

Cost-effectiveness of camrelizumab versus chemotherapy for the treatment of advanced or metastatic esophageal squamous cell carcinoma

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Background: To evaluate the cost-effectiveness of camrelizumab versus chemotherapy for patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC) from the perspective of health system and to provide a basis for health decisions in China.

Methods: A Markov model of 3 health states throughout the lifetime was established based on data from the ESCORT trial. Life-years, quality-adjusted life-years (QALYs), and lifetime costs were estimated. The time horizon of lifetime was 5 years and each model cycle represented 2 months. The cost and utility value adopted a 5% discount rate per year. One-way sensitivity analysis and probability sensitivity analysis were used to test the robustness of the results.

Results: The results of the cost-effectiveness analysis revealed that the camrelizumab group produced a gain of 2.93 QALY, at a cost of \$37,809.12 USD, and the chemotherapy group gained 2.85 QALY, at a cost of \$3,7071.52 USD. Camrelizumab was more cost-effective than chemotherapy for patients with advanced or metastatic ESCC. The results of one-way sensitivity analyses showed that the cost of camrelizumab, cost of chemotherapy and utility of progression-free survival (PFS) state were the top three parameters influencing the model. The probability sensitivity analysis results showed that the results of the basic case analysis were stable.

Conclusions: Under the willingness to pay threshold of three times per capita GDP of China, camrelizumab as second-line treatment could provide more health benefits for advanced or metastatic ESCC in China.

Keywords: Cost-effectiveness; Markov; programmed cell death protein 1 (PD-1); esophageal squamous cell carcinoma (ESCC)

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Introduction

Esophageal cancer (EC) is a common type of cancer in China and constitutes the sixth leading cause of cancer deaths worldwide (1). It be divided into the histological subtypes of esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). In China, more than 90% are ESCC. For patients with advanced or metastatic ESCC, taxanes, platinum, and 5-fluorouracil (5FU) are usually used as first-line treatments (2). However, for patients with advanced or metastatic ESCC who have progressed or are intolerant to first-line standard chemotherapy, there are few choices for second-line treatment. In recent years, immunotherapy has presented a new therapeutic strategy for patients with ESCC. The

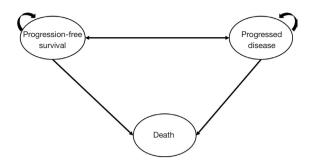


Figure 1 The Markov state transition model.

immune checkpoint programmed cell death protein 1 (PD-1) is expressed in T lymphocytes, B lymphocytes, natural killer cells, and other tumor-infiltrating immune cells (3). By inhibiting the immune checkpoint pathway, the patient's own immune system is used to fight against malignant cells (4). Immune checkpoint inhibitors (ICIs) show good antitumor potential in a variety of human cancers, which can improve the survival rate and quality of life of patients (5). Camrelizumab is a high-affinity, humanized IgG4 monoclonal PD-1 antibody, which can bind to the PD-1 receptor and block its interaction with PD-L1 and PD-L2, and block the immunosuppressive response mediated by PD-1 pathway, including anti-tumor immune response (6). The open-label, phase 3 randomized clinical trial ESCORT reported the efficacy and safety of patients aged 18-75 years with a histological or cytological diagnosis of advanced or metastatic ESCC treated at 43 hospitals in China (7). The results showed that the median overall survival (OS) of the camrelizumab group was 8.3 [95% confidence interval (CI): 6.8 to 9.7] months, and the median OS of the chemotherapy group was 6.2 (95% CI: 5.7 to 6.9) months [hazard ratio (HR) 0.71, 95% CI: 0.57 to 0.87; 2-sided P=0.0010]. In the evaluation of pharmacoeconomics, compared with other decisionmaking models, the Markov model is especially suitable for simulating the progress of chronic diseases that can be divided into different health states. The present analysis investigated the cost-effectiveness of camrelizumab versus chemotherapy for patients with advanced or metastatic ESCC from the perspective of the Chinese healthcare system by constructing a Markov model. We present the following article in accordance with the CHEERS reporting checklist (available at https://jgo.amegroups. com/article/view/10.21037/jgo-21-870/rc).

Methods

Model overview

A Markov model was developed to compare the costeffectiveness of camrelizumab versus chemotherapy for the treatment of advanced or metastatic ESCC. Costeffectiveness analysis (CEA) attempts to determine where more health benefits can be produced at the same cost, or where the same health benefits can be achieved at a lower cost. As shown in Figure 1, the 3 mutually exclusive health states: progression-free disease (PFD), progressive disease (PD), and death constituted the decision-analytic model. All patients started from the state of progression-free survival (PFS) on treatment, then transitioned to PD. Death could occur from any state. The Markov cycle in the model was set at 2 months and the time horizon of the model was 5 years, in view of the short life expectancy of patients with advanced or metastatic ESCC. The primary outputs of the models included the total cost, utility, and incremental cost-effectiveness ratios (ICERs). Costs and outcomes were discounted by 5% each year, and the willingness-to-pay (WTP) was 3-times of the China's per capita gross domestic product (GDP) in 2020, according to the China Guidelines for pharmacoeconomic evaluations (8). The model was implemented by TreeAge Pro 2021 software (TreeAge, Williamstown, MA, USA), and statistical analyses were performed using R software (version 4.0.5; https://www. r-project.org).

Population and treatment regimens

The analysis assumed that the target population is advanced or metastatic ESCC and the first-line standard chemotherapy was advanced or intolerant, consistent with the patient characteristics of the ESCORT trial. Treatments were administered as following: (I) camrelizumab group: camrelizumab was intravenously administered on the first day of every 2-week cycle at a dose of 200 mg; (II) chemotherapy group: docetaxel was given intravenously over 60 min on the first day of every 3 weeks at a dose of 75 mg/m² (7), or irinotecan was infused over 60 min on the first on the first day of every 2 weeks at a dose of 180 mg/m². Treatment was continued until disease progression or unacceptable toxicity, patient withdrawal, or by decision of the investigator. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

 Table 1 AIC and BIC for different parameter distributions of OS and PFS

Survival function	Exponential	Weibull	Logistic	Lognormal	Loglogistic
AIC for survival distributions of OS in chemotherapy group	1,761.287	1,736.983	1,713.536	1,721.821	1,713.536
BIC for survival distributions of OS in chemotherapy group	1,764.72	1,736.094	1,720.404	1,719.688	1,720.404
AIC for survival distributions of OS in camrelizumab group	1,718.234	1,711.386	1,815.845	1,697.217	1,699.7
BIC for survival distributions of OS in camrelizumab group	1,721.685	1,718.288	1,822.747	1,704.119	1,706.603
AIC for survival distributions of PFS in chemotherapy group	1,225.665	1,142.555	1,179.394	1,116.927	1,110.458
BIC for survival distributions of PFS in chemotherapy group	1,229.041	1,149.306	1,186.145	1,123.678	1,117.209
AIC for survival distributions of PFS in camrelizumab group	1,565.863	1,566.586	1,736.87	1,507.639	1,502.902
BIC for survival distributions of PFS in camrelizumab group	1,569.271	1,573.4	1,743.684	1,514.453	1,509.716

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

Clinical data inputs

As individual patient data were not available and followup time was limited, the Getdata Graph Digitizer software (version 2.2.6, https://www.getdata-graph-digitizer.com) was used to extracted survival data, and reconstruction of individual patient data was generated using an algorithm derived by Hoyle et al. (9). Then, these data points were used to fit the following parameter survival functions: Exponential, Weibull, Logistic, Lognormal, and Loglogistic. Combined with visual inspection, the eligible survival function was selected according to the lowest value of the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). The goodness-of-fit results are shown in Table 1. According to the results of AIC and BIC, loglogistic survival function S (t) = $1/(1+\lambda t^{\gamma})$ was used to fit the Kaplan-Meier (KM) OS and PFS probabilities of the chemotherapy group, and lognormal survival function S (t) = $1-\Phi\{(\ln t-\mu)/\sigma\}$ and loglogistic survival function were used to fit the KM OS and PFS probabilities of the camrelizumab group, respectively (10). The KM and parameter survival distributions of OS and PFS reconstructed in the model are shown in Figure 2. The transition probability was estimated based on the following formula tp(tu) = 1-S(t)/S(t-u), where u was the cycle of the model (11). The key clinical inputs are summarized in Table 2.

Cost and utility inputs

In this analysis, only direct medical costs, including costs of camrelizumab and chemotherapy, routine follow-ups and monitoring, best supportive care (BSC), and management of treatment-related adverse events (AEs), were considered. All costs were shown in U.S. dollars and adjusted for the 2020 exchange rate (\$1=\$6.8974). The costs of camrelizumab and chemotherapy were drawn from China's latest drug bid price (https://www.yaozh.com/). Drug-related costs were calculated based on China's per capita body surface area of 1.72 m² (16). The costs of routine follow-ups and monitoring, and best supportive care were obtained based on relevant literature (12-15). In calculating the cost of AE management, we focused only on events of grade 3 or higher. The model assumed that utility is only related to health status, not to therapies. Utility value parameters were derived from published literature and expressed in terms of quality adjustment of life years (QALYs). *Table 2* summarizes all model inputs.

Statistical analysis

In the base-case analysis, CEA was used as the evaluation method to calculate the cost and utility of the chemotherapy group and camrelizumab group respectively. ICERs represents the ratio of the cost difference and the effectiveness difference between different alternatives, and the formula is expressed as:

$$ICER = \frac{\Delta C}{\Delta E} = \frac{(C_1 - C_2)}{(E_1 - E_2)}$$
[1]

where C is the cost of treatment and E is the effectiveness of treatment. To explore the robustness of the costeffectiveness analysis results, one-way sensitivity analyses and probabilistic sensitivity analyses (PSA) were conducted (17). In the one-way sensitivity analyses, assuming that the parameters fluctuate by 20%, the

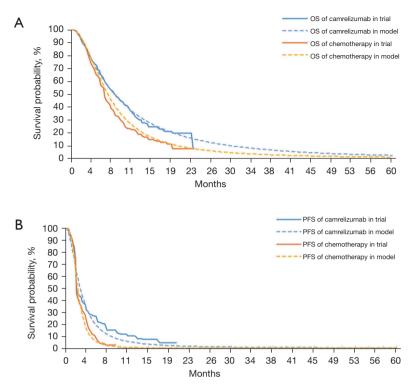


Figure 2 OS curves for the original trial and estimated data (A) and PFS curves for the original trial and model estimated data (B). OS, overall survival; PFS, progression-free survival.

values of the parameters were changed one by one, and the tornado diagram was drawn based on the calculation results (13). To perform the PSA, a second-order Monte Carlo simulation was used to analyze the results through 1,000 random sampling, while the variables varied with a specific distribution pattern (18). Combining parameter constraints and statistical distribution characteristics, we assumed that Gamma distribution was selected for the cost parameters, and the Beta distribution was selected for the utility parameters (19). The PSA was represented by the incremental cost-effectiveness scatter plot and costeffectiveness acceptable curve to verify the uncertainty of the results.

Results

Base-case analysis

Within the 5 years of the lifetime analysis, the camrelizumab group gained 2.93 QALY for \$37,809.12, and the chemotherapy group gained 2.85 QALY for \$37,071.52. Compared with the chemotherapy group, the ICER of the camrelizumab group was \$9,292.19/QALY. With the

China cost-effectiveness WTP threshold of \$31,510.57/ QALY, camrelizumab had more cost-effectiveness for patients with advanced or metastatic ESCC, compared with chemotherapy. The basic analysis results of the model are given in *Table 3*.

Sensitivity analysis

The influence of different parameters on the model results can be shown from the one-way sensitivity analyses. It is suggested in *Figure 3* that the cost of camrelizumab and chemotherapy was most sensitive to the model. Other considerable influential parameters in the model were utility of PFS state, probability, and cost of white blood cell count decreased in chemotherapy group, probability and cost of neutrophil count decreased. Changes in other parameters had weak influences on the model results.

The incremental cost-effectiveness scatter plot for camrelizumab versus chemotherapy is shown in *Figure 4*. A 38.4% proportion of the scatter points were in the fourth quadrant, indicating that the camrelizumab group had an absolute cost-effectiveness advantage. Concurrently, 56.3%

Table 2 Model parameters

Parameters	Baseline value	Ra	nge	- Distribution	Resource
Parameters	Baseline value	Minimum	Maximum		
Clinical input					
Log-logistic OS survival model in chemotherapy group	λ=0.019104, γ=2.060226	-	-	-	-
Log-logistic PFS survival model in chemotherapy group	λ=0.092834, γ=3.066831	-	-	-	-
Lognormal OS survival model in camrelizumab group	μ=2.083120, σ=0.057891	-	-	-	-
Log-logistic OS survival model in camrelizumab group	λ=0.157001, γ=1.933910	-	-	-	-
Probability of chemotherapy group AEs (grade 3/4)					
Anemia	5%	4%	6%	Beta	(7)
Abnormal hepatic function	0.5%	0.4%	0.6%	Beta	(7)
Diarrhea	4%	3.2%	4.8%	Beta	(7)
Lymphocyte count decreased	1%	0.8%	1.2%	Beta	(7)
Neutrophil count decreased	15%	12%	18%	Beta	(7)
White blood cell count decreased	17%	13.6%	20.4%	Beta	(7)
Nausea	4%	3.2%	4.8%	Beta	(7)
Vomiting	5%	4%	6%	Beta	(7)
Probability of camrelizumab group AEs (grade 3/4)					
Anemia	3%	2.4%	3.6%	Beta	(7)
Abnormal hepatic function	2%	1.6%	2.4%	Beta	(7)
Diarrhea	1%	0.8%	1.2%	Beta	(7)
Lymphocyte count decreased	1%	0.8%	1.2%	Beta	(7)
Cost input (\$)					
Camrelizumab per 200 mg	424.51	339.61	509.41	Gamma	Latest bid pric
Docetaxel per 20 mg	43.08	34.47	51.70	Gamma	Latest bid pric
Docetaxel per 60 mg	89.46	71.57	107.35	Gamma	Latest bid pric
Irinotecan per 40 mg	70.95	56.76	85.13	Gamma	Latest bid pric
Irinotecan per 100 mg	138.74	110.99	166.49	Gamma	Latest bid pric
Follow-ups and monitoring per cycle	370.16	296.13	444.19	Gamma	(12)
Best supportive care per cycle	212.43	169.94	254.91	Gamma	(12)
Anemia per event	460.95	368.76	553.14	Gamma	(12)
Abnormal hepatic function per event	380.17	304.13	456.20	Gamma	(13)
Diarrhea per event	303.48	242.78	364.18	Gamma	(14)
Lymphocyte count decreased per event	422.68	338.14	507.21	Gamma	(12)
Nausea	40	32	48	Gamma	(15)
Vomiting	40	324	48	Gamma	(15)
Utility (QALY)					
PFS	0.741	0.5928	0.8892	Beta	(12)
PD	0.581	0.4648	0.6972	Beta	(12)

OS, overall survival; PFS, progression-free survival; AEs, adverse events; QALY, quality adjusted life years; PD, progressive disease.

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Strategy	Cost, \$	Incremental cost, \$	Effectiveness, QALY	Incremental effectiveness, QALY	ICER, \$/QALY			
Camrelizumab	37,809.12	737.60	2.93	0.08	9,292.19			
Chemotherapy	37,071.52	_	2.85	_	-			

Table 3 Base-case results of the model

QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratios.

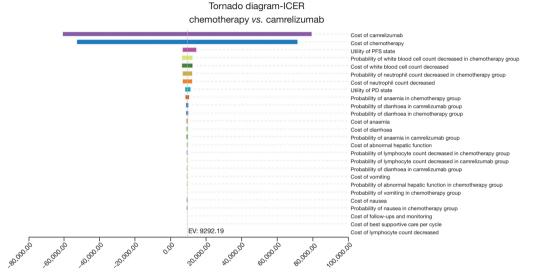


Figure 3 Tornado diagram for one-way sensitivity analyses.

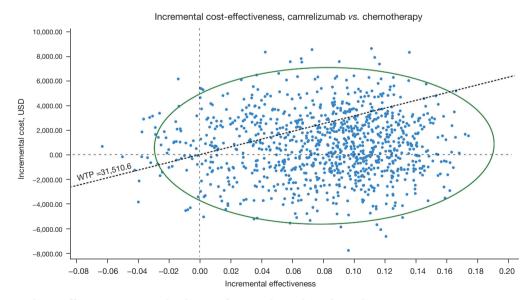


Figure 4 Incremental cost-effectiveness scatter plot diagram for camrelizumab vs. chemotherapy.

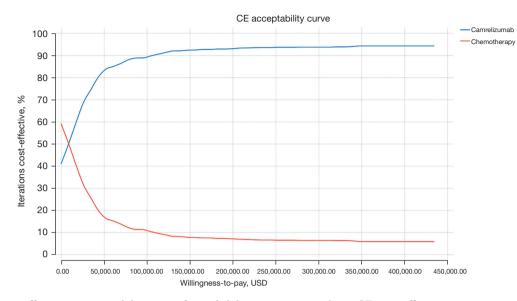


Figure 5 The cost-effectiveness acceptability curves for probabilistic sensitivity analyses. CE, cost-effectiveness.

of the scatter points were in the first quadrant, indicating that patients in the camrelizumab group benefited more, but at the same time the cost was also higher. Generally, more than 50% of the scatter points were below the WTP threshold, which meant camrelizumab was economically meaningful for patients with advanced or metastatic ESCC.

The Cost-effectiveness acceptability curve is shown in *Figure 5*. The cost-effectiveness acceptability curve showed a nearly 50% probability of camrelizumab being a cost-effective strategy at the threshold of \$8,693.64 per additional QALY gained, and the higher the WTP value, the greater the cost-effectiveness advantage of the camrelizumab group. The results of PSA suggested that the results of the basic case analysis were stable.

Discussion

China accounts for about half of all ESCC cases on earth due to its large population and high ESCC rates (20). Most patients are diagnosed late and have a poor prognosis. With the continuous breakthrough of anti-tumor efficacy of immunotherapy in various cancers, the treatment of ESCC in recent years has also opened a new era of immunotherapy (21). Camrelizumab has been approved by the China National Medical Products Administration (NMPA) for patients with locally advanced or metastatic ESCC who have previously received first-line chemotherapy and have progressed or become intolerable. It has become

China's first immunotherapy drug for esophageal cancer in the whole population. In developing countries, the high price of anti-cancer drugs may put cancer patients facing serious economic risks. As immunotherapy plays an increasingly important role in cancer treatment, clinicians should consider both the efficacy and the high cost when making treatment decisions. Although there have been previous pharmacoeconomic evaluations of camrelizumab, based on the previous price, camrelizumab was deemed not economical for patients with ESCC (22). However, camrelizumab entered the National Reimbursement Drug List (NRDL) in 2020. After the efforts of all parties, the price reduction will eventually reach 85%. In this study, we updated part of the model input data, re-evaluated the cost-effectiveness of camrelizumab, and drew different research conclusions. Based on the newly announced winning bid price, combined with the published literature on advanced or metastatic ESCC and the current status of Chinese medical resources, we conducted a costeffectiveness analysis of camrelizumab, aiming to provide a reference for clinical rational use of drugs and related health decisions. Although the treatment cost of camrelizumab after the sharp price reduction is still higher than that of the chemotherapy group, it has a certain cost-effectiveness advantage under the threshold of 3 times China's per GDP. The price adjustment of camrelizumab effectively reduced the economic burden of the healthcare system and provided more value to patients. The epidemiology of esophageal

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cancer in China has significant regional differences, and the main high-incidence areas are located in rural and mountainous areas (23), where the majority of people have lower incomes. According to the Statistical Communiqué of the People's Republic of China on the 2020 National Economic and Social Development, the per capita disposable income of rural residents in China is \$2,483.69 (24). Compared with the chemotherapy group, the ICER value of camrelizumab was \$9,292.19/QALY. As far as rural residents were concerned, the burden of disease was still relatively heavy. How to meet the most basic needs of the population with limited medical insurance resources, deepen the reform of medical service prices, and increase the availability of high-priced drugs remain key public health issues to be considered in decision-making. It should be mentioned that this study also had several limitations. First, the model established in this study was based on specific clinical trials and an ideal state for ESCC development. Due to the limitation of data sources, this study only established a 3-state Markov model, which can be added to the state of the model and make the model closer to the complex ESCC progression. Second, the utility value parameter came from the European population in the previously published literature, and there may be a deviation for the Chinese population. The results of this study revealed that the priceadjusted camrelizumab has certain pharmacoeconomic value in the treatment of advanced or metastatic ESCC. It is hoped that more real-world studies based on camrelizumab and health outcome evaluation scales for the Chinese population can be carried out in the future, so as to provide more references for medical decision-making departments.

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Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-870/rc

Data Sharing Statement: Available at https://jgo.amegroups. com/article/view/10.21037/jgo-21-870/dss

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://jgo.amegroups. com/article/view/10.21037/jgo-21-870/coif). The authors have no 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).

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