

Cost-Effectiveness Analysis of Serplulimab Combined with Nab-Paclitaxel Plus Carboplatin Compared to Nab-Paclitaxel Plus Carboplatin Alone as First-Line Treatment for Advanced Squamous Non-Small Cell Lung Cancer in China

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Purpose: The ASTRUM-004 trial demonstrated the efficacy of serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy in untreated patients with advanced squamous non-small cell lung cancer (NSCLC). Our study aimed to evaluate the cost-effectiveness of this combination therapy compared to that of nab-paclitaxel plus carboplatin chemotherapy alone for advanced squamous NSCLC patients from the perspective of the Chinese healthcare system.

Patients and Methods: A partitioned survival model based on the survival data of the ASTRUM-004 trial was constructed to assess the cost-effectiveness. The direct medical costs and utilities were derived from published literature and real-world medical institutions. The total costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) were calculated. Sensitivity analyses and scenario analyses were conducted to assess the robustness of the model.

Results: The base-case analysis revealed that serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy provided 0.53 incremental QALYs at an incremental cost of \$60,790.77, with an ICER of \$114,207.24/QALY. The ICER significantly exceeded the Chinese willingness-to-pay threshold (\$37,743.79/QALY). Body weight, the utility value of progression-free survival stage, and the price of serplulimab were the main influencing factors of the ICER. Probabilistic sensitivity analysis revealed that there was no possibility of cost-effectiveness under the current threshold. Scenario analyses revealed that this combination therapy would only be cost-effective if the price of serplulimab fell by at least 80.3%.

Conclusion: Compared to nab-paclitaxel plus carboplatin chemotherapy alone, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy might not be economical for advanced squamous NSCLC patients in China under current pricing conditions. This study suggests that future price reductions for serplulimab could make this therapy more economically viable and provide guidance for drug pricing decisions.

Keywords: cost-effectiveness, serplulimab, squamous non-small cell lung cancer, ASTRUM-004 trial

Introduction

Lung cancer is the most common and deadliest cancer worldwide.¹ In 2022, there were 870,982 diagnosed lung cancer cases and 766,898 lung cancer-related deaths in China.² Non-small cell lung cancer (NSCLC) accounts for the majority

(80% - 85%) of all lung cancers, with 20% - 30% being the squamous subtype.³ Early stage lung cancer has no obvious symptoms, and most patients are already in the advanced stage at diagnosis.^{4,5}

Platinum-containing dual drug chemotherapy is the classic treatment regimen for squamous NSCLC patients without targetable gene alterations; Among these regimens, nab-paclitaxel plus carboplatin chemotherapy is widely used and serves as a key treatment option in clinical practice.⁶ However, its therapeutic efficacy is limited, with a median overall survival (OS) of only 7.9 months.⁷ In addition, the incidence of epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) gene rearrangements in squamous NSCLC is relatively low,⁸ resulting in few patients with locally advanced or metastatic squamous NSCLC achieving the expected therapeutic effect through targeted therapies.

The emergence of immune checkpoint inhibitors has changed the therapeutic landscape of advanced squamous NSCLC, with these inhibitors targeting immune checkpoint molecules such as programmed death 1 (PD-1) and programmed death-ligand 1 (PD-L1).⁹ PD-1 inhibitor-based treatment can prolong the survival and progression-free survival (PFS) of cancer patients.¹⁰ Moreover, for patients with advanced squamous NSCLC, adding a PD-1 inhibitor to chemotherapy has been proven to have a better clinical effect than chemotherapy alone.^{11–15} Recently, a randomized Phase III trial (ASTRUM-004) across 6 countries assessed the efficacy of serplulimab combined with nab-paclitaxel and carboplatin chemotherapy as a first-line treatment for untreated patients with stage IIIB/IIIC or IV squamous NSCLC without targetable gene alterations. The results revealed that serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy significantly prolonged the median PFS (8.3 months vs 5.7 months; hazard ratio [HR]: 0.55, 95% confidence interval [CI]: 0.42–0.73; $P < 0.0001$) and OS (22.7 months vs 18.2 months; HR: 0.73, 95% CI: 0.58–0.93; $P = 0.0030$) compared with placebo combined with nab-paclitaxel plus carboplatin chemotherapy. Regardless of PD-L1 expression levels, PFS benefit was observed in all subgroups, with the greatest benefit observed in patients with tumor proportion score $\geq 50\%$. In terms of safety, the incidences of treatment-emergent adverse events (TEAEs) of grade ≥ 3 were 84.4% and 79.9% for serplulimab or placebo combined with nab-paclitaxel plus carboplatin chemotherapy, respectively.

With the results of ASTRUM-004 trial, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy has been approved as a first-line treatment for locally advanced or metastatic squamous NSCLC in China in 2022, which has provided patients with a new therapeutic option. However, the problem that comes with it is its high cost. Serplulimab is currently priced at approximately \$786.40 per 100mg, and based on the recommended dosage of 4.5 mg/kg, at least two doses of the drug would be required for a single treatment, which represents that a single treatment would cost more than \$1500. Moreover, the drug needs to be used every three weeks, which is undoubtedly an ongoing and high financial expense for patients. Compared to China's per capita disposable income of approximately \$5519.15 in 2023, it's easy to see that the cost of serplulimab will be a heavy burden for most Chinese patients, while the high cost of lung cancer treatment also puts significant pressure on the healthcare system.

Although serplulimab has demonstrated superior effects, there are still fewer evaluations of the economics of serplulimab in patients with squamous NSCLC, and its cost-effectiveness still needs to be further explored. Our study aimed to evaluate the cost-effectiveness of serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy as a first-line treatment for untreated advanced squamous NSCLC patients from the perspective of the Chinese healthcare system.

Material and Methods

Patients and Interventions

This study was conducted in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria for economic evaluation (Table S1).¹⁶ The target population and treatment strategy were based on the ASTRUM-004 (NCT04033354) clinical study, which was a randomized, double-blind, multicenter phase III clinical study.¹⁷

Eligible patients were aged 18 years or older and had previously untreated, histologically or cytologically confirmed stage IIIB, IIIC, or IV squamous NSCLC, with at least one measurable lesion as per RECIST v1.1, an Eastern

Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and adequate organ function. Patients who had known *EGFR* mutations or *ALK/ROS1* rearrangements, symptomatic or unstable central nervous system metastases, autoimmune disease or a history of interstitial pneumonia, pneumoconiosis, radiation pneumonitis, drug-related pneumonia or severe impairment of pulmonary function were excluded.

Patients were randomized (2:1) to receive either serplulimab plus chemotherapy or placebo plus chemotherapy. In each group, serplulimab (4.5 mg/kg; Day 1 [D1]) or placebo was given every three weeks. All patients received nab-paclitaxel (100 mg/m²; D1, 8, 15) and carboplatin (at a dose calculated to produce an area under the concentration-time curve of 5 or 6 mg/mL/min according to local guidelines; D1) in 3-week cycles for 4–6 cycles. In the event of progressive disease (PD) or unacceptable adverse reactions during first-line therapy, patients received second-line therapy until death. Second-line treatment followed the criteria of the Chinese Medical Association guidelines for the diagnosis and treatment of lung cancer, with the combination of tislelizumab 200 mg and docetaxel 150 mg every three weeks.⁵

Model Construction

A partitioned survival model with three mutually exclusive health states (PFS, PD, and death) was built to simulate the clinical and economic outcomes of the two therapies. It was assumed that all patients entered the model from the PFS state and progressed along an irreversible sequence of ‘PFS-PD-death’ over time until the model was terminated (Figure 1). Taking patients in the PD state as an example, they might remain in PD state or transition to the death state, but would not return to the PFS state. The model operated on a 3-week cycle, consistent with the dosing cycle of the ASTRUM-004 trial. The time horizon was set to 10 years to fully observe long-term survival trends and the economic impact, enabling simulation of the long-term cost-effectiveness of advanced NSCLC treatments.

The primary outcomes were cost, quality-adjusted life year (QALY), and incremental cost-effectiveness ratio (ICER). QALY is a measure of the value of health outcomes, combining both the quantity and quality of life. ICER, simply put, is the ratio of the difference in treatment costs to the difference in QALYs. Costs and health outcomes utilized the half-cycle correction and 5% annual discount rate.¹⁸ Three times the gross domestic product (GDP) per capita of China was regarded as the willingness-to-pay (WTP) threshold and compared with the ICER values to judge whether serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy was economical.¹⁹ The GDP per capita in China for 2023 was approximately 89,400 Chinese yuan; therefore, the WTP threshold in this study was set at \$37,743.79/QALY.

Clinical Data Input

Due to the unavailability of individual patient data and limited follow-up time, parameter distribution fitting was performed on the survival curve. The GetData Graphical Digitizer (version 2.26) was used to extract PFS and OS data points from the Kaplan-Meier curves in the ASTRUM-004 trial. R software (version 4.2.1) was used to reconstruct the individual level patient data and fit the parameter distribution of the survival curve.²⁰ Through clinical reasoning, visual

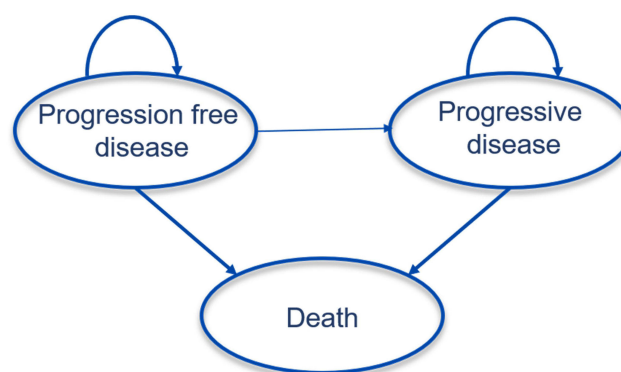


Figure 1 Partitioned survival model structure.

examination, and the application of the Akaike information criterion (AIC) and Bayesian information criterion (BIC), we selected the optimal distributions from the Exponential, Gamma, Weibull, Loglogistic and Lognormal distributions.²¹

The AIC and BIC values for the different distributions are shown in [Table S2](#). In this study, the Loglogistic distribution was chosen as the best fit for the OS curve of the two groups and the PFS curve of the immunochemotherapy group. Only the group receiving nab-paclitaxel plus carboplatin chemotherapy alone chose the Weibull distribution as the best fit for the PFS curve. Finally, we established a survival function and obtained the number of people in each state of each cycle. The fitting results are shown in [Figure S1](#). The proportion of progression-free patients was derived directly from the PFS curve. The proportion of patients who died was calculated by subtracting the OS curve from 100%; similarly, we calculated the proportion of progressive patients as the difference between the PFS and OS curves.

Cost and Utility Input

Only direct medical costs were involved, and included drug costs, subsequent treatment costs, laboratory and imaging examination costs, hospitalization costs, routine follow-up costs and treatment costs for TEAEs. All these expenses were reported in US dollars, using a conversion rate of \$1=¥7.1058 (Jan 2024). Drug costs were derived from the Jiangsu Pharmaceutical Medical Consumables Sunshine Procurement Service Network. We used the standard body surface area and standard body weight (1.72 m², 65 kg) to calculate the drug dose.²² Only TEAEs of grade ≥ 3 with an incidence of $\geq 5\%$ were considered in this study, including anemia, reduced white blood cell count, diminished neutrophil count, and thrombocytopenia. The costs of TEAEs were obtained from the published literature and clinical expert consultation,^{23–26} and the corresponding incidence rates were obtained from the ASTRUM-004 trial.¹⁷ Other direct medical costs were sourced from local charges.

The health utility value refers to people's preference for the specific health state, and is a quantitative indicator of quality of life, with 0 representing death and 1 representing perfect health. The ASTRUM-004 trial did not collect information on patients' quality of life; thus the utility values of the PFS and PD states were obtained from the published literature. The utility values of the PFS and PD states were 0.804 and 0.321, respectively.²⁷ The negative utility values caused by TEAEs of grade ≥ 3 with an incidence of $\geq 5\%$ were also obtained from published literature.²⁸ The main cost and utility parameters are shown in [Table 1](#).

Sensitivity Analyses

To verify the stability of the model, we performed one-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). In the one-way deterministic sensitivity analysis, the parameters in the model varied within $\pm 20\%$ of the baseline values to examine the impact of changes in a certain parameter on the ICERs. The results are presented in a tornado chart. The discount rate was set to fluctuate in the range of 0%-8%.¹⁸ For the PSA, the distribution types of the parameters needed to be determined first. Gamma distributions were selected for cost inputs, and beta distributions were used for utility values and probabilities.²⁹ Then, to execute 2000 Monte Carlo simulations, all parameters were sampled randomly from the corresponding distribution in each simulation. The PSA examined the impact of simultaneous changes in model parameters over a range of distributions on the results, and also demonstrated the accuracy of analytic decisions under specific payment thresholds. The results are presented as a scatter plot and cost-effectiveness acceptability curve (CEAC).

Scenario Analyses

In this study, we simulated a total of three scenarios as follows.

Scenario analysis 1: To improve the accessibility and affordability of new anti-tumor drugs, the National Reimbursement Drug List (NRDL) has been dynamically adjusted, and new anti-tumor drugs have been incorporated. Serplulimab is currently not covered by the NRDL, but given the possibility of a price reduction of serplulimab in the future, we calculated the ICERs for each 10% price reduction of serplulimab to explore the impact on the cost-effectiveness of different price reduction levels.

Table 1 Model Parameters and the Range of the Sensitivity Analysis

Parameters	Baseline Value	Range		Distribution	Source
		Minimum	Maximum		
Survival model for PFS					
Serplulimab plus chemotherapy	Shape=1.5454 Scale=9.1127			Loglogistic	[16]
Placebo plus chemotherapy	Shape=1.5144 Scale=0.0482			Weibull	[16]
Survival model for OS					
Serplulimab plus chemotherapy	Shape=1.3844 Scale=22.9608			Loglogistic	[16]
Placebo plus chemotherapy	Shape=1.509 Scale=16.586			Loglogistic	[16]
Cost inputs, \$					
Serplulimab (100mg)	786.40	629.12	786.40	Gamma	Sunshine Procurement Service Network
Nab-paclitaxel (100mg)	103.58	82.86	103.58	Gamma	Sunshine Procurement Service Network
Carboplatin (50mg)	11.12	8.89	11.12	Gamma	Sunshine Procurement Service Network
Tislelizumab (100mg)	176.41	141.13	176.41	Gamma	Sunshine Procurement Service Network
Docetaxel (20mg)	3.18	2.54	3.18	Gamma	Sunshine Procurement Service Network
Routine follow-up/per cycle	15.48	12.38	18.58	Gamma	Local charges
Supportive care/per cycle	95.41	76.33	114.50	Gamma	Local charges
Laboratory tests and radiological examinations/per cycle	141.91	113.53	170.29	Gamma	Local charges
Hospitalization and daily care/per cycle	57.42	45.93	68.90	Gamma	Local charges
Costs of AEs per cycle, \$					
Anemia	422.22	337.78	506.67	Gamma	[23–26], clinical expert consultation
White blood cell count decreased	423.62	338.90	508.34	Gamma	[23–26], clinical expert consultation
Neutrophil count decreased	358.55	286.84	430.26	Gamma	[23–26], clinical expert consultation
Platelet count decreased	933.32	746.65	1119.98	Gamma	[23–26], clinical expert consultation

(Continued)

Table 1 (Continued).

Parameters	Baseline Value	Range		Distribution	Source
		Minimum	Maximum		
Utility value					
PFS	0.804	0.643	0.965	Beta	[27]
PD	0.321	0.257	0.385	Beta	[27]
Anemia	0.07	0.056	0.084	Beta	[28]
White blood cell count decreased	0.20	0.16	0.24	Beta	[28]
Neutrophil count decreased	0.2	0.16	0.24	Beta	[28]
Platelet count decreased	0.2	0.16	0.24	Beta	[28]
Others					
Body surface area (m ²)	1.72	1.38	2.06	Gamma	[22]
Body weight (kg)	65	52	78	Gamma	[22]
Discount rate (%)	0.05	0	0.08	Beta	[18]

Abbreviations: AEs, adverse events; PD, progressive disease; PFS, progression-free survival.

Scenario analysis 2: There are differences in economic development status and the accessibility of medical resources among regions in China. We used three times the GDP per capita of different geographical divisions and cities as the WTP thresholds to simulate the differences in serplulimab use in different economic contexts.

Scenario analysis 3: Immunotherapy has a unique long-tailing effect, that is related to the memory function of immune cells. We set the simulation time of the model to 5, 10, 15 and 20 years to explore the impact of different time horizons on the ICERs.

Results

Base-Case Analysis

The base-case results are presented in Table 2. The total cost of patients who received serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy was \$81,730.60, and 1.42 QALYs were generated, while the total cost of patients who received nab-paclitaxel plus carboplatin chemotherapy alone was \$20,939.83, and only 0.89 QALYs were generated. The incremental cost of implementing serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy compared to nab-paclitaxel plus carboplatin chemotherapy alone reached \$60,790.77, and the incremental QALYs were 0.53. Consequently, the ICER was \$114,207.24 per QALY gained, which was much greater than the WTP threshold (\$37,743.79/QALY).

Table 2 Results of Base-Case Analysis

Treatment	Total Cost, \$	Incremental Cost, \$	QALYs	Incremental QALYs	ICER, \$/QALY
Chem	20,939.83		0.89		
Ser+Chem	81,730.60	60,790.77	1.42	0.53	114,207.24

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; Chem: nab-paclitaxel plus carboplatin chemotherapy; Ser+Chem, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy.

Deterministic Sensitivity Analysis

The DSA results are presented in Figure 2. As shown in the tornado diagram, body weight, the utility value of the PFS stage and the cost of serplulimab had the most significant impact on the base-case results. Furthermore, changes in the discount rate, body surface area and utility value of the PD stage also had moderate effects on the model. Other parameters had little effect on the model, such as the cost of nab-paclitaxel and carboplatin and the cost of supportive care. The ICERs were always above the WTP threshold, indicating that the base-case analysis results were robust.

Probabilistic Sensitivity Analysis

The Monte Carlo simulation scatterplot and the CEAC are displayed in Figure 3 and Figure S2, respectively. According to the scatter plot, all scatter points were above the WTP threshold line, indicating that at a WTP threshold of \$37,743.79/QALY, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy had no possibility of being cost-effective compared to nab-paclitaxel plus carboplatin chemotherapy alone. The CEAC demonstrated that at a WTP of \$60,800/QALY, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy began to have cost-effective possibilities. As the WTP threshold increased, the acceptable proportion of the serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy increased. When the WTP threshold was \$100,900/QALY, the possibility of cost-effectiveness was 50%, while when the threshold increased to \$124,200/QALY, the possibility of being cost-effective increased to 90%.

Scenario Analyses

In scenario analysis 1, only the total cost of serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy changed, while the QALYs for both groups and the total cost of nab-paclitaxel plus carboplatin chemotherapy alone were unaffected. As the price reduction continued to increase, the ICER showed a significant decreasing trend. When the price reduced by 20%, the ICER decreased to \$95,170.36/QALY; When the price further reduced to 50%, the ICER continued to decrease to \$66,615.05/QALY; When the price reduction reached 80%, the ICER was only \$38,059.73/QALY. It is noteworthy that when the price reduction is more than approximately 80.3%, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy become an economical treatment. When price reductions exceed approximately 80.3%,

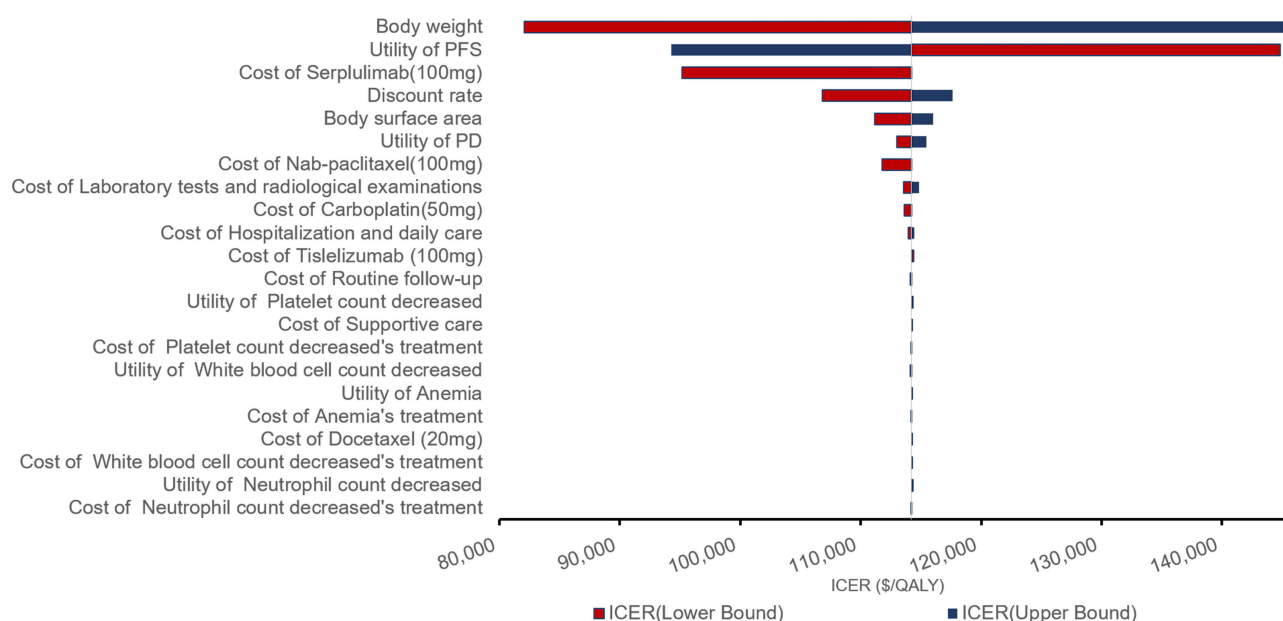


Figure 2 The tornado diagram of deterministic sensitivity analysis. **Abbreviations:** ICER, incremental cost-effectiveness ratio; PD, progressive disease; PFS, progression-free survival.

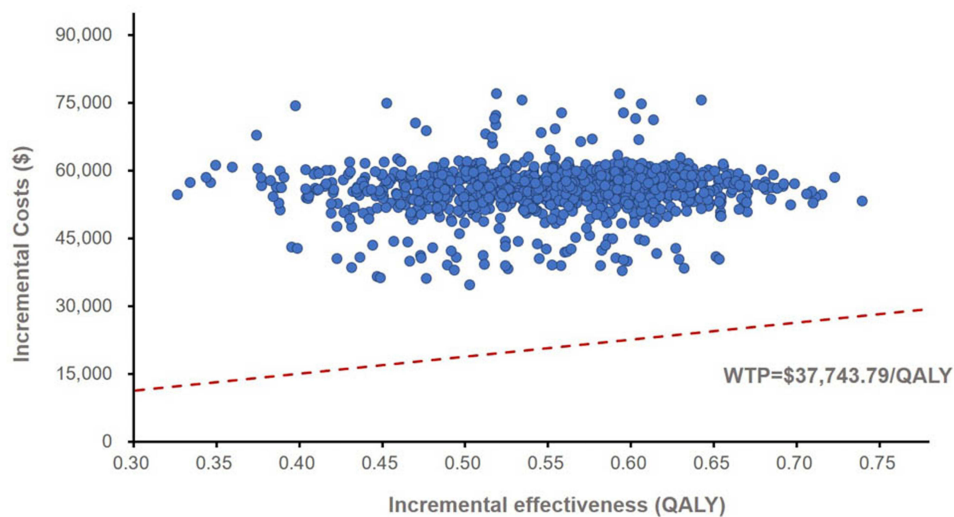


Figure 3 Scatter plot representing Monte Carlo sensitivity analysis. **Abbreviations:** QALY, quality-adjusted life year; WTP, willingness-to-pay.

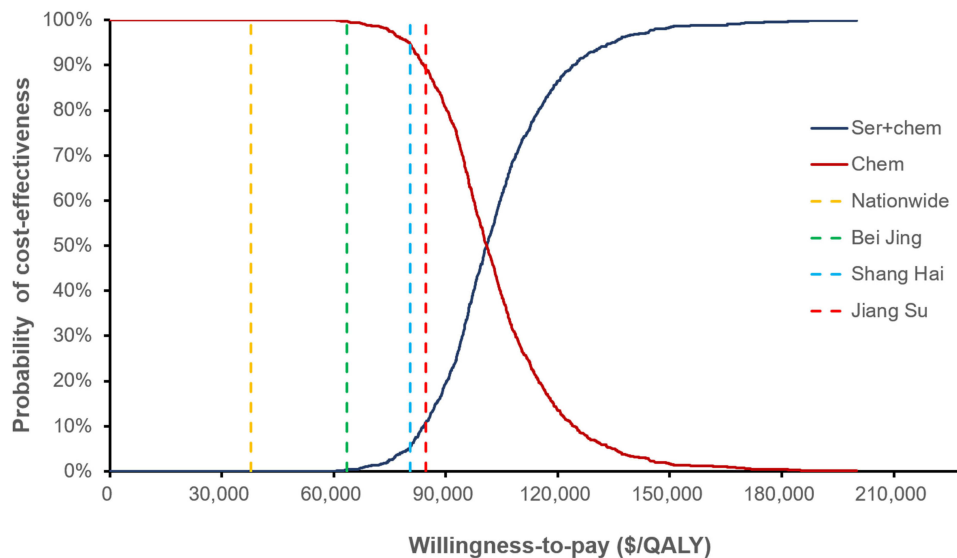


Figure 4 Cost-effectiveness acceptability curves for serplumab combined with nab-paclitaxel plus carboplatin chemotherapy versus nab-paclitaxel plus carboplatin chemotherapy in different economic contexts. **Abbreviations:** QALY, quality-adjusted life year.

serplumab combined with nab-paclitaxel plus carboplatin chemotherapy became a cost-effective treatment option (Table S3).

In scenario analysis 2, the total costs and benefits of both therapeutic strategies remained constant, with the only change being the WTP threshold. The results of scenario analysis 3 are shown in Figure 4. The GDP per capita varies considerably across geographic regions, with east China having the highest GDP per capita at \$18,118.00. The GDP per capita varies even more across cities. Among all cities, Beijing has the highest GDP per capita (\$28,194.13), Shanghai (\$26,839.17) and Jiangsu province (\$21,191.67) in east China have the second and third highest GDP per capita, respectively, while Gansu province has the lowest GDP per capita (\$6,698.68), which is \$21,495.45 lower than Beijing. Even if we used three times the GDP per capita of Beijing as the WTP threshold (\$84,582.39), the combination of immunotherapy with nab-paclitaxel plus carboplatin chemotherapy was still not economical. The probabilities of being cost-effective in Beijing, Shanghai and Jiangsu increased to 10.8%, 5.5%, and 0.3%, respectively.

Table 3 Results of Scenario Analysis 3

Simulation Time	Treatment	Total Cost, \$	Incremental Cost, \$	QALYs	Incremental QALYs	ICER, \$/QALY
5-year	Chem	18,469.43	53,889.61	0.81	0.41	130,161.31
	Ser+Chem	72,359.04		1.22		
10-year	Chem	20,939.83	60,790.77	0.89	0.53	114,207.24
	Ser+Chem	81,730.60		1.42		
15-year	Chem	21,932.22	63,353.40	0.92	0.58	109,309.28
	Ser+Chem	85,285.62		1.50		
20-year	Chem	22,471.08	64,622.76	0.93	0.60	107,053.39
	Ser+Chem	87,093.84		1.53		

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; Chem: nab-paclitaxel plus carboplatin chemotherapy; Ser+Chem, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy.

The results of scenario analysis 3 are shown in Table 3. As the research time horizon increased, both the total costs and benefits of both groups increased. When the time horizon of study was 5 years, the total cost of serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy was \$72,359.04 and 1.22 QALYs were produced, while the cost of nab-paclitaxel plus carboplatin chemotherapy alone was \$18,469.43, resulting in 0.81 QALYs. When the time horizon of study was 20 years, the total cost of serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy was \$87,093.84 and 1.53 QALYs were yielded, whereas the total cost and benefit of nab-paclitaxel plus carboplatin chemotherapy alone was \$22,471.08 and 0.93 QALYs. The ICERs corresponding to the time horizons of 5, 10, 15 and 20 years were \$130,161.31/QALY, \$114,207.24/QALY, \$109,309.28/QALY and \$107,053.39/QALY, respectively. The ICERs showed a downward trend across time horizons, confirming the base-case findings.

Discussion

This study was conducted to evaluate and discuss the cost-effectiveness of serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy as a first-line treatment for patients with advanced squamous NSCLC from the perspective of the Chinese healthcare system. Despite the survival benefit of serplulimab, according to our study, serplulimab combined with chemotherapy was not cost-effective compared to nab-paclitaxel plus carboplatin chemotherapy alone. Serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy provided 0.53 incremental QALYs at an incremental cost of \$60,790.77, resulting in a calculated ICER of \$114,207.24/QALY, which was much greater than the WTP threshold (\$37,743.79/QALY). The DSA indicated that body weight, the utility value of the PFS stage and the cost of serplulimab mainly affected the ICER. The PSA implied that under the current threshold, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy did not have the possibility of being cost-effective. At a WTP threshold of \$100,900/QALY, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy exhibited a 50% probability of being cost-effective compared to nab-paclitaxel plus carboplatin chemotherapy alone. At a WTP threshold of \$124,200/QALY, this probability was 90%.

Novel anti-tumor drugs are inevitably priced high in the market due to the various problems they face during the development process, such as a long upfront research and development time, high cost, low success rate, and patent protection. This high pricing triggers a series of chain reactions: the incremental cost of therapies containing novel anti-tumor drugs rises sharply, but unfortunately, this high investment often brings less than 1 QALY incremental benefit;^{30–33} This situation directly leads to the escalation of the ICER, which makes it difficult to demonstrate satisfactory cost-effectiveness of the majority of novel anti-tumor drugs when they are first introduced to the market.^{34–39}

Currently, immunotherapy drugs approved for first-line treatment of squamous NSCLC in China include pembrolizumab, camrelizumab, sintilimab and so on. In previous studies, the cost-effectiveness of other immunotherapy combined with chemotherapy for treating squamous NSCLC has been calculated. The results of the KEYNOTE-407 study showed

that pembrolizumab combined with chemotherapy improved the OS and PFS of patients, regardless of the PD-L1 expression level.⁴⁰ Similar to our results, the ICER of pembrolizumab combined with chemotherapy as a first-line treatment for untreated advanced squamous NSCLC is much greater than the WTP threshold.³⁴ Camrelizumab is a domestic PD-1 inhibitor developed by China. In the two cost-effectiveness analyses of camrelizumab combined with chemotherapy, the economic results were completely opposite.^{30,35} The initial price of camrelizumab was \$2,861.48/200mg. After NRDL access negotiations, the inclusion of camrelizumab for squamous NSCLC in the NRDL resulted in an 85% price reduction in camrelizumab and the price was reduced to \$423.15/200mg. Therefore, after camrelizumab entered the NRDL, camrelizumab combined with chemotherapy became an economical treatment option. Similarly, for squamous NSCLC, sintilimab and toripalimab have also been included in the NRDL, and their combination with chemotherapy is also economical.^{41,42} Furthermore, in previous pharmacoeconomic studies, serplulimab combined with chemotherapy was not cost-effective as a first-line treatment for extreme-stage small cell lung cancer or esophageal squamous cell carcinoma, possibly because of the extremely high price of serplulimab.^{43–47}

Considering that the cost-effectiveness of serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy may be strongly influenced by drug pricing, we discussed in detail the impact of serplulimab price changes on ICER in our scenario analysis. As the proportion of price reductions for serplulimab gradually increased, the ICER demonstrated a clear downward trend. Specifically, when the serplulimab price was lowered by 10%, the ICER was \$104,688.80/QALY; and when the price reduction climbed to 50%, the ICER has been significantly reduced to around \$66,615.05/QALY. Further, when the price cut was 80% and 90%, the ICER reduced to \$38,059.73/QALY and \$28,541.29/QALY, respectively. But it is also only when the price of serplulimab lowered by more than approximately 80.3% that the ICER of serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy fell below the WTP threshold, making it an economically viable treatment option.

Currently, serplulimab has not been included in the NRDL, and the possibility of its future price adjustment is uncertain. The NRDL access negotiations are a market-oriented mechanism to gather the drug requirements of more than 1.3 billion insured people and engage in a ‘quantity-for-price’ exchange with enterprises, which is equivalent to the negotiators negotiating with enterprises to form a win-win payment price for patients, medical insurance and enterprises. Taking eculizumab as an example, after the NRDL access negotiation in 2023, its price was adjusted from the original approximately \$2,673.87/300mg to approximately \$353.23/300 mg, and after reimbursement from medical insurance, the price of each eculizumab is only a few hundred Chinese yuan. Looking forward, given the remarkable efficacy of serplulimab, we believe that the cost-effectiveness of serplulimab is expected to see a significant improvement if its manufacturer is able to successfully negotiate with the National Healthcare Security Administration.

In addition, the potential impact of the WTP threshold on the final economic outcome was explored in depth in our scenario analysis. Our study followed the China Guidelines for Pharmacoeconomic Evaluations and chose one to three times the GDP per capita as the WTP threshold, in which case the ICER far exceeded the threshold. The criterion of 1–3 times the GDP/QALY per capita is derived from the 2001 report of the WHO’s Commission on Macroeconomics and Health, which was based on outdated research and not rigorously derived.^{48–50} At the same time, there should be variability in threshold levels between different diseases. Anti-tumor drugs are inherently more expensive than general drugs; in addition, tumours are serious life-threatening diseases, and patients are more eager to prolong their lifespan and have a greater willingness to pay.⁵¹ Therefore, it has been suggested that higher thresholds could be set for anti-tumor drugs. Take the United States as an example, the WTP range is usually set between \$50,000/QALY and \$100,000/QALY when cost-effectiveness evaluations of general drugs are conducted, whereas for anti-tumor drugs, the WTP range is usually set between \$100,000/QALY and \$150,000/QALY.⁵² Given China’s vast geographic area and significant differences in economic development levels, willingness to pay varies widely by region and city. We further set three times the GDP per capita of different regions and cities as the threshold for WTP to model the cost-effectiveness of using serplulimab in different economic contexts. However, even in Beijing, a city with a high level of economic development, the combination of serplulimab and nab-paclitaxel plus carboplatin chemotherapy still appeared to be uneconomical. This is still attributed to the exorbitant pricing of serplulimab.

Despite the fact that our study is based on the Chinese healthcare system, the findings may be relevant for other middle-income countries. Although these countries may have different economic conditions, drug pricing mechanisms,

and reimbursement policies, they often face similar challenges such as limited healthcare resources and patients' limited ability to pay. When evaluating new therapies, these factors need to be taken into account collectively. Specifically, the impacts of drug price reductions and regional economic disparities discussed in our scenario analysis provide valuable insights for assessing the economic feasibility of new anti-tumor drugs in middle-income countries. This can help inform treatment choices and drug pricing decisions in these regions.

There are several limitations to our study. First, we modelled real-world patient characteristics and clinical treatment based on data from the ASTRUM-004 trial. The sample size of the clinical trial was small, one-third of the patients in the trial were not from Asia, and owing to the limited follow-up time, the long-term survival beyond the follow-up time was inferred from the distributional characteristics of the survival data. However, these biases were unavoidable. Second, to simplify the model, this study considered only the cost of TEAEs \geq grade 3 with an incidence of $\geq 5\%$, which may have led to a reduction in costs, although the DSA suggested that changes in the cost of TEAEs had little effect on the model. Third, the ASTRUM-004 trial did not provide complete subgroup Kaplan–Meier curves; therefore, we were unable to analyse subgroups of interest, such as the level of PD-L1 expression in tumours, which correlates with immunotherapy efficacy.⁵³ What's more, this study assumes no treatment switching during the progression phase and only considers tislelizumab combined with docetaxel as the second-line treatment. This assumption was made to simplify the model and enhance the feasibility of the analysis. However, in real-world clinical practice, treatment switching may occur due to disease progression or patient response, potentially impacting overall cost-effectiveness. If a significant proportion of patients receive alternative therapies after progression, the total treatment costs and survival benefits may differ from our model's estimations. Future studies incorporating real-world data on treatment switching could provide a more comprehensive economic evaluation.

Conclusion

In conclusion, from the perspective of the Chinese healthcare system, although PFS and OS are prolonged, serplulimab combined with nab-paclitaxel plus carboplatin chemotherapy is not considered cost-effective as the first-line treatment of patients with advanced squamous NSCLC at a WTP threshold of \$37,743.79/QALY under current drug pricing. In pace with more drug price negotiations, the cost of serplulimab is highly likely to decline in the future. These research findings provide a basis for drug pricing decisions.

Data Sharing Statement

The original contributions to the study are included in the article/supplementary materials; please contact the corresponding author for further inquiries.

Ethics Approval

No ethical approval was required, as this research did not involve any human or animal experimental investigations.

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All authors contributed to this publication were listed.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript.

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