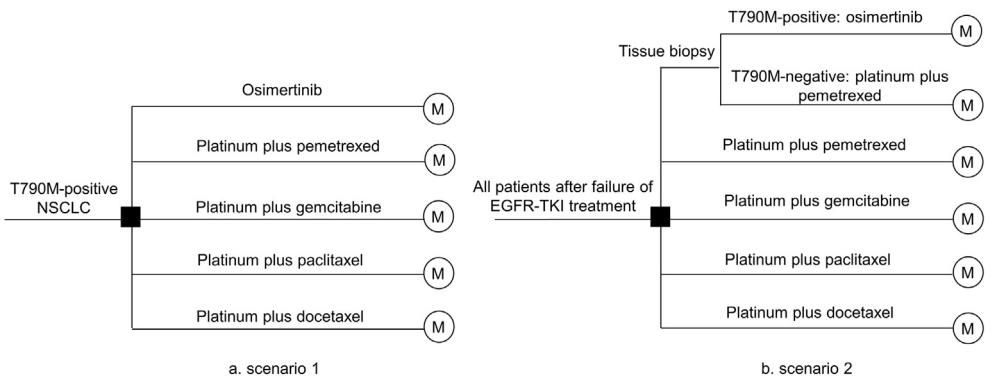

Figure 1. Target population and comparators. NSCLC = non–small cell lung cancer.

The model outcomes included life-years gained, quality-adjusted life-years (QALYs) gained, and costs, with cost-effectiveness assessed through the estimation of the incremental cost effectiveness ratio (ICER). As more than 2 alternatives were being compared, the most cost-effective treatment was inferred through a sequential cost-effectiveness analysis, which involved a comparison of the ICER of a less costly treatment with that of the next most costly treatment, excluding all alternatives that were either dominated or subject to extend dominance. A treatment was *dominated* when it was more costly and less effective than at least one other treatment, and a treatment was *subject to extended dominance* when it would never be cost-effective regardless of the decision maker's willingness-to-pay (WTP) threshold for a QALY.[11,12]

Model Structure

The Markov model consisted of 3 states: *progression-free, progression,* and *death* (Figure 2). All patients were in the progression-free state initially and could experience progression or death. The Markov cycle duration was 3 weeks, which was consistent with the schedule of platinum-based chemotherapies, and the time horizon was 10 years, which effectively equated to a lifetime horizon in the consideration of the poor prognosis of patients with advanced NSCLC.[13]

Patients in the osimertinib group received oral osimertinib 80 mg once a day until disease progression, in accordance with Chinese clinical guidelines.[14] The progression state then consisted of 3 substates: *platinum-based chemotherapy, monochemotherapy,* and *supportive care*. Patients could move to any substate directly when disease progressed. Patients receiving platinum-based chemotherapy could remain stable, move to monochemotherapy or supportive care, or die. Patients receiving monochemotherapy could remain stable, move to supportive care, or die. Patients receiving supportive care could only stay in this substate or die. The patients in the chemotherapy group received 1 of 4 platinum-based chemotherapies (ie, PP, GP, DP, or TP) for 4 cycles, followed by pemetrexed maintenance therapy until disease progression. The progression state consisted of 2 substates: *monochemotherapy* and *supportive care*. Patients receiving monochemotherapy could remain in the same substate, move to supportive care, or die. Patients receiving supportive care could only stay in this substate or die.

Scenario 1 compared the cost-effectiveness between osimertinib and chemotherapy. In scenario 2, the treatment group consisted of osimertinib and PP according to T790M-mutation status, while the comparator groups consisted of the chemotherapies only.

Clinical Inputs

The PFS data associated with osimertinib and PP in treating patients with T790M-positive advanced NSCLC were obtained from the AURA3 trial.[3] Due to the lack of available head-to-head randomized clinical trials comparing PP with other platinum-based chemotherapy (GP, TP, or DP) in patients with T790M-positive NSCLC (the scenario 1 target patients) and in patients with *EGFR* mutation–positive NSCLC (the scenario 2 target patients) from a systematic literature review (see

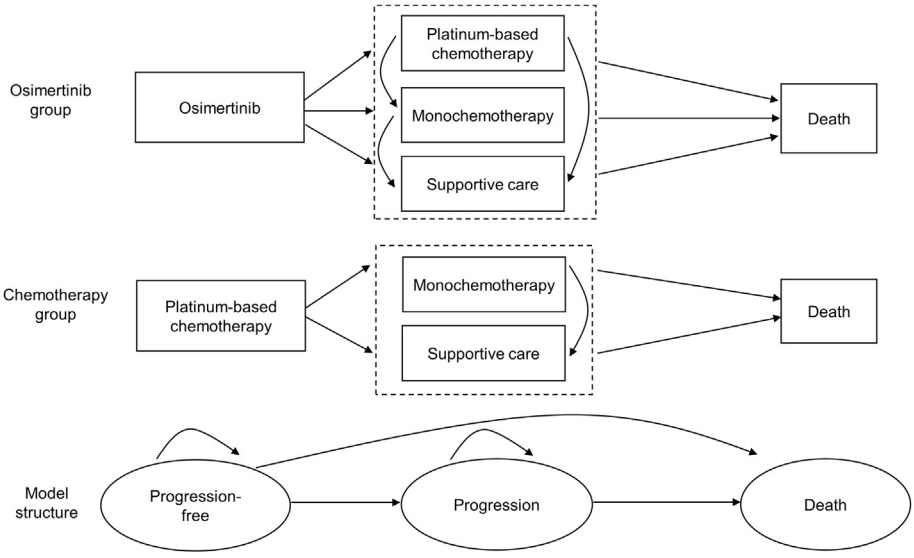

Figure 2. Markov model structure.

Supplemental Materials S1 in the online version at https://doi.org/10.1016/j.clinthera.2019.09.008), it was impossible to conduct indirect treatment comparisons of osimertinib, GP, DP, and TP using PP as the common comparator. Meanwhile, there were no available clinical trials in the second-line setting of GP, DP, and TP in patients with *EGFR* mutation–positive NSCLC or T790M-positive NSCLC. Given that the efficacy of second-line platinum-based chemotherapy after the failure of first-line EGFR-TKIs was similar to that of first-line platinum-based chemotherapy,[15,16] the PFS data on GP, DP, and TP were obtained from ENSURE (First-line Erlotinib Versus Gemcitabine/Cisplatin in Patients With Advanced *EGFR* Mutation-positive Non–Small Cell Lung Cancer: Analyses From the Phase III, Randomized, Open-Label, ENSURE Study),[17] WJTOG3405 (Gefitinib Versus Cisplatin Plus Docetaxel in Patients With Non-Small-Cell Lung Cancer Harbouring Mutations of the Epidermal Growth Factor Receptor [WJTOG3405]: An Open Label, Randomised Phase 3 Trial),[18] and NEJ002 (Gefitinib or Chemotherapy for Non–Small Cell Lung Cancer With Mutated EGFR),[19] respectively. The PFS data on PP as used in treating patients with T790M-negative and *EGFR* mutation–positive advanced NSCLC were derived from corresponding Kaplan–Meier curves from the IMPRESS (Gefitinib Plus Chemotherapy Versus Placebo Plus Chemotherapy in *EGFR* Mutation–Positive Non–Small Cell Lung Cancer After Progression on First-Line Gefitinib) trial.[20,21] These trials were chosen on the basis of the similarities of the patients' baseline characteristics. The patients in these trials all met the following criteria: locally advanced or metastatic (Stage IIIB/IV) NSCLC, *EGFR* mutation positive, WHO performance status of 0–2, and including Asian patients (Table I).

The OS data associated with osimertinib were obtained from the pooled data from 2 single-arm Phase II studies,[22] the AURA extension and AURA2, in which osimertinib used as a second- and further-line treatment was evaluated, because the OS data from AURA3 were not available at the time of the present study. There were 2 different estimations of the median OS of osimertinib based on the pooled data: one estimated value was 40.2 months, with 23.8% of patients having died at the November 2015 data cutoff,[6] and the other was 26.8 months, with 46% of patients having died at the November 2016 data cutoff.[22] The latter estimation was adopted in this study due to the longer period of follow-up time. OS data on PP used in treating patients with T790M-positive, T790M-negative or *EGFR* mutation–positive advanced NSCLC were obtained from the IMPRESS trial.[21] For GP, DP, and TP, due to the lack of OS data on any of these treatments in

Table I. Information on clinical trials and survival model parameters in base-case analysis.

Clinical Input	Clinical Trial	Patient Characteristics	Parameter Value
Osimertinib			
PFS	AURA3 (Phase III)[3]	Age 62 y; T790M positive (exon 19 deletion, 68%; L858R mutation, 30%); Stage IIIB/IV; WHO PS 0 to1	$\lambda = 0.0230$; $\gamma = 1.4611$
OS	AURA extension/AURA2 (Phase II)[22]	—	$\lambda = 0.0069$; $\gamma = 1.3989$
Platinum + pemetrexed			
PFS	AURA3 (Phase III)[3]	Age 63 y; T790M positive (exon 19 deletion, 62%; L858R mutation, 32%); Stage IIIB/IV; WHO PS 0 to 1	$\lambda = 0.0559$; $\gamma = 1.5404$
OS	IMPRESS (Phase III)[21]	Age 56 y; T790M positive; Stage IIIB/IV; WHO PS 0 to 1	$\lambda = 0.0133$; $\gamma = 1.3984$
PFS	IMPRESS (Phase III)[21]	Age 59 y; T790M negative; Stage IIIB/IV; WHO PS 0 to 1	$\lambda = 0.0516$; $\gamma = 1.5835$
OS	IMPRESS (Phase III)[21]	Age 59 y; T790M negative; Stage IIIB/IV; WHO PS 0 to 1	$\lambda = 0.0119$; $\gamma = 1.2579$
PFS	IMPRESS (Phase III)[20]	Age 58 y; *EGFR* mutation (exon 19 deletion, 65%; L858R mutation, 32%); Stage IIIB/IV; WHO PS 0 to 1	$\lambda = 0.0547$; $\gamma = 1.6182$
OS	IMPRESS (Phase III)[21]	Age 58 y; *EGFR* mutation (exon 19 deletion, 65%; L858R mutation, 32%); Stage IIIB/IV; WHO PS 0 to 1	$\lambda = 0.0123$; $\gamma = 1.3327$
Platinum + gemcitabine			
PFS	ENSURE (Phase III)[17]	Age 56 y; *EGFR* mutation (exon 19 deletion, 57%; L858R mutation, 43%); Stage IIIB/IV; WHO PS 0 to 2	$\lambda = 0.0361$; $\gamma = 1.7378$
OS	Tseng et al (retrospective study)[23]	Age 63 y; *EGFR* mutation; Stage IV; WHO PS 0 to 2 (99%)	$\lambda = 0.0127$; $\gamma = 1.4646$
Platinum + docetaxel			
PFS	WJTOG3405 (Phase III)[18]	Age 64 y; *EGFR* mutation (exon 19 deletion, 43%; L858R mutation, 57%); Stage IIIB/IV; WHO PS 0 to 1	$\lambda = 0.0345$; $\gamma = 1.8256$
OS	Tseng et al (retrospective study)[23]	Age 63 y; *EGFR* mutation; Stage IV; WHO PS 0 to 2 (99%)	$\lambda = 0.0127$; $\gamma = 1.4646$

Table I. (*Continued*)

Clinical Input	Clinical Trial	Patient Characteristics	Parameter Value
Platinum + paclitaxel			
PFS	NEJ002 (Phase III)[19]	Age 63 y; *EGFR* mutation (exon 19 deletion, 52%; L858R mutation, 42%); Stage IIIB/IV (92.1%); WHO PS 0 to 2	$\lambda = 0.0396$; $\gamma = 1.7571$
OS	Tseng et al (retrospective study)[23]	Age 63 y; *EGFR* mutation; Stage IV; WHO PS 0 to 2 (99%)	$\lambda = 0.0127$; $\gamma = 1.4646$

OS = overall survival; PFS = progression free survival; WHO PS = World Health Organization performance status.

patients with T790M-positive disease and in patients with *EGFR* mutation–positive advanced NSCLC after the failure of EGFR-TKI therapy, an integrated OS was used in accordance with a recently published retrospective study, in which different combinations of chemotherapies were used separately in patients with *EGFR* mutation–positive NSCLC after the failure of EGFR-TKI treatment.[23]

PFS and OS from the clinical trials listed here were used for calculating the transition probabilities. The individual patient data on PFS and OS with each treatment were replicated, following the methodology of Guyot et al.[24] Then we fit 5 commonly used parametric survival models, including exponential, Weibull, Gompertz, log-logistic, and log-normal. Weibull survival function ($S[t] = \exp[-\lambda t^{\gamma}]$) was chosen based on the visual inspection and statistical goodness-of-fit testing (see Supplemental Materials S2 in the online version at https://doi.org/10.1016/j.clinthera.2019.09.008). The mortality in the progression-free state was derived from the age-related mortality rate in the general population from Chinese life tables.[25] The elevated mortality was applied only in the progression state. When patients were moved to the progression state, 52.1% of the patients would receive subsequent active anticancer treatment in accordance with the treatment pattern of third-line therapy in patients with advanced NSCLC in clinical practice in China,[26] and the remaining patients would receive supportive care directly. The tissue biopsy was assumed to detect the T790M-mutation status, and the detection rate of T790M in patients with advanced NSCLC after the failure of EGFR-TKI therapy was 50.21% according to a systematic review.[27]

Costs and Utilities

The *direct medical costs* considered in this study were as follows: drug costs of osimertinib and chemotherapies, T790M genetic testing costs, follow-up costs, supportive care costs, serious adverse event (SAE)-treatment costs, and terminal care costs (Table II). The *drug cost of osimertinib* was based on the latest reimbursement price set by the National Healthcare Security Administration in October 2018. The *drug costs of chemotherapy* were estimated based on national average prices in China (see Supplemental Materials S3 in the online version at https://dogi.org/10.101c6/j.linthera.2019.09.008). 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.[41] The *cost of T790M genetic testing* was obtained from a published economic evaluation.[7]

If patients moved to the substate of receiving platinum-based chemotherapy in the progression state, they could receive any 1 of the 4 chemotherapies (ie PP, GP, DP, or TP) with the same probabilities (25%). Patients progressing with platinum-based chemotherapy could receive monochemotherapy (ie, pemetrexed, gemcitabine, docetaxel, paclitaxel) that they had not previously received (see Supplemental Materials S4 in the online version at https://doi.org/10.1016/j.clinthera.2019.09.008). The *cost of supportive care* came from a published economic evaluation from China.[33]

The *costs of follow-up* included the costs of outpatient-based physician visits, hospitalizations, and laboratory tests (impatient and/or outpatient), and were obtained from a published study comparing the costs of 4 treatments of advanced NSCLC in

Table II. Input parameters for the Markov model.

Parameter	Base Value	Distribution	Source
Costs, year-2018 USD			
Drug costs per cycle			
Osimertinib	1682	Fixed	Reimbursement price
Pemetrexed	1562	γ (74,21.2)	Calculation
Gemcitabine	634	γ (16,39.4)	Calculation
Paclitaxel	1100	γ (21,51.3)	Calculation
Docetaxel	712	γ (18, 39.9)	Calculation
Cisplatin	16	γ (6.3,2.4)	Calculation
Carboplatin	87	γ (19,4.5)	Calculation
Costs of adverse events			
Diarrhea	6	γ (96,0.06)	Zhang et al[28]
Vomiting	94	γ (96,0.98)	Chen et al[29]
Nausea	51	γ (96,0.53)	Wu et al[30]
Fatigue/Asthenia	133	γ (96,1.39)	Wu et al[30]
Neutropenia	533	γ (96,1.15)	Wu et al[30]
Anemia	614	γ (96,5.87)	Wu et al[30]
Stomatitis	6	γ (96,0.06)	Chen et al[29]
Rash	6	γ (96,0.06)	Zhang et al[28]
Leukopenia	111	γ (96,1.15)	Zheng et al[31]
Thrombocytopenia	560	γ (96,5.53)	Zheng et al[31]
Other costs			
Tissue biopsy for T790M	282	γ (96,2.94)	Wu et al[7]
Follow-up cost for osimertinib per cycle	125	γ (96,1.30)	Liu et al[32]
Follow-up cost for chemotherapy per cycle	494	γ (96,5.14)	Liu et al[32]
Supportive care	358	γ (96,4.7)	Lu et a[33]
Terminal care cost	2467	γ (15,161)	Cao et al[34]; Lu et al[35]
Utility values			
Utility of progression-free state	0.77	β (198,60)	Shen et al[36]
Utility of progression state	0.70	β (21,9)	Shen et al[36]
Disutility from diarrhea	0.07	β (88,1187)	Nafees et al[37]
Disutility from vomiting	0.12	β (83,620)	Nafees et al[37]
Disutility from nausea	0.12	β (83,620)	Nafees et al[37]
Disutility from fatigue/asthenia	0.07	β (88,1187)	Nafees et al[37]
Disutility from neutropenia	0.20	β (76,307)	Nafees et al[37]
Disutility from anemia	0.09	β (86.883)	Beusterien et al[38]
Disutility from stomatitis	0.15	β (81,458)	Lloyd et al[39]
Disutility from rash	0.10	β (85,778)	Nafees et al[37]
Disutility from leukopenia*	0.20	β (76,307)	Assumption
Disutility from thrombocytopenia*	0.20	β (76,307)	Assumption
Duration of adverse events, wk			
Diarrhea	1	γ (96,0.01)	Expert opinion
Vomiting	2	γ (96,0.02)	Expert opinion
Nausea	4	γ (96,0.04)	Expert opinion

Table II. (*Continued*)

Parameter	Base Value	Distribution	Source
Fatigue/asthenia	4	γ (96,0,04)	Expert opinion
Neutropenia	13	γ (96,0.14)	Expert opinion
Anemia	1	γ (96,0.01)	Expert opinion
Stomatitis	2	γ (96,0.02)	Expert opinion
Rash	4	γ (96,0.04)	Expert opinion
Leukopenia	12	γ (96,0.12)	Expert opinion
Thrombocytopenia	1	γ (96,0.01)	Expert opinion
T790M mutation rate	50.21%	β (47.3,46.9)	Wang et al[27]
Discount rate	3%	Uniform (0,0.08)	Liu[40]

* Assuming the disutility of leukopenia and thrombocytopenia are the same as that of neutropenia.

China.[32] As in previous economic evaluations,[34,35] the *costs of terminal care* during the final month of life were adopted from a cost analysis of advanced cancer in China. To incorporate the impact of AEs into this analysis, the estimation of the prevalence of each AE in the osimertinib group was derived from the AURA3 trial, and from IMPRESS, ENSURE, WJTOG3405, and NEJ002 trials for PP, GP, DP, and TP respectively.[3,17–21] Because of the potential considerable impact on health care resource utilization, the effects of the following SAEs (grade 3/4) were considered: diarrhea, vomiting, nausea, fatigue, neutropenia, anemia, stomatitis, rash, leukopenia, and thrombocytopenia. The *health care resource utilization associated with treating an SAE* was calculated by multiplying the prevalence of the SAE by the cost of treating each event of the SAE.[28–31] All costs were adjusted by Consumer Price Index for medical care services and discounted at 3% per year, and are presented in year-2018 US dollars (USD) using an exchange rate of 1 USD = 6.367 CHY.

Health utility values were obtained from a cross-sectional survey conducted at the Shanghai Chest Hospital in China, using the EQ-5D-3L to elicit preferences in patients with advanced NSCLC.[36] The mean (SD) health utilities of second-line treatment and third- or later-line treatment were 0.77 (0.17) and 0.70 (0.20), respectively. *Disutility* associated with SAEs per event were derived from published literature,[37–39] and the duration of each SAE came from expert opinion (Table II). The health outcomes also were discounted by 3% per year.

Sensitivity Analyses

In consideration of the uncertainty of parameters and assumptions, deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA) were conducted to evaluate the robustness of the base-case results. In the deterministic sensitivity analysis, the following scenarios were considered. For PFS of PP in scenario 1, the analysis was conducted using the Kaplan–Meier curve from the IMPRESS trial.[21] For PFS of GP in both scenarios, the analysis was conducted using the clinical data from the OPTIMAL (Erlotinib Versus Chemotherapy as First-Line Treatment for Patients With Advanced *EGFR* Mutation-Positive Non–Small Cell Lung Cancer [OPTIMAL, CTONG-0802]: A Multicentre, Open-Label, Randomised, Phase 3 Study) trial.[42] For utilities of the progression-free and progression states, the analysis was conducted based on a review of health state utility values used in UK National Institute for Health and Care Excellence appraisals in patients with advanced NSCLC,[43] which showed the ranges of utility values used for progression-free and progressive disease as 0.62 to 0.82 and 0.47 to 0.69, respectively. For utilities of osimertinib and chemotherapy in the progression-free state, the analysis was conducted on the basis of utilities derived from the AURA2 and IMPRESS trials.[6]

The PSA was conducted using second-order Monte Carlo simulation by running 5000 iterations to account for uncertainty in model parameters. γ Distributions were used for costs and duration of SAEs; β distributions were used for utilities and

percentages. Uncertainty of all parameters of the parametric survival model were assessed through the Cholesky decomposition.[44] Within the PSA, values were randomly drawn from the distribution of each parameter to obtain estimates of the costs and QALYs of each treatment. Cost-effectiveness acceptability curves were considered to show the probabilities of each treatment being cost-effective at a wide range of WTP thresholds.

RESULTS

Base-Case Analysis

In scenario 1, in patients with T790M-positive disease, DP was associated with the lowest QALYs and costs, while osimertinib was associated with the highest QALYs and costs (Table III). Treatment with osimertinib resulted in 1.849 QALYs gained, with increases of 0.846, 0.798, 0.814, and 0.671 QALY when compared with those of DP, GP, TP, and PP, respectively. The sequential analysis showed that TP was dominated by GP, PP was subject to extended dominance through GP and osimertinib, and the ICERs were $7791 for GP versus DP, and $24,976 for osimertinib versus GP.

In scenario 2, in all patients with *EGFR* mutation–positive disease, the orders of the QALYs and costs of each treatment were consistent with those in scenario 1. DP was associated with both the lowest QALYs and costs, while osimertinib was associated with the highest QALYs and costs. Treatment with osimertinib resulted in 1.811 QALYs gained, an increase of 0.808, 0.760, 0.776, and 0.376 QALY when compared with those of DP, GP, TP, and PP, respectively. The sequential analysis showed that TP was dominated by GP, and the ICERs were 7791 USD for GP versus DP, 13,861 USD for PP versus GP, and 25,821 USD for osimertinib versus PP.

Sensitivity

The deterministic sensitivity analysis showed that the ICERs of osimertinib were between 25,000 and 30,000 USD (see Supplemental Materials S5 in the online version at https://doi.org/10.1016/j.clinthera.2019.09.008). When the PFS data on PP in patients with T790M-positive disease were obtained from the IMPRESS trial,[21] the costs and QALYs of PP were 28,832 USD and 1.174 QALYs gained, respectively, resulting in an ICER of 20,204 USD/QALY compared with GP. When the PFS data on GP were obtained from the OPTIMAL trial,[42] DP and TP were dominated by GP in both scenarios. When the analysis was conducted on the basis of utilities derived from other sources,[6,43] the sequential analysis

Table III. Cost-effectiveness of osimertinib and four chemotherapies as second-line treatments in patients with advanced NSCLC.

Scenario/Treatment	Costs, year-2018 USD	QALYs	LYs	Difference		ICER, USD/QALY
				Costs, year-2018 USD	QALYs	
Scenario 1						
DP	25,972	1.003	1.475	—	—	—
GP	26,344	1.051	1.475	371	0.048	7791
TP	26,644	1.035	1.475	300	–0.016	Dominated
PP	30,328	1.178	1.641	3985	0.127	Extended dominance
Osimertinib	46,271	1.849	2.539	19,927	0.798	24,976
Scenario 2						
DP	25,972	1.003	1.475	—	—	—
GP	26,344	1.051	1.475	371	0.048	7791
TP	26,644	1.035	1.475	300	–0.016	Dominated
PP	31,669	1.435	2.009	5325	0.384	13,861
Osimertinib	41,379	1.811	2.519	9710	0.376	25,821

GP = gemcitabine + platinum; DP = docetaxel + platinum; ICER = incremental cost-effectiveness ratio; LYs = life-years; NSCLC = non–small cell lung cancer; PP = pemetrexed + platinum; QALYs = quality-adjusted life-years; TP = paclitaxel + platinum.

results were very similar to those from the base-case analysis.

The PSA results are shown in Figure 3. In scenario 1, when the WTP threshold was 30,000 USD/QALY, the probability that osimertinib would be cost-effective was 57.7%, followed by 13.3% with GP, 11.9% with PP, 7.0% with DP, and 10.1% with TP. In scenario 2, when the WTP threshold was 30,000 USD/QALY, the probability that osimertinib would be cost-effective was 58.4%, followed by 38.4% with PP, 1.1% with GP, 1.1% with DP, and 1.0% with TP. When the WTP threshold was 50,000 USD/QALY, the probabilities that osimertinib would be cost-effective were 78.6% and 77.3% in scenarios 1 and 2, respectively.

DISCUSSION

To our knowledge, this study is the first to have compared the cost-effectiveness of osimertinib and 4 platinum-based chemotherapies used as second-line treatments of *EGFR*-mutated advanced NSCLC in China. We adopted a perspective of China's health care system, used the latest discounted price of osimertinib in China, and utilized administrative databases and published studies to obtain costs and health care resource utilization associated with advanced NSCLC in China. The model structure and clinical practice patterns were tailored to comply with Chinese clinical guidelines. The results showed that osimertinib could improve QALYs at higher costs compared with 4 chemotherapies, and that when the WTP thresholds were 30,000 USD/QALY and 50,000 USD/QALY, the probabilities of osimertinib being cost-effective were >50% and >75%, respectively.

The patients receiving PP gained more QALYs compared with patients receiving the other 3 chemotherapies, as a result of better clinical outcomes and fewer SAEs; this finding was consistent with those from several previous studies.[8,9] Meanwhile, based on Kaplan−Meier curves in published clinical trials, the median PFS and OS of PP in T790M-positive patients were 4.4 and 14.1 months, and 5.4 and 19.5 months in patients with EGFR mutation−positive disease,[3,20,21] which yielded more QALYs with PP in scenario 2 than in scenario 1. The differences in QALYs among GP, TP, and DP were relatively small. With regard to the clinical efficacy of GP, TP, and DP, a meta-analysis by Brown et al[45] showed no significant differences in OS between GP and TP (HR = 1.03; 95% CI, 0.94−1.13), and between TP and DP (HR = 1.02; 95% CI, 0.79−1.32) in advanced NSCLC, which might to some extent demonstrate that it was reasonable to use the same OS data for analyses of GP, DP, and TP in this study. Given the similar efficacy among GP, DP, and TP, the differences in QALYs might have depended mostly on differences in SAEs. Because DP may be associated with more SAEs compared with GP and TP, the QALYs with DP were less than those with GP and TP.

Our finding of benefits with osimertinib over chemotherapies was different from the findings from the study by Wu et al,[7] in which osimertinib was reported not likely to be cost-effective. Different results between these 2 studies likely were mostly due

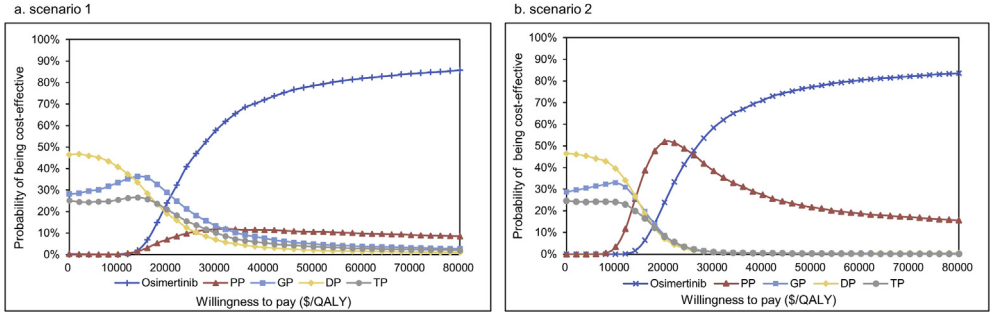

Figure 3. Cost-effectiveness acceptability curves in scenario 1 and scenario 2. The probabilities of each treatment being cost-effective at different willingness-to-pay thresholds are shown. DP = docetaxel + platinum; GP = gemcitabine + platinum; PP = pemetrexed + platinum; TP = paclitaxel + platinum.

to the different prices of osimertinib. When the same drug price was used in the present study, the probabilities that osimertinib would be cost-effective were only 23.3% and 26.6% in scenarios 1 and 2, respectively, when the WTP threshold was 30,000 USD/QALY, which meant the 71% discount in price of osimertinib could improve the probability of osimertinib being cost-effective by 30%. During the National Reimbursement Drug List negotiation between the National Healthcare Security Administration and pharmaceutical companies in 2018, the prices of the 17 cancer drugs were cut by an average of 56.7% compared with their original prices, and osimertinib was discounted by 71% compared with its original price,[10] which would remarkably reduce the economic burden of patients with cancer in China.

There were some limitations in this study. First, no head-to-head randomized clinical trials comparing osimertinib with GP, DP, or TP were available; thus, the survival data on osimertinib, GP, DP, and TP were derived from their corresponding clinical studies. The WHO performance status in the AURA3 trial was 0−1, while the performance statuses in the ENSURE, WJTOG3405, and NEJ002 trials were 0−2, which might have led to an overestimation of the efficacy of osimertinib. Second, the baseline characteristics of the patients (ie, age, race, and *EGFR* mutation type) were not exactly the same in the selected clinical studies, which might have led to bias in this economic evaluation. However, the sensitivity analysis indicated that the results of this study were robust when we considered the potential changes in efficacy of these treatments. Third, due to the lack of OS data on osimertinib from head-to-head randomized clinical trials, we could only estimate the OS from the pooled data from the AURA extension and AURA2. Because patients receiving third- or later-line treatment were involved, the OS of osimertinib might have been underestimated. Therefore, it is essential to further examine the current findings when mature OS data on osimertinib are available. Fourth, the clinical efficacies of GP, DP, and TP in patients with T790M-positive NSCLC were assumed to have been consistent with those in patients with *EGFR* mutation−positive NSCLC due to the current paucity of T790M-positive specific efficacy of these 3 chemotherapies. Fortunately, this uncertainty had little effect on the estimations of cost-effectiveness of osimertinib. Finally, the adoption of osimertinib as a second-line treatment of advanced NSCLC might change the clinical pathway, but the effect of osimertinib on follow-up treatments remains unknown. Although the model structure and medication patterns were conducted based on Chinese clinical guidelines and practice in this study, studies from clinical practice would be useful for further confirming these findings.

CONCLUSION

Osimertinib is likely to be cost-effective compared with 4 platinum-based chemotherapies commonly used as second-line treatment of advanced NSCLC, based on the latest reimbursement price of osimertinib in China.

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DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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SUPPLEMENTARY MATERIAL

S1 Systematic literature review

AURA3 trial compared progression-free survival (PFS) for osimertinib versus platinum–pemetrexed (PP) in patients with EGFR T790M positive advanced non-small cell lung cancer (NSCLC) (scenario 1 target population). PFS and overall survival (OS) for PP in the treatment of patients with EGFR mutation positive advanced NSCLC (scenario 2 target population) were obtained from IMPRESS trial. Therefore, we searched for relevant clinical studies to obtain the survival data (PFS and OS) for platinum plus paclitaxel (TP), platinum plus docetaxel (DP) and platinum plus gemcitabine (GP) in treating these target patients. In addition, the baseline characteristics of patients from these studies should be consistent with AURA3 and IMPRESS as much as possible to ensure the comparability of these clinical studies.

Inclusion and exclusion criteria

To be eligible for inclusion, clinical studies had to meet all of the following criteria.

- Population: Locally advanced or metastatic (state IIIB/IV) NSCLC, EGFR mutation-positive; WHO performance status score of 0–2, including Asian patients.
- Interventions: TP, DP and GP
- Comparators: no restriction
- Outcomes: PFS and OS data, which had sufficient data to derive individual patient data (IPD) for the estimation of transition probabilities
- Design: Randomized control trial (RCT) study or real-world observational study
- Language: English or Chinese

Studies were excluded if any of the following exclusion criteria was met:

- Duplicates;
- Non-clinical research literature (economic evaluation research; pharmacological research, etc.);
- Case study;
- Literature review;
- Conference abstracts;
- Published before 2008;
- Others (receiving treatment after second-line, etc.).

Search strategy

A systematic literature review was conducted to identify published clinical studies that evaluated the clinical efficacy of TP, DP and GP in patients with EGFR T790M positive advanced NSCLC and patients with EGFR mutation-positive advanced NSCLC up to September 30, 2018. We conducted the search process in PubMed, the Cochrane library, Embase, China National Knowledge Infrastructure Database (CNKI), Wan-Fang Database, Chinese Scientific Journals Full-text Database (VIP). The search strategy included the following terms:

#1 "Gemcitabine [Title/Abstract]"
#2 "Docetaxel [Title/Abstract]"
#3 "Paclitaxel [Title/Abstract]"
#4 "non-small cell lung cancer [Title/Abstract]" OR "NSCLC[Title/Abstract]"
#5 "Cisplatin [Title/Abstract]" OR "Carboplatin [Title/Abstract]" OR "Platinum [Title/Abstract]" OR "combined chemotherapy [Title/Abstract]"
#6 #1 AND #4 AND #5
#7 #2 AND #4 AND #5
#8 #3 AND #4 AND #5

Literature screening and data extraction

Two researchers independently screened the literature and cross-checked, and disagreements were resolved by discussion or judged by the third researcher. The following information was extracted from each selected study:1) name of clinical trial 2) baseline characteristics of patients 3) PFS and OS Kaplan–Meier curves 4) the number of patients at risk at each time point.

Results

Figure S1, Figure S2 and Figure S3 represent the selection flowcharts of clinical studies for TP, DP and GP respectively. A total of 8800, 5416 and 9511 relative studies for TP, DP and GP were identified respectively through database searching. There were no available clinical studies for GP, TP and DP in patients with T790M positive advanced NSCLC, thus we assumed that the clinical efficacy of GP, DP and TP for these patients was consistent with that of patients with EGFR mutation-positive NSCLC. In addition, there were no available clinical studies for

GP, TP and DP as second-line treatments after failure of EGFR-TKI therapy. Fortunately, Miyauchi et al.[1] and Tseng et al.[2] reported that the efficacy of second-line platinum-based chemotherapy after progression following first-line EGFR-TKI was similar to first-line platinum-based chemotherapy in advanced patients with EGFR mutation-positive NSCLC, thus the clinical studies that the patients received GP, TP and DP as first-line treatment were adopted. PFS data for GP in ENSURE trial were used in the base-case analysis based on the similarities of patient baseline characteristics with other chosen clinical studies,[3] and PFS data for GP in OPTIMAL trail were used in sensitive analysis.[4] PFS data for DP and TP were derived from WJTOG3405 trial and NEJ002 trial,[5,6] respectively.

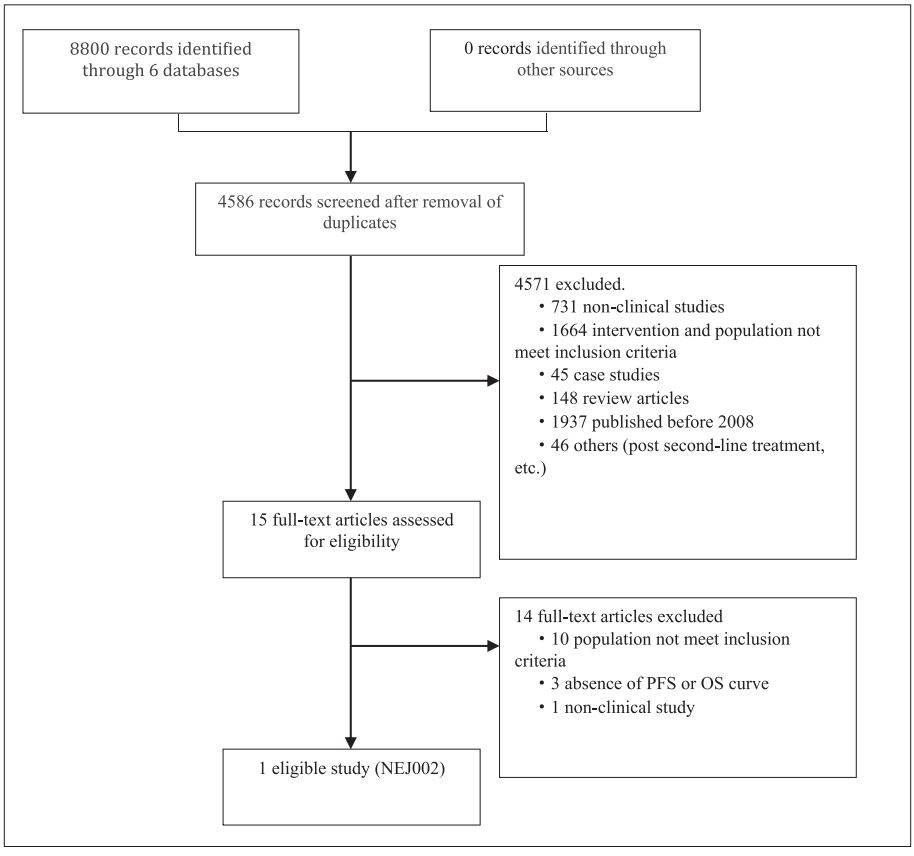

Figure S1. Flowchart of searching clinical trials for TP.

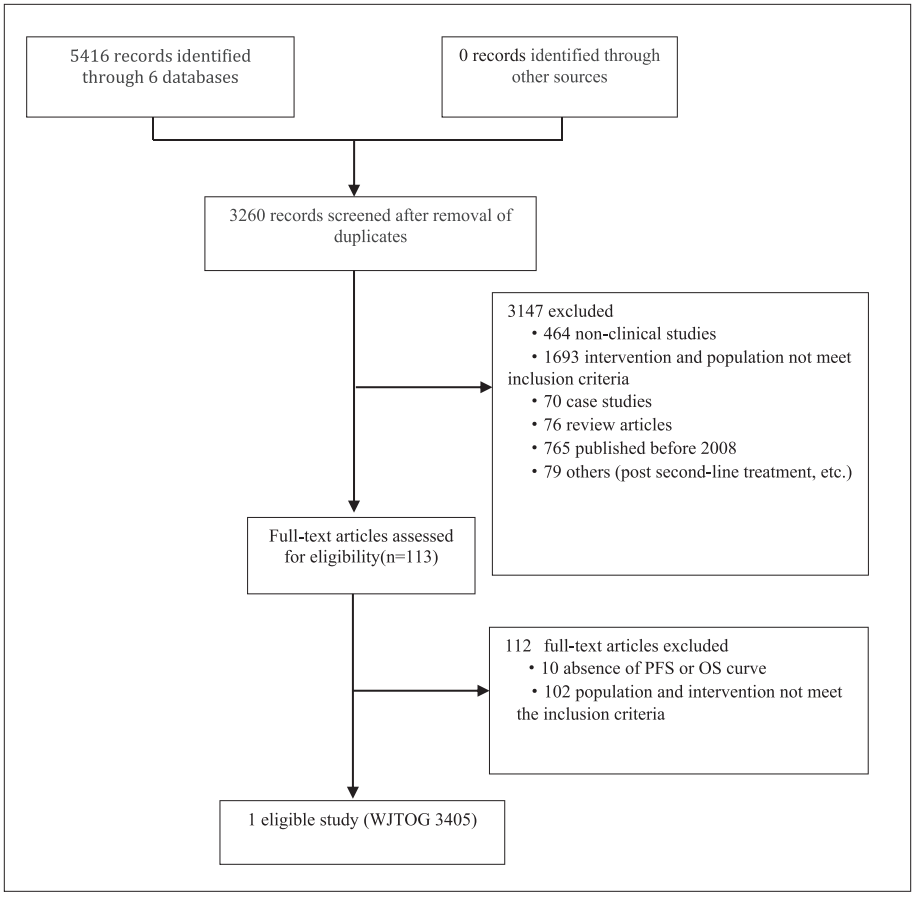

Figure S2. Flowchart of searching clinical trials for DP.

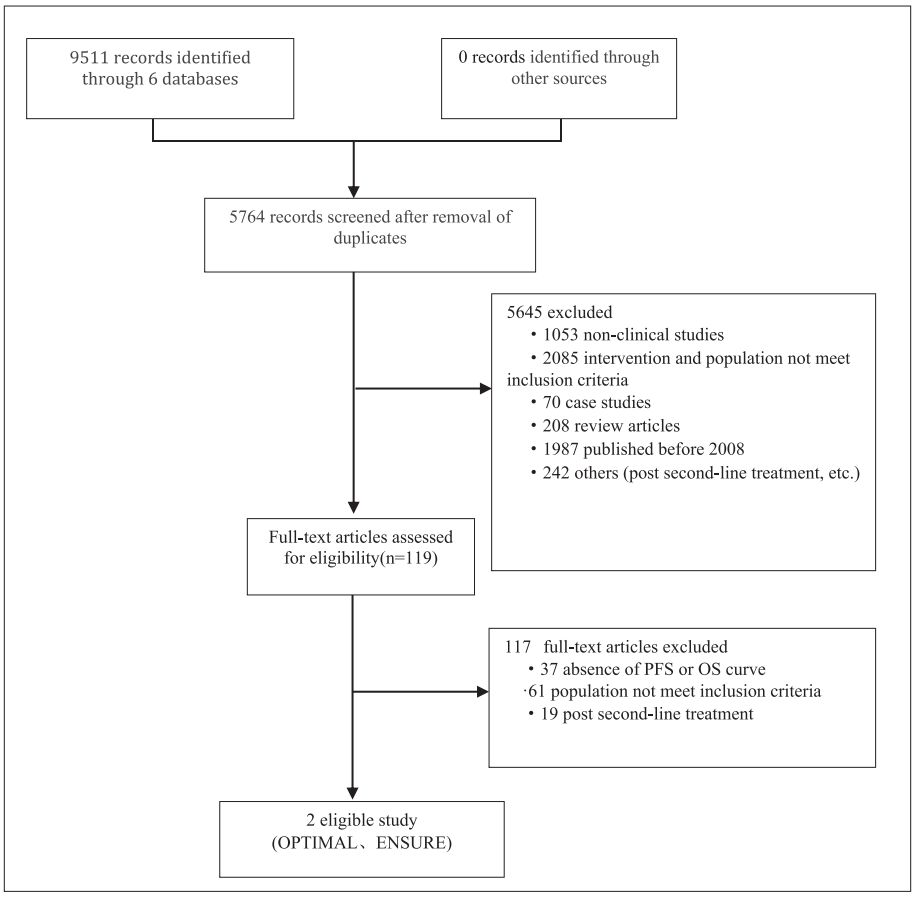

Figure S3. Flowchart of searching clinical trials for GP.

S2 Survival model selection

The fitting and extrapolation of PFS and OS Kaplan–Meier curves were based on the commonly used parametric models, including exponential, Weibull, Gompertz, log-logistic, log-normal, and the most reasonable survival function was chosen based on visual inspection and statistical goodness-of-fit using Bayesian information criteria (BIC) and Akaike information criteria (AIC).

Here, we just took the PFS data of osimertinib and PP for example. The visual fits and statistical fits of five parametric survival models for PFS of osimertinib are presented in Figure S4 and Table S1. The visual inspection of the PFS curves showed that all curves had a similar fit until 10th month where 50% patients had progressed. Disease progression was underestimated by the exponential model prior to this point and was overestimated beyond it. The extrapolation of both the log-logistic and log-normal produced extended tails that probably overestimated PFS beyond 40th month even if they had better statistical fits. For instance, about 7% and 3% of patients would remain in progression-free state at 40th months and 60th months respectively using log-logistic and log-normal function, while only 0.6% and 0.0% patients would remain in this state at corresponding months using Weibull survival function. Of the two remaining distributions, the Weibull distribution had the higher statistical fit than Gompertz distribution. Therefore, the Weibull distribution was the most reasonable parametric model for PFS of osimertinib.

Visual fits and statistical fits of five parametric survival models for PFS of PP are presented in Figure S5 and Table S2. PFS was overestimated by the exponential model, log-logistic model and log-normal model since the 8th month, and the worst statistic fit was observed in exponential model. The Gompertz distribution had a relatively poor statistical fit compared with Weibull distribution. Therefore, the Weibull model was the most reasonable parametric model for PFS of PP.

Therefore, the Weibull distribution was selected for all PFS and OS of each treatment on the basis of the visual inspection and statistical goodness-of-fit in base-case analysis.

S3 Chemotherapy drugs cost

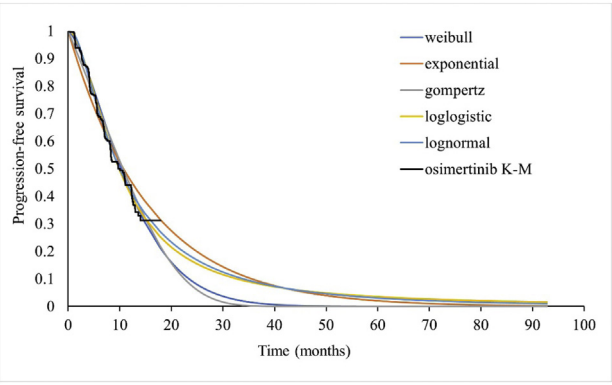

Figure S4. Osimertinib (AURA3) PFS Kaplan–Meier curve fitting and extrapolation.

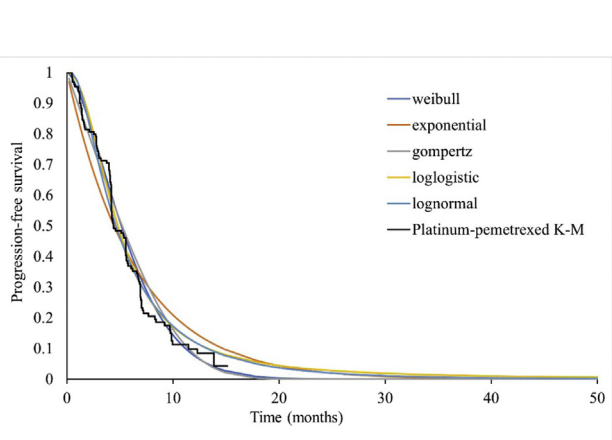

Figure S5. Platinum-pemetrexed (AURA3) PFS Kaplan–Meier curve fitting and extrapolation.

Table S1. The summary of osimertinib (AURA3) PFS distributions

Distribution	Median PFS	% Alive at 10 months	% Alive at 40 months	% Alive at 60 months	AIC	BIC
Weibull	10.29	51.4%	0.6%	0.0%	560.00	567.20
Exponential	10.73	52.4%	7.5%	2.1%	581.80	585.50
Gompertz	10.63	52.8%	0.0%	0.0%	574.50	581.80
Log-logistic	9.86	49.3%	7.2%	3.6%	552.40	559.60
Log-normal	9.97	50.0%	7.3%	3.0%	549.10	556.40

AIC, Akaike information criteria; BIC, Bayesian information criteria; PFS, progression-free survival.

Table S2. The summary of platinum-Pemetrexed (AURA3) PFS distributions

Distribution	Median PFS	% Alive at 10 months	% Alive at 40 months	% Alive at 60 months	AIC	BIC
Weibull	5.13	14.4%	0.0%	0.0%	299.4	305.3
Exponential	4.43	21.0%	0.2%	0.0%	324.0	327.0
Gompertz	5.20	16.1%	0.0%	0.0%	310.7	316.6
Log-logistic	4.80	17.0%	1.0%	0.0%	300.8	306.7
Log-normal	4.61	17.3%	0.4%	0.0%	301.9	307.7

AIC, Akaike information criteria; BIC, Bayesian information criteria; PFS, progression-free survival.

The drug costs of chemotherapies were estimated based on national average biding prices in China. The prices of one drug may have a relatively wide range due to a large number of manufactures in China. In order to find a representative price in base-case analysis, we obtained the average price following three steps: Firstly, the manufacturers and specifications of chemotherapy drugs were obtained from China Food and Drug Administration (CFDA). Then, we obtained the latest prices for each manufacturer and specification from a drug price database that need to pay for access, named MINEI, which include detailed information of drug prices in different provinces every year. Secondly, we calculated the average price of specific specification based on manufacturers' market shares, which were derived from more than 400 public hospitals in 16 cities. Using the average price of specific specification, we calculated the drug costs per cycle of specific specification according to clinical usage and dosage. Finally, we obtained the average drug costs per cycle of chemotherapy, which were the average cost of each specification weighted by its market share. 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.

Table S3. Dosage and schedule for chemotherapy drugs

Regimens	Agents	Treatment dose	Schedule
Pemetrexed-cisplatin/carboplatin	Pemetrexed Cisplatin Carboplatin	500 mg/m^2, d1 75 mg/m^{2,} d1 AUC 5, d1	Every 3 weeks for a maximum of 4 cycles. a cycle: 21-day
Gemcitabine-cisplatin/carboplatin	Gemcitabine Cisplatin Carboplatin	1000 mg/m^2, d1, d8 75 mg/m^2, d1 AUC 5, d1	Every 3 weeks for a maximum of 4 cycles. a cycle: 21-day
Paclitaxel-cisplatin/carboplatin	Paclitaxel Cisplatin Carboplatin	200 mg/m^2, d1 75 mg/m^2, d1 AUC 5, d1	Every 3 weeks for a maximum of 4 cycles. a cycle: 21-day
Docetaxel-cisplatin/carboplatin	Docetaxel Cisplatin Carboplatin	75 mg/m^2, d1 75 mg/m^2, d1 AUC 5, d1	Every 3 weeks for a maximum of 4 cycles. a cycle: 21-day

Table S4. Drug costs of pemetrexed per cycle

Specification	Manufacturer (number)		Price ($) Mean (range)	Market share	Costs per cycle ($)
	Domestic	Foreign	Mean (range)		
100 mg	8	1	193 (78–511)	12.14%	1656
200 mg	6	0	306 (133–329)	64.42%	1359
500 mg	13	1	1237 (245–1751)	23.44%	2073
					Average cost: 1562

Table S5. Drug costs of gemcitabine per cycle

Specification	Manufacturer (number)		Price ($) Mean (range)	Market share	Costs per cycle ($)
	Domestic	Foreign	Mean (range)		
200 mg	14	1	37 (9–59)	76.01%	634
1 g	10	1	184 (54–270)	23.99%	635
					Average cost: 634

Table S6. Drug costs of docetaxel per cycle

Specification	Manufacturer (number)		Price ($) Mean (range)	Market share	Costs per cycle ($)
	Domestic	Foreign	Mean (range)		
0.5 ml:20 mg	15	1	119 (28–233)	91.32%	758
1.5 ml:60 mg	2	0	124 (82–124)	5.55%	267
1 ml:40 mg	6	0	43 (41–106)	2.99%	139
1 ml:20 mg	6	1	124 (21–124)	0.13%	800
2 ml:80 mg	10	0	158 (117–213)	0.01%	254
					Average cost: 712

Table S7. Drug costs of paclitaxel per cycle.

Specification	Manufacturer (number)		Price ($) Mean (range)	Market share	Costs per cycle ($)
	Domestic	Foreign	Mean (range)		
5 ml:30 mg	40	2	100 (4.5–144)	94.22%	1151
10 ml:60 mg	10	0	48 (18–55)	4.28%	263
16.7 ml:100 mg	11	1	64 (30–97)	1.51%	220
					Average cost: 1100

S4 Treatment pathway

S5. The results of deterministic sensitivity analysis (DSA)

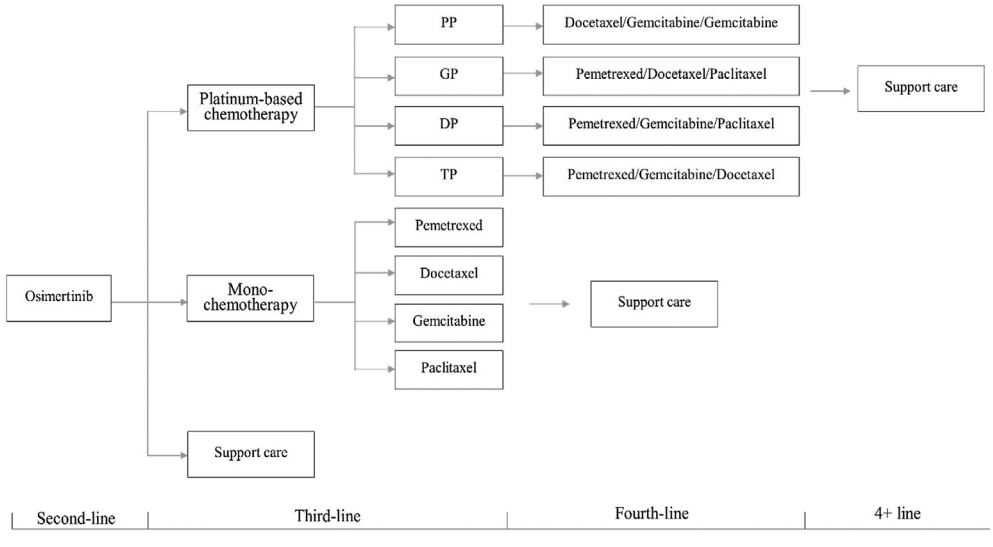

Table S8. The results of DSA for scenario 1

	Costs ($)	QALYs	LYs	Difference		ICER ($/QALY)
				Costs ($)	$/QALY	
1) PFS data of PP obtained from IMPRESS trial						
DP	25972	1.003	1.475	—	—	—
GP	26344	1.051	1.475	371	0.048	7791
TP	26644	1.035	1.475	300	−0.016	Dominated
PP	28832	1.174	1.641	2489	0.123	20204
Osimertinib	46271	1.849	2.539	17439	0.675	25847
2) PFS data of GP obtained from OPTIMAL trial						
GP	24415	1.046	1.475	—	—	—
DP	25972	1.003	1.475	1557	−0.043	Dominated
TP	26644	1.035	1.475	2229	−0.011	Dominated
PP	30328	1.178	1.641	5913	0.131	Extended dominance
Osimertinib	46271	1.849	2.539	21856	0.803	27234
3) utility of Progression-free state (0.82)						
DP	25972	1.029	1.475	—	—	—
GP	26344	1.078	1.475	371	0.049	7523
TP	26644	1.061	1.475	300	−0.018	Dominated
PP	30328	1.204	1.641	3985	0.126	Extended dominance
Osimertinib	46271	1.901	2.539	19927	0.823	24220
4) utility of progression-free state (0.62)						
DP	25972	0.931	1.475	—	—	—
GP	26344	0.973	1.475	371	0.043	8671
TP	26644	0.963	1.475	300	−0.011	Dominated
PP	30328	1.102	1.641	3985	0.129	Extended dominance
Osimertinib	46271	1.700	2.539	19927	0.727	27411
5) utility of progression state (0.47)						
DP	25972	0.775	1.475	—	—	—
GP	26344	0.830	1.475	371	0.055	6719
TP	26644	0.806	1.475	300	−0.024	Dominated
PP	30328	0.914	1.641	3985	0.085	Extended dominance
Osimertinib	46271	1.491	2.539	19927	0.661	30125
6) utility of progression state (0.69)						
DP	25972	0.991	1.475	—	—	—
GP	26344	1.039	1.475	371	0.048	7723
TP	26644	1.023	1.475	300	−0.016	Dominated
PP	30328	1.163	1.641	3985	0.124	Extended dominance
Osimertinib	46271	1.829	2.539	19927	0.790	25217

(*continued on next page*)

Table S8. (*Continued*)

	Costs ($)	QALYs	LYs	Difference		ICER ($/QALY)
				Costs ($)	$/QALY	
7) utilities for osimertinib and chemotherapy from AURA2 and IMPRESS						
DP	25972	1.008	1.475	—	—	—
GP	26344	1.056	1.475	371	0.048	7738
TP	26644	1.040	1.475	300	−0.016	Dominated
PP	30328	1.183	1.641	3985	0.126	Extended dominance
Osimertinib	46271	1.886	2.539	19927	0.830	24016

GP, platinum plus gemcitabine; PP, platinum plus pemetrexed; DP, platinum plus docetaxel; TP, platinum plus paclitaxel; LYs, life-years; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival.

Table S9. The results of DSA for scenario 2

	Costs ($)	QALYs	LYs	Difference		ICER ($/QALY)
				Costs ($)	$/QALY	
1) PFS data of GP obtained from OPTIMAL trial						
GP	24415	1.046	1.475	—	—	—
DP	25972	1.003	1.475	1557.36	−0.043	Dominated
TP	26644	1.035	1.475	2229	−0.011	Dominated
PP	31669	1.435	2.009	7254	0.389	18655
Osimertinib	41379	1.811	2.519	9710	0.376	25821
2) utility of Progression-free state (0.82)						
DP	25972	1.029	1.475	—	—	—
GP	26344	1.078	1.475	371	0.049	7523
TP	26644	1.061	1.475	300	−0.018	Dominated
PP	31669	1.460	2.009	5325	0.382	13958
Osimertinib	41379	1.851	2.519	9710	0.391	24846
3) utility of progression-free state (0.62)						
DP	25972	0.931	1.475	—	—	—
GP	26344	0.973	1.475	371	0.043	8671
TP	26644	0.963	1.475	300	−0.011	Dominated
PP	31669	1.365	2.009	5325	0.392	13592
Osimertinib	41379	1.699	2.519	9710	0.334	29070
4) utility of progression state (0.47)						
DP	25972	0.775	1.475	—	—	—
GP	26344	0.830	1.475	371	0.055	6719
TP	26644	0.806	1.475	300	−0.024	Dominated
PP	31669	1.078	2.009	5325	0.248	21489
Osimertinib	41379	1.401	2.519	9710	0.323	30029
5) utility of progression state (0.69)						
DP	25972	0.991	1.475	—	—	—
GP	26344	1.039	1.475	371	0.048	7723

Table S9. (*Continued*)

	Costs ($)	QALYs	LYs	Difference		ICER ($/QALY)
				Costs ($)	$/QALY	
TP	26644	1.023	1.475	300	−0.016	Dominated
PP	31669	1.415	2.009	5325	0.377	14141
Osimertinib	41379	1.788	2.519	9710	0.373	26025
6) utilities for osimertinib and chemotherapy from AURA2 and IMPRESS						
DP	25972	1.008	1.475	—	—	—
GP	26344	1.056	1.475	371	0.048	7738
TP	26644	1.040	1.475	300	−0.016	Dominated
PP	31669	1.440	2.009	5325	0.384	13880
Osimertinib	41379	1.833	2.519	9710	0.392	24739

GP, platinum plus gemcitabine; PP, platinum plus pemetrexed; DP, platinum plus docetaxel; TP, platinum plus paclitaxel; LYs, life-years; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival.

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