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Original Research

Cost-effectiveness analysis of serplulimab in combination with cisplatin plus 5-fluorouracil chemotherapy compared to cisplatin plus 5-fluorouracil chemotherapy as first-line treatment for advanced or metastatic esophageal squamous cell carcinoma in China

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Ying-Tao Lin, Chong-Chong Zhou, Kai Xu, Meng-Die Zhang and Xin Li

Abstract

Background: This study evaluated the cost-effectiveness of serplulimab plus chemotherapy *versus* chemotherapy alone in treating advanced/metastatic esophageal squamous cell carcinoma (ESCC) within the Chinese health care system.

Methods: A partitioned survival model based on ASTRUM-007 trial patient characteristics was developed. Efficacy, safety, and medical/economic data were obtained from the trial and real-world clinical practice. Costs, quality-adjusted life years (QALY), and incremental cost-effectiveness ratios (ICERs) were calculated for both treatment strategies. Sensitivity, subgroup, and scenario analyses were performed to assess the uncertainty impact.

Results: Serplulimab combined with chemotherapy yielded an ICER of US$ 53,538.27/QALY. Deterministic sensitivity analysis identified patient survival and serplulimab price as influential parameters. Probabilistic sensitivity analysis showed a 47.33% probability of cost-effectiveness at a willingness-to-pay (WTP) threshold of US$ 53,541/QALY and 0.05% at three times China's GDP per capita. Subgroup analysis revealed that patients with a programmed death-ligand 1 (PD-L1) expression combined positive score (CPS) ⩾10 had a lower hazard ratio (0.59) and ICER (US$ 29,935.23/QALY), with a 95.36% probability of cost-effectiveness. Scenario analysis demonstrated that the drug donation discount policy significantly increased the likelihood of cost-effective serplulimab-chemotherapy combinations in Jiangsu, Fujian, and Guangdong at 99.99%, 99.90%, and 94.16%, respectively.

Conclusion: Compared to chemotherapy alone, serplulimab combined with chemotherapy is currently not a cost-effective first-line treatment for advanced/metastatic ESCC in China. However, as serplulimab plus chemotherapy regimens evolve and price competition among programmed death 1 (PD-1) inhibitors intensifies, this combination may become a cost-effective treatment option.

Plain language summary

Assessing Serplulimab's Value in Treating Advanced Esophageal Cancer in China

In China, esophageal cancer patients often need chemotherapy due to late diagnosis.

Serplulimab, an expensive new treatment, is not cost-effective when combined with chemotherapy for most patients.

Correspondence to:
Xin Li
Center for Global Health, School of Public Health, Nanjing Medical University, No.101 Longmian Avenue, Nanjing, Jiangsu 210029, China

Department of Pharmaceutical Regulatory Science and Pharmacoeconomics, School of Pharmacy, Nanjing Medical University, No.101 Longmian Avenue, Nanjing, Jiangsu, China
xinli@njmu.edu.cn

Ying-Tao Lin
Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, Jiangsu, China

Department of Drug Clinical Trial Institution, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian, China

Department of Pharmaceutical Regulatory Science and Pharmacoeconomics, School of Pharmacy, Nanjing Medical University, Nanjing, Jiangsu, China

Chong-Chong Zhou
Kai Xu
Meng-Die Zhang
Department of Pharmaceutical Regulatory Science and Pharmacoeconomics, School of Pharmacy, Nanjing Medical University, Nanjing, Jiangsu, China

However, for specific patient groups with a PD-L1 expression CPS ⩾ 10, it is both effective and affordable. This finding helps health care leaders create better pricing strategies.

Keywords: chemotherapy, cost-effectiveness, esophageal squamous cell carcinoma, partitioned survival model, serplulimab

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Introduction

Esophageal cancer is the seventh most commonly diagnosed cancer globally, with over half of new cases and deaths occurring in China, where approximately 246,000 new cases and 188,000 deaths are reported annually.[1,2] High-incidence areas are mainly concentrated near the Taihang Mountains, including Henan, Hebei, Shanxi, Shandong Taian, Shandong Jining, Shandong Heze, Anhui, and the northern Jiangsu region.[3] Other high-incidence areas include Nanchong in Sichuan, Yanting in Sichuan, Shantou in Guangdong, and Fuzhou in Fujian.[4]

In China, esophageal squamous cell carcinoma (ESCC) accounts for 90% of esophageal cancers, and early symptoms are not obvious.[5,6] Most patients are diagnosed at advanced stages or with metastasis, missing the chance for surgical treatment. The disease progresses quickly and is fatal, with a median survival time of only 4–6 months and a 5-year survival rate of <5%.[7] Chemotherapy comprising paclitaxel or fluorouracil combined with platinum-based drugs as palliative care is the most common treatment for advanced or metastatic (advanced/metastatic) ESCC. However, its effect is limited.[8,9] Recently, immunotherapy using immune checkpoint inhibitors (ICIs) has made significant advances,[10,11] with pembrolizumab and serplulimab being used as first-line treatments for advanced esophageal cancer. Pembrolizumab combined with chemotherapy has been approved by the Food and Drug Administration (FDA) and National Medical Products Administration (NMPA) for locally advanced unresectable or metastatic esophageal cancer or gastroesophageal junction (GEJ) adenocarcinoma based on the results of the KEYNOTE-590 study.[12] Similarly, serplulimab combined with chemotherapy has been adopted as the first-line treatment for advanced esophageal cancer in China.[13] This strategy stems from the findings of the ASTRUM-007 study. This study revealed that within the full patient cohort, the median progression-free survival (PFS) was 5.8 months for the group receiving serplulimab and chemotherapy, as opposed to 5.3 months for the placebo plus chemotherapy group [hazard ratio (HR) = 0.60, 95% confidence interval (CI) 0.48–0.75, $p < 0.0001$]. Additionally, the overall survival (OS) was 15.3 months *versus* 11.8 months (HR = 0.68, 95% CI, 0.53–0.87, $p = 0.0020$). In the patient subgroup with a programmed death-ligand 1 (PD-L1) combined positive score (CPS) ⩾10, the median PFS was 7.1 months *versus* 5.3 months (HR = 0.48, 95% CI, 0.34–0.68, $p < 0.0001$), and the OS was 18.6 months *versus* 13.9 months (HR = 0.59, 95% CI, 0.40–0.88, $p = 0.0082$). Given these trial outcomes, the NMPA has accepted the application for market authorization of serplulimab in combination with chemotherapy for the treatment of ESCC, thereby potentially introducing a novel treatment option for patients.

While ICIs have shown improved efficacy compared to existing clinical treatments,[14–16] they are expensive.[17] In 2022, pembrolizumab cost approximately US$ 2,600 per 100 mg and serplulimab cost approximately US$ 810 per 100 mg, while the per capita GDP in China in the same year was approximately US$ 12,400. This puts a heavy economic burden on patients, especially in rural areas and western regions where esophageal cancer is highly prevalent. Therefore, medical decision-makers should take into account the economic cost of a treatment, and not only its clinical efficacy, when choosing treatment options. Our study aimed to evaluate the cost-effectiveness of serplulimab combined with cisplatin plus 5-fluorouracil (5-FU) as a replacement for chemotherapy alone from the perspective of Chinese society by measuring and comparing the treatment costs and efficacy based on data from the ASTRUM-007 trial.

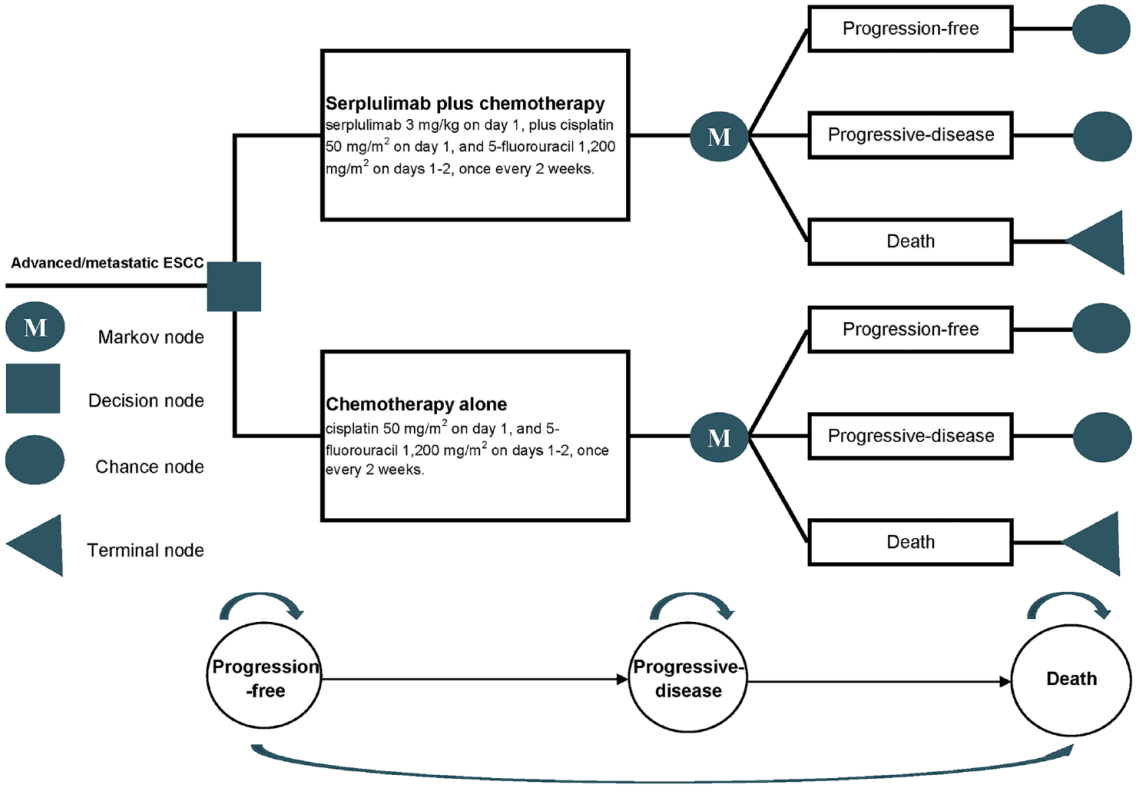

Figure 1. Profile of the partitioned survival model for ASTRUM-007.

Materials and methods

Target population

Our study faithfully adhered to the Comprehensive Health Economic Evaluation Report standards for conducting an economic evaluation.[18] Our target population mirrored the demographics of the patients in the ASTRUM-007 clinical trial, a randomized, double-blind, multicenter phase III trial conducted in China. In this trial, patients were randomized (2:1) to receive either serplulimab and chemotherapy or placebo and chemotherapy. Randomization was stratified by PD-L1 expression level (CPS $\geqslant$ 10 *versus* CPS $<$ 10), age ($\geqslant$65 years *versus* $<$ 65 years), and disease status (locally advanced disease *versus* distant metastasis). This trial involved 62 cancer centers and hospitals from diverse regions of China, including eastern, central, and western areas, with the Fujian Cancer Hospital being one of them. Out of the 551 patients who were randomized, 550 underwent at least one cycle of investigational drug therapy. These patients were aged 18–75, had not previously received systemic antitumor therapy for current recurrence or metastasis, had histologically confirmed advanced ESCC (including GEJ) that was not curable by surgery or chemoradiotherapy, and had a PD-L1-positive combined positive score (CPS) $\geqslant$ 1.

Model construction

Clinical trial data from ASTRUM-007 were used to build a partitioned survival model[19] for assessing the cost-effectiveness of serplulimab combined with cisplatin plus 5-FU (serplulimab plus chemotherapy) compared to cisplatin plus 5-FU (chemotherapy alone). This model is frequently employed to analyze advanced tumor diagnosis and treatment clinical efficacy and health care costs.[20–23] Three mutually exclusive health states were constructed in the current study: disease-free progression, disease progression, and the terminal stage, as depicted in Figure 1. The model operated on a 2-week (14 days) cycle over an evaluation horizon of 240 weeks, consistent with the ASTRUM-007 trial's clinical treatment timeline. The model's main outputs were cost, quality-adjusted life years (QALY), and incremental cost-effectiveness ratios (ICERs).

Cost

Our study factored in various clinical costs linked to cancer treatment, which comprised drug acquisition, laboratory tests, imaging examinations, drug management, disease progression visits, treatment-related adverse events (AEs), and terminal costs. All these expenses represent direct medical costs and were converted to US dollars using the exchange rate in March 2023 (1 USD = 6.907 CNY). Cost data were collected from reliable sources such as the National Health Commission of China, the Health Commission of Fujian Province, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, and expert consensus. Key cost parameters are provided in Table 1.

Table 1. Key input parameters to our model and ranges of the sensitivity analyses.

Input parameters	Base case value	Lower bound	Upper bound	Distribution	Source
Weibull OS survival model					
Serplulimab + CF group	Scale (λ) = 0.014 Shape (γ) = 1.416	–	–	Weibull	Song *et al.*[13]
CF Chemotherapy group	Scale (λ) = 0.015; Shape (γ) = 1.530	–	–	Weibull	Song *et al.*[13]
Weibull PFS survival model					
Serplulimab + CF group	Scale (λ) = 0.057; Shape (γ) = 1.264	–	–	Weibull	Song *et al.*[13]
CF Chemotherapy group	Scale (λ) = 0.068; Shape (γ) = 1.409	–	–	Weibull	Song *et al.*[13]
Drug acquisition, cost per cycle, US$					
serplulimab (Shanghai Henlius Biotech Inc.) per 100 mg	809.03	647.23	970.84	Gamma	National Health Commission of China
cisplatin (Jiangsu Hengrui Medicine Co., Ltd.) per 30 mg	2.77	2.21	3.32	Gamma	National Health Commission of China
5-fluorouracil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd.) per 500 mg	42.28	33.82	50.73	Gamma	National Health Commission of China
Drug administration, cost per cycle, US$					
Drug administration Hospitalization	36.20	28.96	43.43	Gamma	Local medical data
Drug administration Preventive medication	86.87	69.49	104.24	Gamma	Local medical data
Drug administration Infusion	1.72	1.37	2.06	Gamma	Local medical data
Laboratory and imaging examination, US$					
12-lead ECG	3.91	3.13	4.69	Gamma	Fujian Provincial Health Commission
Hematology	3.62	2.90	4.34	Gamma	Fujian Provincial Health Commission
Serum chemistry	26.06	20.85	31.27	Gamma	Fujian Provincial Health Commission
Urinalysis	4.34	3.47	5.21	Gamma	Fujian Provincial Health Commission
Coagulation parameters	9.64	7.71	11.56	Gamma	Fujian Provincial Health Commission
Thyroid function	21.72	17.37	26.06	Gamma	Fujian Provincial Health Commission

(Continued)

Table 1. (Continued)

Input parameters	Base case value	Lower bound	Upper bound	Distribution	Source
Pulmonary function tests	56.46	45.17	67.76	Gamma	Fujian Provincial Health Commission
Contrast-enhanced CT	402.85	322.28	483.42	Gamma	Fujian Provincial Health Commission
Costs of AE (Grade > 3), cost per cycle, US$					
Anemia	39.81	31.85	47.78	Gamma	CSCO clinical practice guidelines for tumor-associated anemia
Neutrophil count decreased	228.03	182.42	273.64	Gamma	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy
White blood cell count decreased	228.03	182.42	273.64	Gamma	Expert consensus on the diagnosis and treatment of neutropenia caused by tumor chemotherapy
Serplulimab + CF group AE risks (grade > 3), %					
Anemia	0.177	0.141	0.21	Beta	Song *et al.*[13]
Neutrophil count decreased	0.187	0.150	0.22	Beta	Song *et al.*[13]
White blood cell count decreased	0.113	0.091	0.14	Beta	Song *et al.*[13]
CF Chemotherapy group AE risks (grade > 3), %					
Anemia	0.204	0.163	0.24	Beta	Song *et al.*[13]
Neutrophil count decreased	0.174	0.139	0.21	Beta	Song *et al.*[13]
White blood cell count decreased	0.066	0.053	0.08	Beta	Song *et al.*[13]
Terminal cost, US$					
Funeral expenses	4178.37	3,342.70	5014.04	Gamma	Local data
Utility value					
Progression-free disease	0.74	0.59	0.89	Beta	Wu *et al.*,[24] Lin *et al.*,[25] Zheng *et al.*[26]
Progressive disease	0.58	0.46	0.70	Beta	Wu *et al.*,[24] Lin *et al.*,[25] Zheng *et al.*[26]
Anemia	−0.0028	−0.0023	−0.0034	Beta	Zheng *et al.*[26] Xu *et al.*,[27] Zhang *et al.*[28]
Neutrophil count decreased	−0.0035	−0.0028	−0.0041	Beta	Zheng *et al.*[26] Xu *et al.*,[27] Zhang *et al.*[28]
White blood cell count decreased	−0.0035	−0.0028	−0.0041	Beta	Zheng *et al.*[26] Xu *et al.*,[27] Zhang *et al.*[28]
Discount rate	0.05	0	0.08	Beta	Liu *et al.*[29]

AE, adverse events; CF, cisplatin plus 5-fluorouracil; CT, computed tomography; CSCO, Chinese Society of Clinical Oncology; ECG, electrocardiogram; OS, overall survival; PFS, progression-free survival.

In our model, we assessed three drugs and their manufacturers: serplulimab (Shanghai Henlius Biotech Inc.), cisplatin (Jiangsu Hengrui Medicine Co., Ltd.), and 5-FU (Shanghai Xudong Haipu Pharmaceutical Co., Ltd.). Drug prices, sourced from the Chinese National Health Commission's 2023 price list, were as follows: serplulimab, US$ 809/100 mg; cisplatin, US$ 3/30 mg; and 5-FU, US$ 42/500 mg. The dosing regimen followed the ASTRUM-007 trial protocols: serplulimab at 3 mg/kg, cisplatin at 50 mg/m^2, and 5-FU at 2400 mg/m^2, all administered intravenously on Day 1 of each 14-day treatment cycle. The body surface area was 1.73 m^2 based on the average height and weight of the Chinese population reported in the 2022 China Statistical Yearbook published by the National Bureau of Statistics of China.

We simulated real-world drug administration and calculated the costs of preventive administration, hospitalization, nursing, and drug infusion. We rounded the amount of medication used up to the nearest vial since the remaining infusion drugs during administration must be recovered and destroyed rather than being administered to the next patient.

Lab and imaging examinations were assumed to follow the ASTRUM-007 trial schedule. During each treatment cycle, we conducted various tests (12-lead ECG, hematology, serum chemistry, coagulation, urinalysis, pulmonary function tests, and thyroid function checks every two cycles). The imaging examination used remained the same throughout the study. Contrast-enhanced computed tomography (CT) was performed every 6 weeks within the first 48 weeks, and after 48 weeks, contrast-enhanced CT was performed every 12 weeks, with costs including chest, abdominal, and neck examinations, as well as venous puncture and contrast agents.

The costs of treatment-related AEs were derived from the 2023 charging standards of the Fujian Provincial Health Commission, considering only those of grade 3 or higher with an incidence rate greater than 5%. The cost of AEs for serplulimab plus chemotherapy followed the NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities Version 4.2021,[30] while costs for chemotherapy alone were determined through expert consensus. We anticipated that patients would incur costs for physical examinations and visits when the disease progressed and terminal costs when they died, and the terminal costs were estimated based on legal interpretations related to the one-time funeral expenses of personal injury compensation cases reviewed by the Supreme People's Court.[31]

Utility scores

Although the ASTRUM-007 trial did not provide individual patient data on utility scores, scholars have utilized the reported quality of life data in the literature as a point of reference for utility scores in cost-effectiveness analyses of esophageal cancer treatment.[32–36] The published literature and current practice support the realistic assumption that as the disease progresses toward death, esophageal cancer patients will experience a decline in utility scores due to declining physical function and worsening symptoms during and after treatment.[37–40] Therefore, our model determined the utility score for PFS to be 0.74, the utility score for progression disease (PD) to be 0.58, and the utility score for mortality to be 0.[24–26] Additionally, we have considered the negative impact of treatment-related AEs of grade 3 or higher with an incidence greater than 5% on patient quality of life, which could lead to negative utility scores.[26–28] The main utility parameters are shown in Table 1.

Sensitivity analyses

We subjected our model to a deterministic sensitivity analysis, modifying all input parameters by 20% in both positive and negative directions.[32,41] During this process, we held other parameters constant to evaluate the effect of each individual parameter on the model's stability. The discount rate for both costs and health outcomes was set at 5% per annum, varying from 0% to 8%.[29] Moreover, we performed a probabilistic sensitivity analysis employing Monte Carlo simulation.[24,42] Assuming a gamma distribution for cost parameters and a beta distribution for utility parameters,[43] we sampled one sample randomly from the distribution of all parameters for each iteration. We executed 10,000 simulation iterations to observe the effects of simultaneous parameter changes on the model's stability. The World Health Organization (WHO) recommends setting the willingness to pay (WTP) threshold at three times the gross domestic product (GDP) per capita.[44] According to a report by the National Bureau of Statistics of China, the GDP per capita

in China for 2022 was approximately US$ 12,408. Therefore, the WTP threshold in this study was set at US$ 37,223/QALY.

Scenario analyses

Our scenario analyses focused on understanding the economic implications of serplulimab, particularly in Chinese regions with high rates of esophageal cancer. The regions included provinces near the Taihang Mountains, such as Henan, Hebei, Shanxi, Shandong, Anhui, and Jiangsu, along with Sichuan, Guangdong, and Fujian. We concentrated on two primary scenarios. The first was the variation in the WTP threshold among these regions. We simulated the impact of these disparities, given the differing economic contexts, on the potential adoption and use of serplulimab. In the second scenario, we evaluated the influence of the serplulimab discount policy, which permits a 37.50% price reduction from the original cost. By modifying our model's key assumptions relating to the price of serplulimab and the WTP threshold, we examined their collective impact on the robustness of our findings.

Subgroup analyses

In the subgroup analysis, we calculated the incremental cost-effectiveness ratio (ICER) using the subgroup-specific HR for OS derived from ASTRUM-007. Due to insufficient data, we referred to the method from the literature,[45] assuming that the HR of PFS for subgroups was the same as that for the overall population, and we assumed proportional hazards. We analyzed patient subgroups based on age, ECOG performance status, sex, PD-L1 expression, disease status, and smoking status.

Statistical analysis

We used survival curves extracted from the ASTRUM-007 trial data using Get Data Graph Digitizer 2.25 software. We reconstructed individual data using R software to simulate patient survival rates under log-normal, exponential, Weibull, Gompertz, and log-logistic distributions. The selection of distribution functions was based on minimizing the Akaike information criterion (AIC) and Bayesian information criterion (BIC), in addition to visual inspection and published references. We selected Weibull distributions to simulate the 240-week time horizon of patients receiving serplulimab plus chemotherapy and chemotherapy alone. The costs and health outcomes of three mutually exclusive health states, subgroup analyses, and sensitivity analyses were calculated using Excel 2019.

Table 2. Results of our model.

Results	Serplulimab + CF	CF + Chemotherapy
Total costs	US$ 47,101.88	US$ 14,256.81
QALYs	1.39	0.78
ICER, US$/QALYs	US$ 53,538.27	–

CF, Cisplatin plus 5-Fluorouracil; ICER, Incremental cost-effectiveness ratio; QALYs, Quality-adjusted life-years.

Results

Base-case analysis

Over the 240-week simulation period, the total cost for serplulimab plus chemotherapy amounted to US$ 47,101.88, while the chemotherapy alone cost was US$ 14,256.81. Consequently, the incremental cost of implementing serplulimab plus chemotherapy compared to chemotherapy alone reached US$ 32,845.07. Regarding the breakdown of the costs, the serplulimab plus chemotherapy regimen *versus* chemotherapy alone accounted for the following expenses: drug acquisition cost – US$ 34,824.92 *versus* US$ 4,638.02, drug administration cost – US$ 2,165.29 *versus* US$ 1,488.55, laboratory and imaging examination cost – US$ 3,450.10 *versus* US$ 2,371.80, treatment-related AE cost – US$ 1,760.05 *versus* US$ 980.08, PD cost – US$ 902.11 *versus* US$ 725.18, and terminal cost – US$ 3,999.41 *versus* US$ 4,053.18. When considering the QALY gained, serplulimab plus chemotherapy resulted in an incremental gain of 0.61 (1.39 *versus* 0.78) compared to chemotherapy alone. Finally, the ICER of serplulimab plus chemotherapy *versus* chemotherapy alone was US$ 53,538.27/QALY. The primary outcomes are presented in Table 2.

Sensitivity analyses

Deterministic sensitivity analyses. The one-way deterministic sensitivity analysis results indicated that the survival time of serplulimab plus chemotherapy was the most sensitive parameter in the model. Furthermore, changes in other parameters, such as the survival time in the

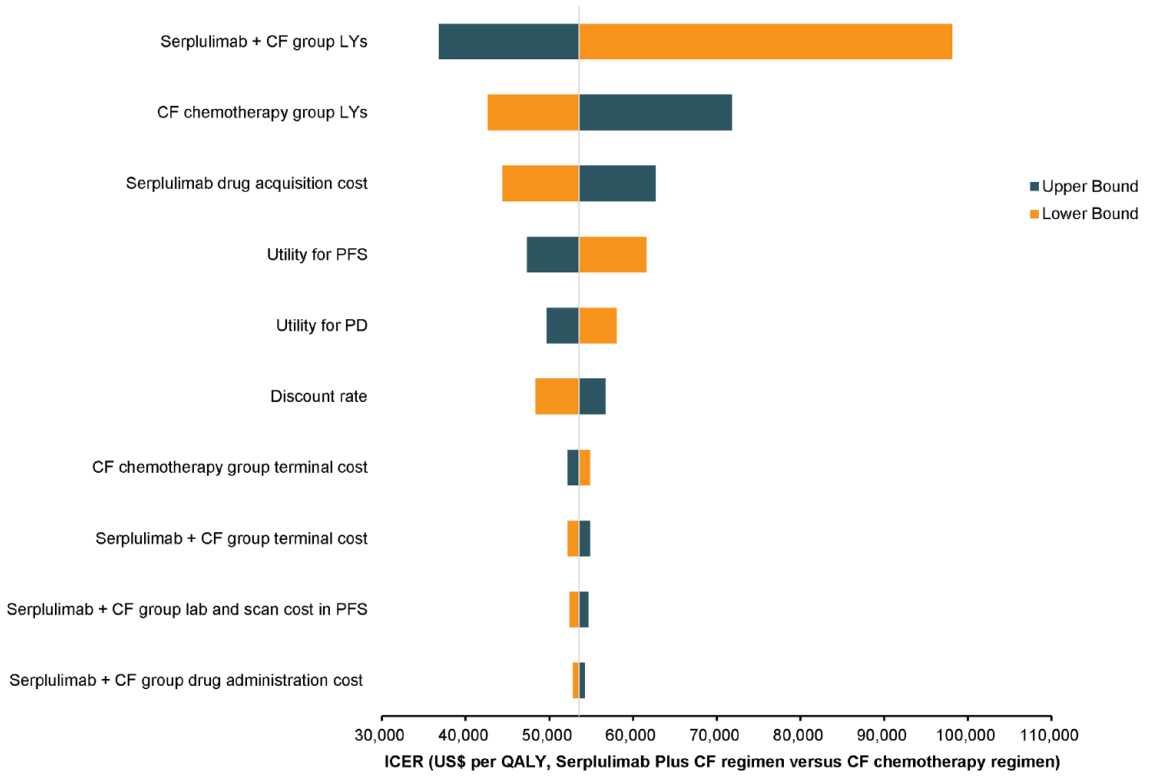

Figure 2. Tornado diagram depicting the top 10 most influential parameters.

chemotherapy alone group, serplulimab drug acquisition cost, utility for PFS, utility for PD, and discount rate, also had a significant impact on the model results. In general, variations in each parameter affected the model results, leading to a fluctuation in the ICER within the range of US$ 36,000/QALY to US$ 100,000/QALY. The tornado diagram, shown in Figure 2, provides a visual representation of the top 10 parameters that had the greatest influence on the model outcomes.

Probabilistic sensitivity analyses. The Monte Carlo probabilistic sensitivity analysis results indicated that serplulimab plus chemotherapy may not be a cost-effective option when compared to chemotherapy alone at the WTP threshold of US$ 37,223/QALY. However, when the WTP threshold was increased to US$ 53,541/QALY (the number closest to US$ 53,538.27/QALY in the simulated iterations), the probability of serplulimab plus chemotherapy being cost-effective compared to chemotherapy alone increased to 47.33%. The Monte Carlo simulation scatterplot and the WTP curve are displayed in Figures 3 and 4, respectively.

Subgroup analysis. Our subgroup analysis revealed that the HR played a significant role in determining the ICER in the first-line treatment of ESCC. Specifically, serplulimab plus chemotherapy demonstrated a lower ICER than chemotherapy alone when considering patients with a lower mortality risk. Based on the results from the probabilistic sensitivity analysis, subgroups that demonstrated higher survival rates also exhibited more cost-effective ICERs. Consistent with a WTP threshold of three times the Chinese per capita GDP, serplulimab plus chemotherapy could be more cost-effective than chemotherapy alone for specific patient subgroups. These included patients aged under 65 years (ICER = US$ 33,925.31/QALY), those with an ECOG performance status = 0 (ICER = US$ 15,810.40/QALY), females (ICER = US$ 18,520.67/QALY), patients with a PD-L1 expression CPS $\geqslant$ 10 (ICER = US$ 29,935.23/QALY), and those with locally advanced disease (ICER = US$ 22,570.92/QALY). For these patient populations, the ICER was less than US$ 37,223/QALY. In contrast, the treatment was not deemed cost-effective for patients aged 65 years or older (ICER = US$ 65,480.17/QALY), those with an ECOG

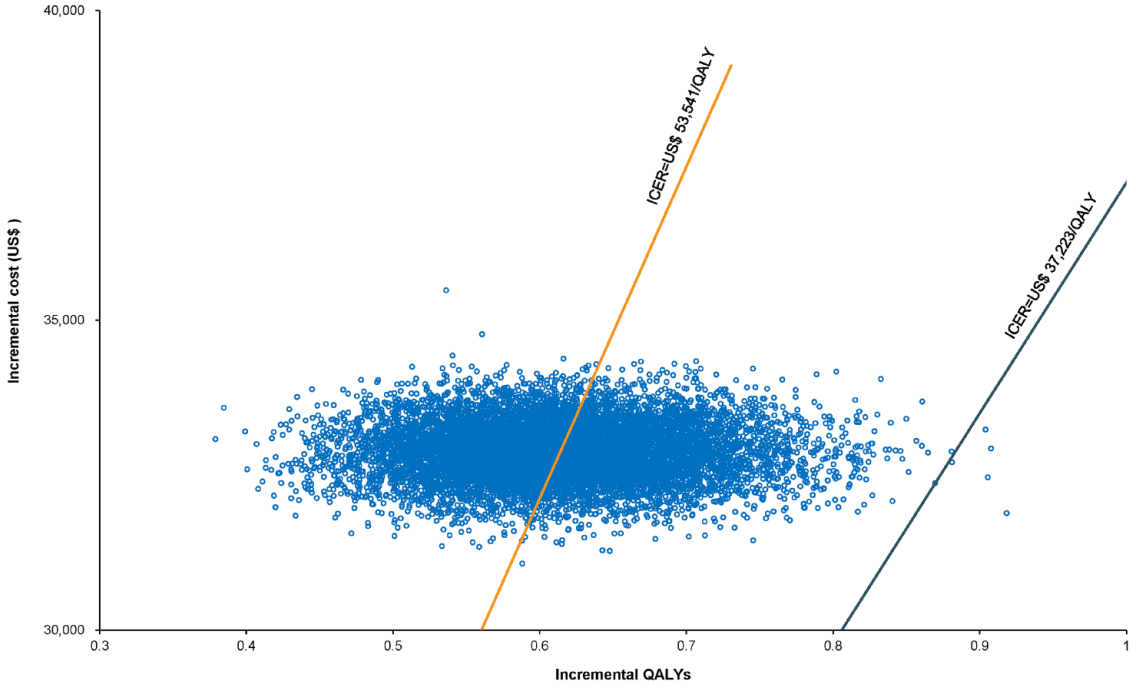

Figure 3. Scatter plot representing Monte Carlo sensitivity analysis.

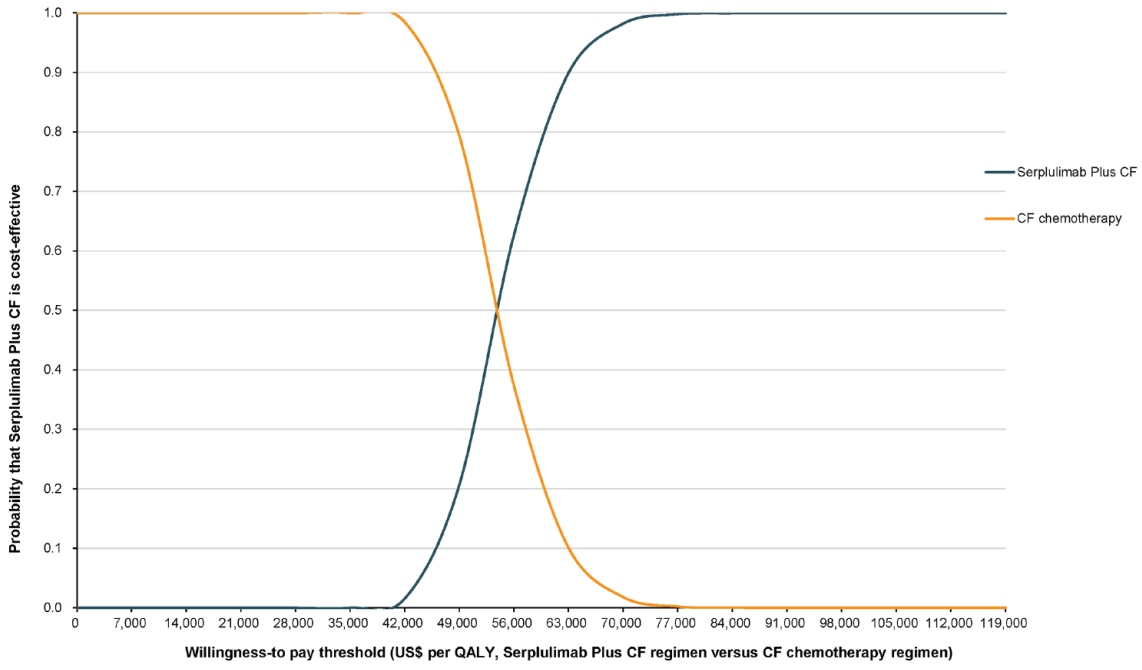

Figure 4. Cost-effectiveness acceptability curve comparing serplulimab plus CF *versus* CF chemotherapy.
CF, cisplatin plus 5-fluorouracil.

performance status = 1 (ICER = US$ 48,422.50/QALY), males (ICER = US$ 42,174.25/QALY), patients with a PD-L1 expression $1 \leqslant CPS < 10$ (ICER = US$ 58,942.89/QALY), those with distant metastasis (ICER = US$ 48,422.50/QALY), current or former smokers (ICER = US$

Table 3. Subgroup analysis results.

Subgroup	HR for OS (95%CI)	ICER, US$/QALY (range)	Cost-effectiveness probability of serplulimab plus CF, %
Age			
<65	0.62 (0.45–0.87)	33,925.31 (17,113.76, 135,282.74)	75.49
⩾65	0.76 (0.52–1.12)	65,480.17 (22,570.92, dominated)	0.00
ECOG			
0	0.43 (0.24–0.78)	15,810.40 (7,130.24, 73,166.20)	100.00
1	0.70 (0.53–0.93)	48,422.50 (23,487.12, 255,776.72)	1.06
Sex			
Male	0.67 (0.51–0.88)	42,174.25 (21,692.87, 147,557.49)	13.62
Female	0.47 (0.21–1.03)	18,520.67 (6,204.68, dominated)	100.00
PD-L1 expression			
1⩽CPS<10	0.74 (0.54–1.03)	5,8942.89 (24,443.86, dominated)	0.00
CPS⩾10	0.59 (0.40–0.88)	29,935.23 (14,028.22, 147,557.49)	95.36
Disease status			
Locally advanced	0.52 (0.26–1.04)	22,570.92 (7,801.54, dominated)	99.98
Distantly metastatic	0.70 (0.54–0.92)	48,422.50 (24,443.86, 224,365.03)	0.99
Smoking status			
Current or former smoker	0.65 (0.47–0.89)	38,595.01 (18,520.67, 161,902.68)	36.31
Never smoked	0.73 (0.47–1.14)	56,027.84 (18,520.67, dominated)	0.04

CF, Cisplatin plus 5-Fluorouracil; CI, Confidence Interval; CPS, Combined positive score; Dominated, a regimen is an absolute disadvantaged one.; ECOG, Eastern cooperative oncology group; HR, hazard ratio; ICER, Incremental cost-effectiveness ratio; OS, Overall survival; PD-L1, Programmed death-ligand 1; QALYs, Quality-adjusted life-years.

38,595.01/QALY), and never smokers (ICER = US$ 56,027.84/QALY). The results of the subgroup analyses are presented in Table 3.

Scenario analyses. We assessed two scenarios for patients in esophageal cancer high-incidence areas: the WTP threshold for purchasing serplulimab and the serplulimab donation discount policy. Esophageal cancer is highly prevalent in the provinces of Henan, Hebei, Shanxi, Shandong, Anhui, and Jiangsu near the Taihang Mountains as well as in the western province of Sichuan and the eastern provinces of Guangdong and Fujian. Economic development varies across China's provinces, influencing patients' WTP based on the local GDP. We replaced the WTP threshold of three times the Chinese per capita GDP with the WTP threshold of three times the per capita GDP for each of the nine provinces in our probabilistic sensitivity analysis. The probabilities of serplulimab plus chemotherapy being more cost-effective than chemotherapy alone in Jiangsu, Fujian, Guangdong, and Shandong were 89.41%, 57.17%, 4.12%, and 0.07%, respectively, while the probabilities in Anhui, Shanxi, Sichuan, Henan, and Hebei were 0 (Figure 5).

However, Shanghai Henlius Biopharmaceuticals Co., Ltd. has implemented a serplulimab drug discount policy across China, enabling patients to purchase serplulimab at a 37.50% discount (62.50% of the original price). Under this policy, the probability of serplulimab plus chemotherapy being more cost-effective than chemotherapy

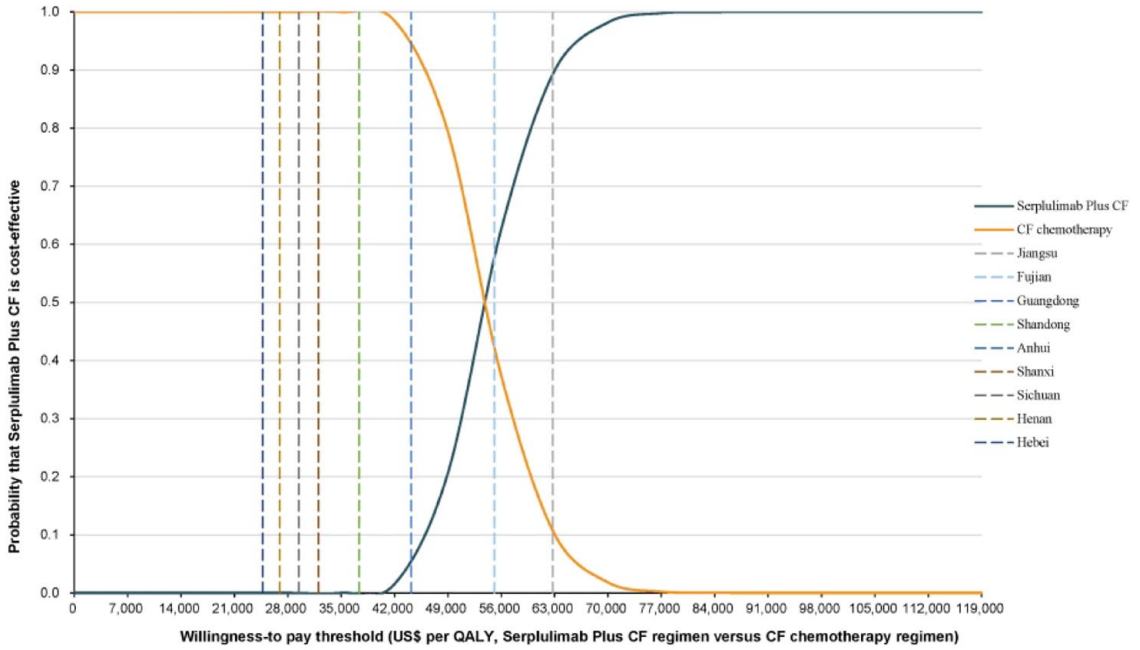

Figure 5. Acceptability curve for serplulimab plus CF *versus* CF chemotherapy in China's nine high-incidence esophageal cancer provinces.
CF, cisplatin plus 5-fluorouracil.

alone at the WTP threshold of three times the Chinese per capita GDP increased to 56.69% in the probabilistic sensitivity analysis. The probabilities of being cost-effective in Jiangsu, Fujian, Guangdong, and Shandong increased to 99.99%, 99.90%, 94.16%, 57.81%, respectively, while the probabilities in Anhui, Shanxi, Sichuan, Henan, and Hebei increased to 12.75%, 12.74%, 3.12%, 0.3%, 0.03%, respectively (Figure 6).

Discussion

In recent years, the high cost of health care has emerged as a significant global issue.[46] Along with treatment outcomes, health economists and policy experts are increasingly focusing on the economic burden of drugs. The cost-effectiveness of drugs is now a crucial consideration when selecting treatment options and formulating health insurance policies. Advanced/metastatic ESCC is a rapidly progressing and fatal disease that severely impacts patients' quality of life,[40] even with immunotherapy. However, the high costs of treatment may offset the clinical benefits, and patients and their families may face significant financial challenges. According to our simulation results based on the ASTRUM-007 trial, serplulimab plus chemotherapy first-line treatment for advanced/metastatic ESCC results in higher survival rates than chemotherapy alone. However, serplulimab plus chemotherapy also significantly increases health care costs. The cost of adding one quality-adjusted life year for patients treated with serplulimab plus chemotherapy is US$ 53,538.27 compared with the chemotherapy alone regimen. From the perspective of the Chinese health care system, serplulimab plus chemotherapy may not be a cost-effective treatment option compared to chemotherapy alone. The probabilistic sensitivity analysis results indicate that the possibility of serplulimab plus chemotherapy being a cost-effective alternative to chemotherapy alone when the WTP threshold is set at US$ 53,538.27/QALY is 47.33%, and when the WTP threshold is reduced to US$ 37,223/QALY, the probability drops to 0.01%. In addition to the ASTRUM-007 trial, three phase III clinical trials (KEYNOTE-590,[12] ESCORT-1st,[47] and JUPITER-06[48]) have evaluated the efficacy and safety of pembrolizumab, camrelizumab, and toripalimab combined with chemotherapy compared to chemotherapy alone as first-line treatment for advanced/metastatic ESCC. Health economists have reported economic analysis reports based on Markov models or partition survival models for these three

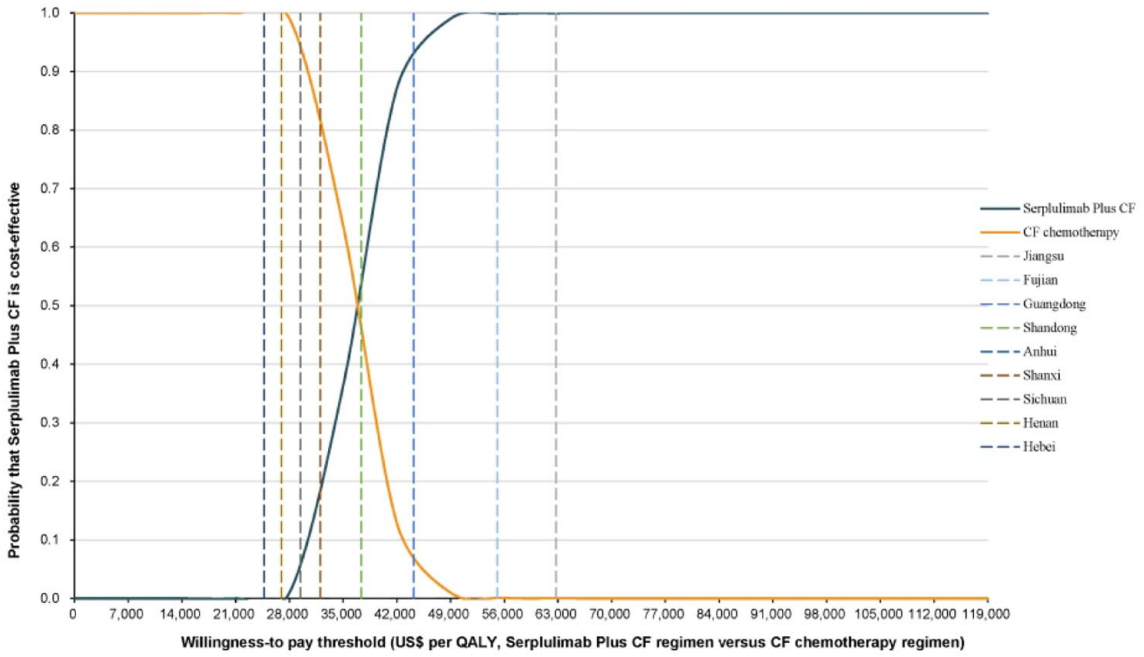

Figure 6. Acceptability curve for serplulimab plus CF *versus* CF chemotherapy in China's nine high-incidence esophageal cancer provinces with the serplulimab drug discount policy.
CF, cisplatin plus 5-fluorouracil.

trials.[26–28] The research results show that using three times China's per capita GDP as the WTP threshold, pembrolizumab, camrelizumab, or toripalimab combined with chemotherapy are not cost-effective alternative treatments to chemotherapy. Although the KEYNOTE-590, ESCORT-1st, and JUPITER-06 clinical trials have many similarities with the ASTRUM-007 trial and the cost-effectiveness analysis results are consistent with our research results, it seems that serplulimab combined with chemotherapy may not be an economic alternative to chemotherapy alone. However, as our research shows, the situation does not seem to be that simple.

Our subgroup analysis reveals that for patients with advanced/metastatic ESCC and a PD-L1 expression CPS $\geqslant$ 10, the probability of serplulimab plus chemotherapy therapy being a cost-effective treatment option compared to chemotherapy alone is as high as 95.36%. The CPS serves as a more effective marker for identifying patient populations that benefit from immunotherapy.[49,50] Numerous studies on first-line or second-line treatments for esophageal cancer suggest a correlation between PD-L1 expression and the efficacy of immunotherapy,[51–53] making research on the CPS a current hot topic in esophageal cancer diagnosis and treatment. CheckMate-648 indicated that patients with a CPS $<$ 1 do not experience significant benefits from immunotherapy combined with chemotherapy compared to chemotherapy alone.[54] ASTRUM-007 further demonstrated that among patients with a CPS $\geqslant$ 1, those with a CPS $\geqslant$ 10 exhibited substantially greater clinical benefits than those with a CPS $<$ 10. However, no studies have yet explored the relationship between CPS and treatment cost-effectiveness. We believe that precision medicine tailored to individual patients is the current trend in oncology. Detection technology for the CPS has become well established and affordable, allowing for easy identification of patients with a CPS $\geqslant$ 10. Consequently, serplulimab plus chemotherapy represents a viable alternative to chemotherapy in this population, offering both clinical and economic benefits. For patients with a CPS between 1 and 10, radiotherapy could be added to the treatment plan to improve the immune microenvironment, promote tumor antigen release, and upregulate PD-L1 expression.[55]

Our study revealed that the drug acquisition cost of serplulimab accounts for 91.91% of the total incremental cost, indicating that the cost of

obtaining serplulimab is significantly higher than that of chemotherapy drugs. Lowering the price of serplulimab could significantly enhance its cost-effectiveness, a finding supported by our model's one-way deterministic sensitivity analysis results. The drug acquisition cost of serplulimab is a crucial parameter in the model, ranking third after the survival time of serplulimab plus chemotherapy and the survival time of chemotherapy alone. Furthermore, it is the most significant cost parameter affecting the model results. The price of serplulimab in China must drop by 35.5% to reach the WTP threshold of three times the per capita GDP. We believe that adjusting the price of serplulimab to improve its cost-effectiveness is not an impossible task. In 2019, the Chinese State Council initiated a national health care reform to negotiate drug prices for drugs included in the National Medical Insurance Catalog to address the rising cost of health care.[56] This led to a substantial decrease in the prices of programmed death 1 (PD-1) inhibitors included in the catalog. For instance, the price of camrelizumab declined by 85.25% from US$ 2867/200 mg in 2019 to US$ 423/200 mg in 2021. The price of toripalimab also fell by 70.83% from US$ 1042/240 mg to US$ 304/240 mg.

Currently, serplulimab is not included in the National Medical Insurance Catalog in China. To compete with other low-priced PD-1 inhibitors on the market, Shanghai Henlius Biopharmaceuticals Co., Ltd. has proactively implemented a drug discount policy. According to our simulations, this discount allows patients to obtain serplulimab at 62.50% of its original price, significantly increasing the probability of serplulimab emerging as an affordable treatment option for ESCC in high-incidence provinces such as Jiangsu, Fujian, Guangdong, and Shandong. Nevertheless, purchases made at this discounted rate are out-of-pocket and ineligible for medical insurance reimbursement. Despite serplulimab not being approved for first-line treatment, many patients opt to pay the full price and subsequently seek reimbursement through Diagnosis Related Groups and commercial insurance. In China, most patients favor treatment at tertiary hospitals,[57,58] which generally do not permit the administration of externally purchased serplulimab. As a result, patients must resort to treatment at lower-tier facilities, an option not widely accepted among Chinese oncology patients. Cancer treatment requires ongoing monitoring and flexible strategies, which might be lacking in these lower-tier institutions.[59,60] Nonetheless, the 37.5% discount could benefit patients with mobility issues, those living in remote locations, or those without insurance coverage for this treatment, as they might opt for a more affordable medication and comprehensive treatment at primary health care institutions.

In addition, we have considered the possibility that serplulimab may substantially prolong the survival time of patients, potentially justifying the price differential between serplulimab and chemotherapy in long-term treatment and ultimately achieving cost-effectiveness. In our model, the survival time of the serplulimab group was the parameter with the greatest impact on the results. Based on the findings of the one-way deterministic sensitivity analysis, if the survival time of the serplulimab group can be extended by a further 19.3%, the combination of serplulimab with chemotherapy could emerge as a more cost-effective alternative to chemotherapy. In such a scenario, the ICER would be US$ 37,219.88/QALY, which is slightly lower than the WTP threshold of three times China's per capita GDP. ASTRUM-007, KEYNOTE-590, ESCORT-1st, and JUPITER-06 have demonstrated that the combination of PD-1 inhibitors and chemotherapy can improve OS in patients with advanced/metastatic ESCC. In these trials, the median OS for the PD-1 inhibitor plus chemotherapy group ranged from 12.6 to 17.0 months, while the chemotherapy group exhibited a median OS of 9.8–12.0 months, with survival improvements varying between 21.57% and 35.29%. The investigational drugs in these trials, such as serplulimab, pembrolizumab, camrelizumab, and toripalimab, are all immunoglobulin G4 (IgG4) class monoclonal antibodies with similar molecular targets, structures, and pharmacological actions. These drugs share the common characteristic of not activating complement or inducing cytotoxicity in the Fc region.[61] Assuming drug production technology remains constant, these drugs should exhibit similar efficacy in treating advanced/metastatic ESCC. Currently, the improvement of combination treatment strategies has emerged as a new research direction in PD-1 immunotherapy for esophageal cancer. Based on clinical experience with dense chemotherapy in other cancer treatments, such as advanced ovarian cancer chemotherapy and adjuvant therapy following breast cancer surgery,[62,63] experts have incorporated dense chemotherapy into esophageal cancer clinical practice. Earlier studies such as KEYNOTE-590, ESCORT-1st,

and JUPITER-06 utilized conventional chemotherapy with drug administration every 3 weeks, while the more recent ASTRUM-007 employed a cutting-edge dense chemotherapy regimen with drug administration every 2 weeks. Although no head-to-head studies have demonstrated that 2-week dense chemotherapy is superior to 3-week or 4-week conventional chemotherapy for esophageal cancer treatment, some scholars posit that compared to conventional chemotherapy, the combination of PD-1 inhibitors and dense chemotherapy may offer greater benefits in modulating the immune microenvironment, thereby enhancing the drugs' ability to kill tumor cells. Consequently, we believe that with continuous improvements in chemotherapy regimens, the efficacy of serplulimab plus chemotherapy holds the potential for further enhancement. Moreover, from a statistical standpoint, only ASTRUM-007 used a 2:1 randomized controlled design, while the other studies employed a 1:1 design, making it more challenging for ASTRUM-007 to achieve superior survival data.[64–66] Considering the research process, ASTRUM-007 was conducted during the peak of the COVID-19 pandemic, which hindered patients from receiving timely treatment at hospitals.[67] Therefore, we believe that the objective of further improving patient survival with serplulimab plus chemotherapy, compared to the other three PD-1 inhibitors, is attainable.

There are some limitations to our study. First, our model primarily relied on data from the ASTRUM-007 trial. However, it is worth noting that patients enrolled in clinical trials may not accurately reflect the characteristics of patients in real-world settings, which could lead to biased economic evaluation results. Given the lack of multicenter real-world studies, the clinical evidence from the ASTRUM-007 trial was utilized as the best alternative for real-world cost-effectiveness research. Although the trial data provided a reasonable approximation to observe real-world clinical practice, the limitations of this approach should be acknowledged. Second, the utility values, originally sourced from published literature instead of individual patient data from the trial, were predominantly based on international data. These may not entirely represent the actual situation of patients in China. This approach may have affected the stability of the model results and needs to be taken into account when interpreting the findings. Third, the model did not include expenditures related to grade 1–2 treatment-related AEs. This could potentially undermine the economic evaluation results. However, deterministic sensitivity analysis indicated that the impact of cost variation related to treatment-related AEs on model results was minimal. Perhaps in future research, collecting more survival follow-up information and safety data to fully reproduce the clinical process of serplulimab plus chemotherapy first-line treatment for advanced/metastatic ESCC may generate more accurate economic evaluation results.

Conclusion

This study evaluated the cost-effectiveness of serplulimab combined with chemotherapy compared to chemotherapy alone for the treatment of advanced/metastatic ESCC. At present, serplulimab combined with chemotherapy is not yet a cost-effective alternative to chemotherapy for treating advanced/metastatic ESCC. However, with the evolution of PD-1 combined chemotherapy regimens and intense competition in the Chinese PD-1 inhibitor market, serplulimab in combination with chemotherapy compared to chemotherapy alone holds the potential to emerge as a cost-effective treatment option in the future.

Declarations

Ethics approval and consent to participate

In this study, we only used mathematical modeling to compare the economics of medication therapies. Thus, no ethical approval was needed.

Consent for publication

All authors contributed to the article and approved the submitted version.

Author contributions

Ying-Tao Lin: Data curation; Methodology; Software; Writing – original draft.

Chong-Chong Zhou: Methodology; Writing – review & editing.

Kai Xu: Data curation; Software; Writing – review & editing.

Meng-Die Zhang: Data curation; Software; Visualization.

Xin Li: Conceptualization; Supervision; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author/s.

ORCID iD
Xin Li https://orcid.org/0000-0003-3951-8061

Supplemental material
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