



Comparing the cost-effectiveness of sintilimab + pemetrexed plus platinum and pemetrexed plus platinum alone as a first-line therapy for Chinese patients with nonsquamous non-small cell lung cancer

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Background: Pemetrexed plus platinum alone is the conventional first-line therapy for locally advanced metastatic nonsquamous non-small cell lung cancer (NSCLC) without targetable genetic aberrations. The ORIENT-11 trial revealed that sintilimab + pemetrexed plus platinum could yield more survival benefits for patients with nonsquamous NSCLC. The present study aimed to assess the cost-effectiveness of sintilimab + pemetrexed plus platinum *vs.* that of pemetrexed plus platinum alone as the first-line therapy for patients with nonsquamous NSCLC to inform clinically rational drug use and provide a basis for medical decision-making.

Methods: A partitioned survival model was created to evaluate the cost-effectiveness of two groups from the perspective of the healthcare system in China. The clinical data for adverse event probabilities and extrapolating long-term survival originally collected in a phase III clinical trial (ORIENT-11) were retrieved. Local public databases and literature were used to acquire data on utility and cost. The heemod package in R software was used to calculate the life years (LYs), quality-adjusted LYs (QALYs), and total costs in each group to generate the incremental cost-effectiveness ratio (ICER) in the base case and to conduct deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA).

Results: Our base case analysis (BCA) revealed that sintilimab combined with pemetrexed plus platinum provided an increase of 0.86 in QALYs with an increasing cost of United State dollar (USD) \$4,317.84 relative to pemetrexed plus platinum in Chinese patients with nonsquamous NSCLC who were negative for targetable genetic variations, which induced an ICER of USD \$5,020.74/QALY. The ICER value was lower than the set threshold value. The results exhibited strong robustness in the sensitivity analysis. In DSA, the parameter for the overall survival (OS) curve in chemotherapy and the cost of best supportive care were the main factors that impacted the result of the ICER. The PSA indicated that sintilimab and chemotherapy combination therapy was cost-effective.

Conclusions: This study suggests that the combination of sintilimab + pemetrexed plus platinum is cost-effective as a first-line therapy in Chinese patients with nonsquamous NSCLC who are negative for targetable genetic variations from the perspective of the healthcare system.

Keywords: Cost effectiveness; sintilimab; chemotherapy; first-line therapy; nonsquamous non-small cell lung cancer (nonsquamous NSCLC)

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Introduction

Lung cancer is a malignancy with high morbidity and mortality both worldwide and in China (1,2). There are several subtypes of lung cancer, of which non-small cell lung cancer (NSCLC) has the highest incidence and represents 80–90% of all lung cancer cases (3). In clinical practice, only a few patients with NSCLC are diagnosed early (4). Around 70% of patients with NSCLC are not diagnosed until local advancement or metastasis occurs when the lesions become unresectable, resulting in poor long-term prognosis (5,6). Historically, chemotherapy has remained the major treatment for patients with NSCLC who exhibit local advancement or metastasis (7). Within the last decade, the number of targeted therapies has increased rapidly for patients with targetable genetic aberrations as genomic research has advanced (8). Recently, the development of immunotherapy and immune-checkpoint inhibitors (ICIs) has provided new options for treating NSCLC (9).

Sintilimab is an immunoglobulin G₄ monoclonal antibody capable of binding with programmed cell death protein 1 (PD-1) to impede its interaction with the ligand and enhance the immune-monitoring and tumor-killing capabilities of T cells, thereby generating a tumor immune response (10,11). In the treatment of squamous NSCLC, a phase 3 clinical trial (ORIENT-3) found that sintilimab significantly improved the overall survival (OS), progression-free survival (PFS), and objective response rate of Chinese patients compared with docetaxel (12). In the treatment of nonsquamous NSCLC, a phase I B clinical study evaluated the efficacy and safety of sintilimab in combination with pemetrexed and platinum, which showed tolerable safety and excellent efficacy in Chinese patients (13). Given its favorable benefits reported in a phase 3 clinical trial (ORIENT-11), sintilimab has gained approval from the National Medical Products Administration (NMPA) as a first-line drug for patients with advanced nonsquamous NSCLC without targetable genetic aberrations. Furthermore, the addition of sintilimab to chemotherapy regimens was found to enhance their efficacies, as evidenced by significant improvements in PFS and OS, and provide tolerable safety (14,15).

The emergence of new treatment regimens further increases the economic burden on the healthcare system. A recent study showed that the total economic burden of lung cancer in China was estimated to be United State dollar (USD) \$25.069 million [0.121% of gross domestic product (GDP)] in 2017. According to the prevalence-based approach, the projected total economic burden will increase to USD \$30.1 billion, USD \$40.4 billion, and USD \$53.4 billion USD in 2020, 2025, and 2030, respectively, demonstrating that the cost of lung cancer is enormous (16). Health insurance can alleviate the heavy economic burden on patients. In China, the national medical insurance is mainly composed of the New Rural Cooperative Medical Scheme (NCMS), Urban

Highlight box

Key findings

- The combination of sintilimab + pemetrexed plus platinum is cost-effective as a first-line therapy in Chinese patients with nonsquamous NSCLC who are negative for targetable genetic variations from the perspective of the healthcare system.

What is known and what is new?

- The safety and efficacy benefit of the additional use of sintilimab for patients with nonsquamous NSCLC during chemotherapy has been demonstrated in clinical trials.
- This study added pharmacoeconomic evidence for the additional use of sintilimab.

What is the implication, and what should change now?

- This study suggests that the additional use of sintilimab is cost-effective for Chinese patients with nonsquamous NSCLC from the perspective of the healthcare system.

Employed Basic Medical Insurance (UEBMI), and Urban Resident Basic Medical Insurance (URBMI) (17). The reimbursement rate is 50–65% for NCMS, which is much lower than the 85–95% for UEBMI, but similar to the 50% for URBMI. Individuals with no insurance or low reimbursement rates may be disadvantaged in the face of lung cancer (18). From a healthcare system perspective, reducing medical costs is urgently needed to lower the burden on patients and the medical insurance system. The Chinese government has already taken measures to reduce these burdens. Recently, national negotiation was promoted in China, which significantly decreased the price of drugs price in China. The price of sintilimab was significantly reduced from Chinese yuan (CNY) ¥7,838/100 mg in 2019 to CNY ¥1,080/100 mg in 2022 (19,20). Although the price of sintilimab significantly decreased, the pharmacoeconomic information for sintilimab plus chemotherapy as a first-line therapy for nonsquamous NSCLC without targetable genetic aberrations is still insufficient in China. Therefore, evaluating the cost-effectiveness of sintilimab in combination with chemotherapy for these patients is particularly important.

A model study that follows pharmacoeconomic methodology is useful for cost-effectiveness analysis since only limited data can be obtained from routine observation. Some pharmacoeconomic guidelines even see model-based economic evaluations as the gold standard practice in this regard (21). A range of alternative models can be used for cost-effectiveness analysis, such as the partitioned survival model, decision trees, Markov state transition models, and individual sampling models (22). The partitioned survival model has been used extensively in the National Institute for Health and Care Excellence (NICE) to appraise interventions for advanced or metastatic cancers. The partitioned survival model is similar in concept to the Markov state transition model. It is characterized by the use of survival curves to define a series of different health states for cost and output estimation. For example, in the field of economic evaluation of cancers, PFS and OS are generally reported in clinical trials. Accordingly, the health status of patients can be divided into 3 classes: progression-free (PF), post-progression (PP), and death. The model structure of partitioned survival for patients with cancer is transparent, and additional transition computations are unnecessary. Therefore, the partitioned survival model is more suitable for the economic evaluation of diseases that can be divided into limited health states and need long-term simulation (22,23).

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(CSCO) NSCLC guidelines stated that both sintilimab combined with pemetrexed plus platinum and pemetrexed plus platinum were all class I recommended treatment regimens for patients with nonsquamous NSCLC without targetable genetic aberrations (24). Hence, we conducted a partitioned survival model with the primary aim of appraising the cost-effectiveness of the additional use of sintilimab in combination with pemetrexed plus platinum and chemotherapy alone for patients with nonsquamous NSCLC negative for targetable genetic alterations in the context of the healthcare system in China. The ultimate aim of this study is to inform the rational use of drugs in clinic and provide a basis for medical insurance decision-making. We present the following article in accordance with the CHEERS reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2030/rc>).

Methods

This study used a partitioned survival model to appraise the cost-effectiveness of sintilimab plus chemotherapy as the first-line therapy for patients with nonsquamous NSCLC who were negative for sensitizing epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic alterations in the context of the healthcare system in China. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Chinese pharmacoeconomic guidelines (23). An ethical review was not required in this study because only publicly available and deidentified data were used.

Model structure and simulation

We constructed the partitioned survival model using 3 disease statuses: PF, PP, and death. These 3 disease statuses are mutually exclusive because 1 simulated patient can only have 1 disease status at a specific time point. PF was the starting status for all patients. PP was the interim status; patients could gradually progress into this status from PF. The last status was death; all patients could eventually have this disease status. By subtracting the number of surviving patients by that of patients with PF, the number of patients with PP could be obtained. The model structure is shown in *Figure 1*. In accordance with the program of treatment options, each cycle lasted for 3 weeks for the simulation. The duration of the investigation was set as 450 cycles because in that time, 99% of the simulated patients would reach the death state.

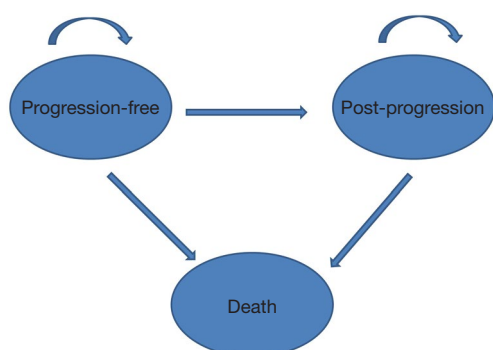


Figure 1 The structure of the partitioned survival model.

Model inputs

Clinical information and survival estimation

Data on effectiveness and safety primarily came from the ORIENT-11 trial, a randomized, double-blind, phase III trial performed in 47 Chinese clinical institutions. The trial included 397 treatment-naïve NSCLC participants exhibiting local advancement or metastasis who were negative for sensitizing genetic alterations in the *EGFR* and *ALK* genes. A combination group, in which patients were treated with both sintilimab- and platinum-based chemotherapy, and a chemotherapy group, in which the participants were given a placebo plus platinum-based chemotherapy, were compared in this trial. The participants were randomly assigned into the combination and chemotherapy groups at a ratio of 2:1. Among the two groups, the baseline disease characteristics and demographic were well balanced. The participants in the combination group initially received 4-cycle induction therapy with sintilimab (200 mg), pemetrexed (500 mg/m²), and either carboplatin (area under the concentration-time curve, 5 mg/mL/min) or cisplatin (75 mg/m²) on the first day of each 3-week cycle; then they were subjected to maintenance therapy with sintilimab (200 mg) plus pemetrexed (500 mg/m²) in each cycle for as long as 24 months. Patients in the chemotherapy group received the same platinum-based chemotherapy plus a placebo. More details of the trial design, efficacy, and safety of the ORIENT-11 trial were obtained from published literature (14,15). The published Kaplan-Meier curves for OS and PFS were reconstructed using GetData Graph Digitizer v.2.26 combined with the *survHE* package in R software (The R Foundation for Statistical Computing), and the R *flexsurv* package was used for estimating the subsequent survival curve for PFS and OS (25,26). The estimated distributions for the survival curve were log-logistic, log-normal, Weibull

(accelerated failure time), gamma, gompertz, and exponential distributions. We used the Bayesian information criterion (BIC), Akaike information criterion (AIC), and visual checking to find the distribution with the best fit. Relevant clinical data are listed in *Table 1*.

Utility

Utility scores for patients with NSCLC in China were predominantly derived from a study by Nafees *et al.* (30), who calculated the utility scores by using the time trade-off technique in the societal context of several countries, including China. Accordingly, the utility scores in our study for PF and PP statuses were 0.804 and 0.321, respectively. Meanwhile, adverse events with a grade of no less than 3 and an incidence $\geq 5\%$ in the PF status were considered disutilities with scores reported in the literature (28,30-32). Utility scores combined with the time spent in each status were used to calculate the overall quality-adjusted life years (QALYs). Relevant utility scores are listed in *Table 1*.

Cost

The patients' direct expenses on the administration of drugs, management of adverse events, and medical tests, as well as their follow-up expenditure, best supportive care expenditure in the PP status, terminal phase expenditure, and hospitalization fees, were taken into account in this work. Drug price information was acquired from the local bid-winning price (Drugdataexpy) (20), which is equal to the drug prices for most Chinese hospitals. Other information was sourced from the existing literature (14,15,27-33). Based on an assumption of a mean area of 1.72 m² of the patient's body surface, we calculated the drug dosage for chemotherapy in each cycle (29). The glomerular filtration rate reported in ORIENT-11 was used to calculate the dosage of carboplatin. Furthermore, the proportions of carboplatin and cis-platinum were also considered in the induction treatment cost. Relevant costs in USD are listed in *Table 1*.

Statistical analysis

Based on the above input data, we used a partitioned survival model to simulate patients in the base case and different scenarios. In the base case analysis (BCA), we determined the life years (LYs), QALYs, and total costs for each group. The incremental cost-effectiveness ratio (ICER) was also calculated to compare the cost-effectiveness of the combination group and the chemotherapy group. The

Table 1 Input items for BCA, one-way DSA, and PSA

Items	Values for BCA	Range of values for DSA	Distribution of values for PSA	Reference
Costs (USD \$¹)				
Sintilimab (100 mg)	170.05	102.03–578.18	Gamma	(20)
Pemetrexed (500 mg)	218.05	79.63–323.37	Gamma	(20)
Cisplatin (20 mg)	2.72	1.19–6.90	Gamma	(20)
Carboplatin (100 mg)	8.15	4.78–8.49	Gamma	(20)
Best support care expenditure in PP	337.5	158.7–793.7	Log-normal	(27)
Follow-up in each cycle	55.6	41.7–69.4	Log-normal	(27)
Terminal phase	2,627.8	2,291.8–2,966.6	Log-normal	(27)
Management of anemia	138.75	106.73–160.10	Log-normal	(28)
Management of neutrophil count decreased	115.01	51.11–357.80	Log-normal	(28)
Management of platelet count decreased	1,505.92	1,240.17–1,771.67	Log-normal	(28)
Management of white blood cell count decreased	115.01	51.11–357.80	Log-normal	(28)
Physiological parameters				
Body surface area (m ²)	1.72	1.38–2.07	Normal	(29)
Glomerular filtration rate	95.23	48.08–142.38	Normal	(14)
Rate of adverse events (≥ grade 3)				
Anemia in combination group	15%	–	–	(15)
Reduced white blood cell count in combination group	14.7%	–	–	(15)
Reduced platelet count in combination group	12%	–	–	(15)
Neutrophil count decreased in combination group	36.5%	–	–	(15)
Anemia in combination group	19.1%	–	–	(15)
Reduced white blood cell count in combination group	15.3%	–	–	(15)
Reduced platelet count in combination group	12.2%	–	–	(15)
Reduced neutrophil count in combination group	30.5%	–	–	(15)
Utility				
PF state	0.804	0.64–0.96	Beta	(30)
PP state	0.321	0.26–0.39	Beta	(30)
Disutility				
Reduced neutrophil count	0.2	0.16–0.24	Beta	(30)
Reduced white blood cell count	0.2	0.16–0.24	Beta	(30)
Reduced platelet count	0.11	0.09–0.13	Beta	(31)
Anemia	0.07	0.06–0.09	Beta	(32)
Duration of adverse event (≥ grade 3)				
Reduced neutrophil count	13 weeks	–	–	(33)
Reduced white blood cell count	12 weeks	–	–	(33)
Reduced platelet count	1 week	–	–	(33)
Anemia	1 week	–	–	(33)

¹, USD \$1 = CNY ¥6.3509 on April, 1, 2022. BCA, base case analysis; DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis; PP, post-progression; PF, progression-free.

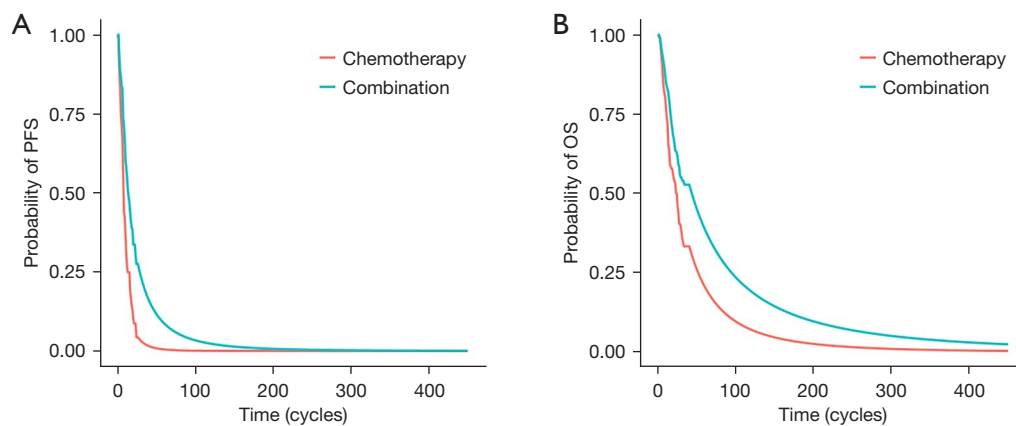


Figure 2 Survival curves for the model. (A) Survival curves for PFS. (B) Survival curves for OS. PFS, progression-free survival; OS, overall survival.

ICER between the combined strategies group and the chemotherapy group was defined as follows: $(C_{\text{combination}} - C_{\text{chemotherapy}}) / (E_{\text{combination}} - E_{\text{chemotherapy}})$, where C is the total cost of a group and E is its total expected effect (QALY). With consideration to the variability of the input items and the model, the robustness of BCA results was evaluated by conducting a series of sensitivity assays. For one-way deterministic sensitivity analysis (DSA), the influences of change for a single input item on the result were analyzed. The change in range for each parameter was set as its reported 95% confidence interval (CI) or as its base case value $\pm 20\%$ if its 95% CI was unavailable. The detailed ranges are listed in Table 1. The data are displayed in a tornado plot. Probabilistic sensitivity analysis (PSA) was conducted with parameters that changed simultaneously for robustness verification of the data. A Monte Carlo simulation was performed to generate 1,000 ICERs via a random sampling of the key parameters among their distributions. The utilities and percentages were assigned beta distributions. The prices of drugs were assigned gamma distributions. The detailed distributions are also listed in Table 1. A scatter plot was used to present the simulated ICERs. Based on the simulated result, cost-effectiveness acceptability curves were drawn to show the likelihood that the cost-effectiveness of treatment regimens corresponded to the variable willingness to pay (WTP) thresholds. Based on the China Guidelines for Pharmacoeconomic Evaluations 2020, we defined the 2021 per capita GDP of China (USD \$12,718) as the WTP threshold for Chinese patients.

All the statistical analyses were carried out with R

software (<https://www.r-project.org>). Moreover, the packages *survHE* and *flexsurv* were used to fit survival curves. The *beemod* package was used to calculate the total costs, QALYs, and ICERs for the treatment regimens in the base case scenario and to generate sensitivity analysis results (25,26,34). In accordance with the reported guidelines, the discount rate was set as 3% per year to adjust the costs and effectiveness.

Results

BCA

Based on the reconstructed survival curves and the best-fitted distribution for OS and PFS curves in the combination group and the chemotherapy group (log-normal distribution for both OS and PFS curves for each group; Tables S1,S2, Figures S1-S6), survival curves for the model were drawn (Figure 2). In addition, LYs in PF and PP state were calculated (Table 2).

On average, patients in the combination group spent 1.44 and 3.02 years in the PF and PP statuses, respectively, resulting in a total of 4.46 LYs. In the chemotherapy group, patients spent an average of 0.62 and 1.82 years in the PF and PP statuses, respectively, for a total of 2.44 LYs. In the combination group, the total cost was USD \$24,320.68 (USD \$15,951.19 in the PF state; USD \$6,049.26 in the PP state; USD \$2,320.23 in the terminal state), and the total QALY was 1.84 (1.05 in the PF state; 0.79 in the PP state). In the chemotherapy group, the total cost was USD \$20,002.84 (USD \$4,590.83 in the PF state; USD \$12,941.07 in the PP state; USD \$2,470.94 in the terminal

Table 2 BCA results

Results	Combination group	Chemotherapy group	Difference
LYs in the PF state	1.44	0.62	0.82
LYs in the PP state	3.02	1.82	1.20
LYs	4.46	2.44	2.02
Cost in the PF state (\$)	15,951.19	4,590.83	11,360.36
Cost in the PP state (\$)	6,049.26	12,941.07	-6,891.81
Cost in the terminal phase (\$)	2,320.23	2,470.94	-150.71
QALY of PF	1.05	0.46	0.59
QALY of PP	0.79	0.52	0.27

BCA, base case analysis; LYs, life years; PF, progression-free; PP, post-progression; QALY, quality-adjusted life year.

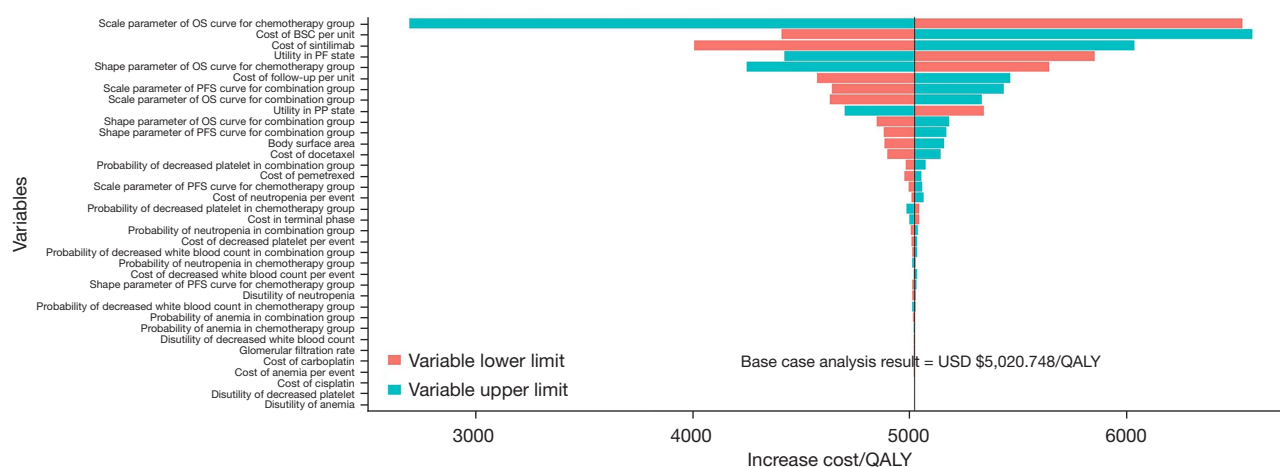


Figure 3 A tornado diagram for DSA. OS, overall survival; BSC, best support care; PF, progression-free; PFS, progression-free survival; PP, post-progression; QALY, quality-adjusted life year; DSA, deterministic sensitivity analysis.

state), and the total QALY was 0.98 (0.46 in the PF state; 0.52 in the PP state). As a result, the combination group gained 2.02 LYs, which yielded an additional 0.86 QALY with an ICER of USD \$5,020.74/QALY. The detailed results are listed in *Table 2*.

Sensitivity analysis

The robustness of the BCA result was analyzed with sensitivity analysis. The tornado diagram in *Figure 3* shows the DSA findings, indicating that the parameter for the OS curve in chemotherapy and the cost of best supportive care are the main factors that impact the result of the ICER. Regardless of the influence of these key factors, the ICERs remained under USD \$12,718 per QALY gained.

Regarding PSA, the cost-effectiveness acceptability curve showed the cost-effectiveness probability of treatment regimens under different WTP thresholds (*Figure 4*). Compared with chemotherapy alone, sintilimab plus chemotherapy had a 100% probability of being cost-effective at the specified WTP threshold (USD \$12,718 per QALY). The bivariate scatter plot of increasing costs over increasing QALY (*Figure 5*) depicts the result of PSA with 1,000 simulations.

Discussion

Recently, the clinical benefit of immune therapy on lung cancer has been verified by a series of clinical trials, but the high cost of immune therapy hinders its widespread

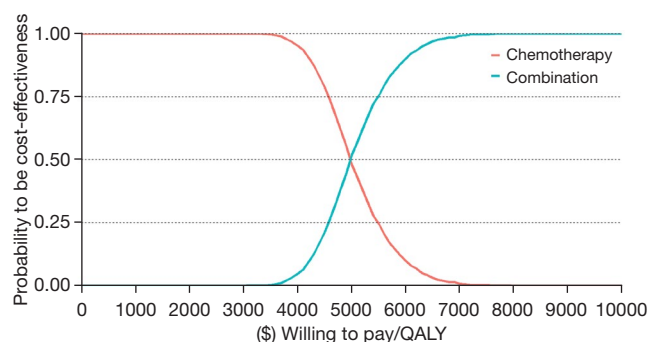


Figure 4 Cost-effectiveness acceptability curves for PSA. QALY, quality-adjusted life year; PSA, probabilistic sensitivity analysis.

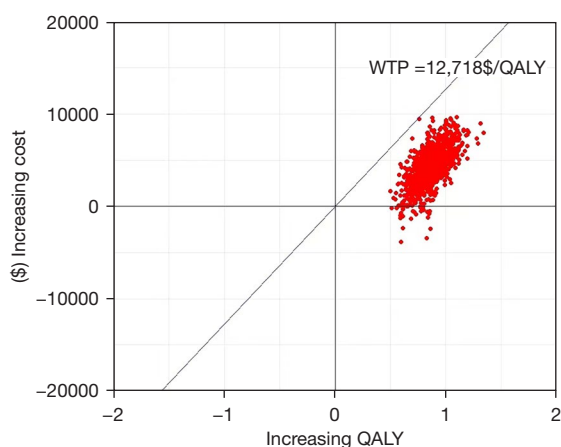


Figure 5 Scatter plot for PSA. WTP, willingness to pay; QALY, quality-adjusted life year; PSA, probabilistic sensitivity analysis.

application (3,35). Under the circumstances of medical reform in China, the price of various high-cost drugs is continuously decreasing (4). Therefore, the price of sintilimab has decreased significantly, and an economic assessment of sintilimab is needed. We thus performed the first evaluation of the cost-effectiveness of the combinatorial use of sintilimab and chemotherapy in managing Chinese patients with nonsquamous NSCLC exhibiting local advancement or metastasis. Based on our study, the sintilimab and chemotherapy combination therapy provided an extra 0.86 QALYs with an increasing cost of USD \$4,317.84. As a result, the ICER has a gain of USD \$5,020.74/QALY. The results suggested that sintilimab and chemotherapy combination therapy is cost-effective at the WTP setting of a onefold GDP/QALY in China. These findings were also demonstrated to be robust by conducting one-way DSA and PSA. As in one-way DSA, the parameter

for the OS curve in the chemotherapy group and the cost of the best supportive care were considered the major factors that affected the results of the ICER. The tornado diagram revealed that the upper bound of the ICER was still lower compared with the preset WTP threshold with the change in the value of the major parameters. In PSA, we found that sintilimab and chemotherapy combination therapy was cost-effective because almost all of the simulated ICERs were lower than onefold of GDP/QALY.

In China, several immunotherapy regimens have been approved as first-line treatments in combination with chemotherapy for nonsquamous NSCLC. These new drugs offer hope to patients with cancer, but the high drug price may hinder their accessibility (36). Furthermore, head-to-head trial data to compare their safety and efficacy are insufficient. Reported pharmacoeconomic research with different models showed that pembrolizumab and atezolizumab are not cost-effective (37,38). Zhu *et al.* (39) showed that the decrease in the price of camrelizumab (USD \$452 per cycle) was considered cost-effective in China because it could gain QALY and decrease cost (ICER = USD \$-7,382.72/QALY). This study added another treatment regimen for Chinese patients with nonsquamous NSCLC that could be considered cost-effective for these patients.

This study used the clinical data of the ORIENT-11 trial, in which 45% of participants in the chemotherapy group crossed over to the combination group. As a result, the true clinical effectiveness of sintilimab might be underestimated. In addition, the cost of chemotherapy in the PP status also included the expenditure of sintilimab, which led to more costs than for the combination group in this state. Thus, sintilimab combined with chemotherapy as a first-line treatment might be more cost effective. In addition, clinicians also identified the predictive biomarkers for patients treated with sintilimab. The updated ORIENT-11 results show that high expression of the antigen presentation pathway mediated by major histocompatibility complex class II was significantly associated with longer PFS and OS for patients in the combination group (15). Thus, patients with high expression of this pathway would benefit more from the additional use of sintilimab during chemotherapy.

In general, long-term survival data are necessary for appraising the cost-effectiveness of cancer drugs. In practice, lifetime survival projections are often extrapolated based on short-term regulatory trials (40). Even though rigorous methodological approaches are used in the extrapolation, uncertainty remains. In this study, the

24-month follow-up clinical data were used, and the OS and PFS data were deduced by fitting several parametric survival models. To explore the uncertainty, the influence of changing extrapolated parameters was analyzed. As a result, the scale parameter for the OS curve in the chemotherapy group had a great influence on the ICER. Despite this finding, the results were robust in our setting WTP.

Our work has some limitations. First, the clinical data used were derived from the ORIENT-11 trial, which is a precisely designed phase III randomized controlled trial that compared first-line sintilimab in the combination of chemotherapy with chemotherapy alone in a specific cohort of Chinese patients with nonsquamous NSCLC. This study depends heavily on the trial's validity and generalizability. Thus, our results will inevitably be affected by bias within the trial. Second, data on the quality of life of participants of the ORIENT-11 trial were not reported. Consequently, in this study, we used utility according to published literature, which might not reflect the true value of this study. However, the sensitivity analysis indicated the robustness of the results when potential changes in the utility value were considered. In addition, as long-term follow-up records were not generated in the ORIENT-11 trial, we extrapolated survival data with several criteria and tested the robustness of sensitivity analyses. Given the durable effects of ICIs, it is still necessary to apply matured survival data to verify our model. Furthermore, in sensitivity analyses, the range of variation of several variables could not be obtained. A commonly used method that assumed a variance of 20% above and below the baseline values was used. This range might be inaccurate for some variables. Additionally, in real-world settings, the treatment options for PP are more complex, and variations in the cost and utility might affect the results of our model.

Conclusions

Based on the partitioned survival model, we propose that in the context of the healthcare system in China, the use of sintilimab plus chemotherapy as the first-line therapy is cost-effective for patients with nonsquamous NSCLC who are negative for genetic alterations in the *EGFR* and *ALK* genes when the WTP threshold is set at USD \$12,718 per QALY.

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Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2030/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2030/coif>). The authors report support from the China Society for Drug Regulation. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Chinese pharmacoeconomic guidelines. An ethical review was not required in this study, as only publicly available and deidentified data were used.

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Appendix 1

Data extraction

The OS and PFS curves in the ORIENT-11 trial were extracted with GetData Graph Digitizer (version 2.26). The survHE package in R combined with the number at risk reported in the ORIENT-11 trial was used to reconstruct the OS and PFS curves. The package survminer in R was used to draw the reconstructed survival curve (Figures S1-S4). The hazard ratios between groups, median OS, and PFS reported in the original trial are listed and combined with the reconstructed values (Table 1).

Fitting of PFS and OS curves

The best-fitting distributions for the reported OS and PFS curves in the ORIENT-11 trial were chosen using the BIC, AIC, and visual inspection (Table S2, Figures S5,S6).

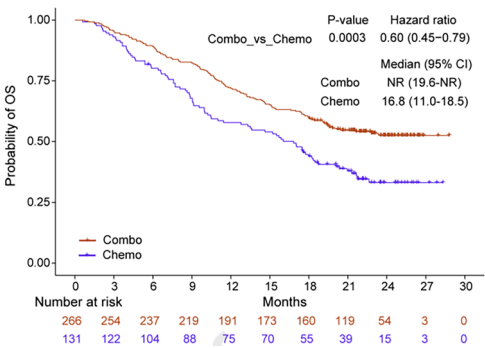


Figure S1 Original OS curve. OS, overall survival; CI, confidence interval; NR, not reported; combo, combination; chemo, chemotherapy.

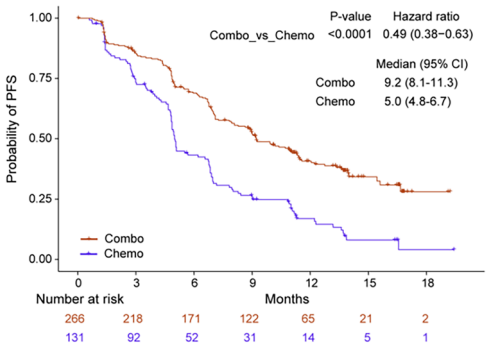


Figure S3 Original PFS curve. PFS, progression-free survival; CI, confidence interval; combo, combination; chemo, chemotherapy.

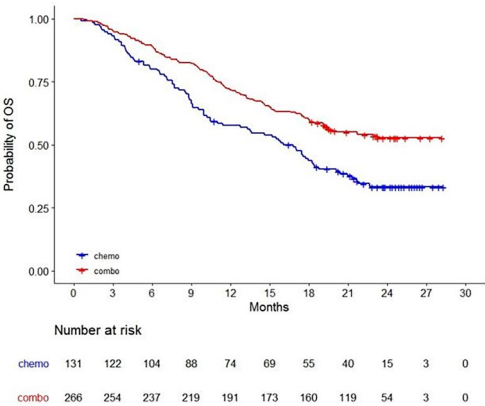


Figure S2 Reconstructed OS curve. OS, overall survival; combo, combination; chemo, chemotherapy.

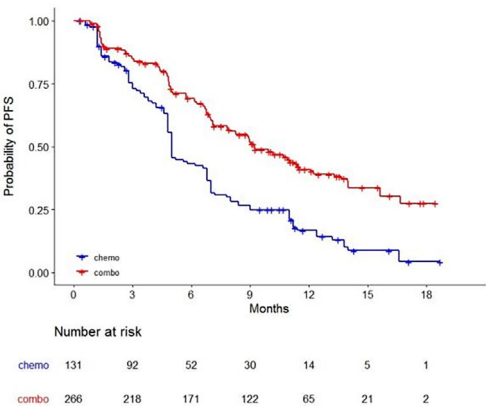


Figure S4 Reconstructed PFS curve. PFS, progression-free survival; combo, combination; chemo, chemotherapy.

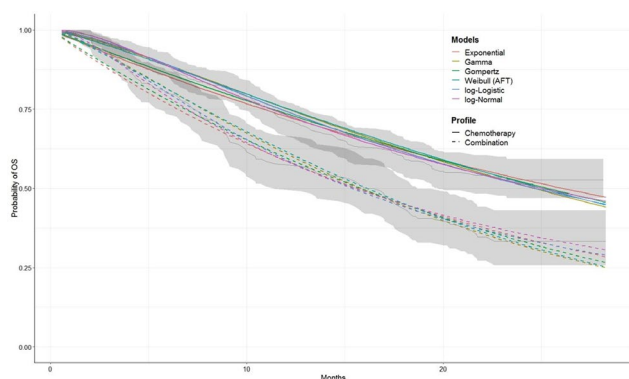


Figure S5 Visual inspection of the distributions of the OS curve. OS, overall survival; AFT, accelerated failure time.

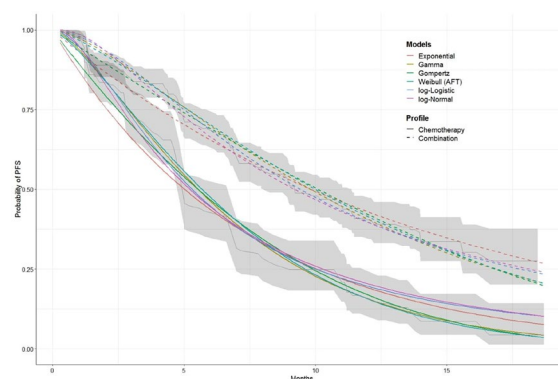


Figure S6 Visual inspection of the distributions of the PFS curve. PFS, progression-free survival; accelerated failure time.

Table S1 Hazard ratio, median OS, and median PFS of the original trial and reconstructed results

Result	Original trial data	Reconstructed data
Hazard ratio of OS, combo vs. chemo	0.60 (0.45–0.79)	0.59 (0.45–0.78)
Median OS in the combination group (months)	NR (19.60–NR)	NR (19.82–NR)
Median OS in the chemotherapy group (months)	16.80 (11.00–18.50)	16.04 (11.42–18.72)
Hazard ratio of PFS, combo vs. chemo	0.49 (0.38–0.63)	0.48 (0.38–0.62)
Median PFS in the combination group (months)	9.20 (8.10–11.30)	9.23 (8.28–11.40)
Median PFS in the chemotherapy group (months)	5.00 (4.80–6.70)	5.00 (4.80–6.80)

Data are presented as hazard ratio (95% CI), median OS (95% CI), or median PFS (95% CI). OS, overall survival; PFS, progression-free survival; combo, combination; chemo, chemotherapy; NR, not reported.

Table S2 AIC and BIC results of the fitted OS and PFS curves

Parameters	OS of combination		OS of chemotherapy		PFS of combination		PFS of combination	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Log-logistic	1,221.062	1,228.229	748.2234	753.9738	1,232.436	1,239.603	708.5327	714.2831
Log-norm	1,217.827	1,224.994	746.8404	752.5908	1,229.776	1,236.943	706.8776	712.628
Weibull (AFT)	1,226.539	1,233.706	751.9135	757.6639	1,236.548	1,243.715	710.793	716.5434
Exponential	1,229.355	1,232.939	754.1091	756.9843	1,245.921	1,249.504	723.857	726.7322
Gamma	1,224.982	1,232.149	750.6623	756.4127	1,234.451	1,241.618	708.1119	713.8623
Gompertz	1,231.071	1,238.238	755.275	761.0254	1,243.853	1,251.02	719.0497	724.8001

AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; PFS, progression-free survival; AFT, accelerated failure time.