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Cost-Utility Analysis of Nivolumab plus Chemotherapy in the First-Line Treatment of Upper Gastrointestinal Adenocarcinoma

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Abstract

Objective: To evaluate the cost-utility of nivolumab plus chemotherapy compared with chemotherapy alone as the first-line treatment for advanced gastric, gastro-oesophageal junction, and esophageal adenocarcinoma in China. Methods: Based on CheckMate649, a partitioned survival model was carried out with a circulation cycle of 6 weeks to simulate the patient's lifetime. Sensitivity analysis were adopted to verify the robustness of the results. Results: The results of the base-case analysis showed that both the total cost and utility of the nivolumab group were higher, and the ICUR value was CNY 267498.67/QALY, more than 3 times the GDP per capita of China in 2020. The results of deterministic sensitivity analysis indicated that the three most influential factors were the utility value of PFS state, the cost of nivolumab and the discount rate. The results of probabilistic sensitivity analysis were consistent with those of base-case analysis, proving that the results were robust. The scenario analysis illustrated that economical price of nivolumab was CNY 3652.71. Conclusions: Under the willing-to-pay threshold of three times the GDP per capita of China in 2020, compared with chemotherapy alone, nivolumab plus chemotherapy is not a cost-effective option in China.

Keywords

Nivolumab, Gastric Adenocarcinoma, Gastro-Oesophageal Junction Adenocarcinoma, Esophageal Adenocarcinoma, Partitioned Survival Model, Cost-Utility Analysis

1. Introduction

Malignant tumors originating from the upper gastrointestinal tract have a significant burden on both morbidity and mortality, which have always been the

main diseases threatening human health. Upper gastrointestinal cancers include gastric, gastro-oesophageal junction, and esophageal cancer. According to global cancer statistics, esophageal cancer is the seventh most common cancer worldwide, with the sixth-highest death rate. Gastric cancer is the fifth most common cancer, accounting for 5.6% of new cases and 7.7% of new deaths in 2020, making it the fourth leading cause of cancer-related deaths [1]. Adenocarcinoma is the most common histological subtype of upper gastrointestinal carcinoma. The incidence rate of gastric (GA) and gastro-oesophageal junction adenocarcinoma (GEJA) is more than 90% in gastric and gastro-oesophageal junction cancers, and esophageal adenocarcinoma (EA) accounts for about 15% of global esophageal cancer cases [2]. Studies have found that upper gastrointestinal adenocarcinomas share a high degree of similarity in molecular profiles [3] and genomic characteristics [4], so advanced systemic treatment regimens are similar.

According to the Chinese Society of Clinical Oncology (CSCO) guidelines for the diagnosis and treatment of gastric cancer, fluoropyrimidine combined with platinum-based chemotherapy has been the standard first-line therapy for unresectable and advanced GA and GEJA. Nivolumab, a fully human immunoglobulin G4 monoclonal antibody, can block the PD-1/PD-Ls signaling pathway, restore T cell function, and thus inhibit tumor growth. Nivolumab has been shown to be effective in a variety of cancers. On August 30, 2021, nivolumab was approved by the National Medical Products Administration (NMPA) for the first-line treatment of advanced or metastatic GA, GEJA and EA [5], based on CheckMate649. Data from CheckMate649, a multicenter, randomized, open-label, phase3 clinical trial in 2021, showed that nivolumab could improve both the median progression-free survival (mPFS) and the median overall survival (mOS) in patients with previously untreated GA, GEJA and EA [6].

Despite significant clinical benefits, the use of nivolumab could increase the economic burden on patients and families. However, economic evaluation has not yet been done. Thus, in this study, a partitioned survival model was established to evaluate the cost-effectiveness of nivolumab plus chemotherapy compared with chemotherapy alone from the perspective of the Chinese healthcare system.

2. Materials and Methods

2.1. Patients and Intervention

The target patient population was consistent with that from CheckMate649. The trial enrolled 1581 patients with previously untreated, unresectable, advanced or metastatic GA, GEJA and EA, all aged 18 years or older, from 175 hospitals and cancer centers in 29 countries.

Patients were randomly assigned to the nivolumab plus chemotherapy group (789 patients) and chemotherapy alone group (792 patients). In chemotherapy alone group, 47% of patients received XELOX (oxaliplatin 130 mg/m^2, day 1, and capecitabine 1000 mg/m^2 twice a day, days 1 - 14, every 3 weeks) and the other re-

ceived FOLFOX (oxaliplatin 85 mg/m^2, day 1, leucovorin 400 mg/m^2, day 1, and fluorouracil 400 mg/m^2, day 1 and 1200 mg/m^2, days 1 - 2, every 2 weeks). In the nivolumab plus chemotherapy group, 46% of patients received nivolumab plus XELOX (nivolumab 360 mg, plus XELOX, every 3 weeks), and the other received nivolumab plus FOLFOX (nivolumab 240 mg, plus FOLFOX, every 2 weeks). Besides, the administration time of nivolumab could not exceed 2 years. Therefore, patients received Subsequent therapy after two years regardless of disease progression.

2.2. Model Structure

Microsoft Excel 2016 was used to develop a partitioned survival model from the perspective of the Chinese healthcare system. The model structure consisted of three states, including progression-free survival (PFS) state, progressed disease (PD) state, and death state (as shown in **Figure 1**). All patients entered the model in the PFS state. According to CheckMate649, the circulation cycle of the model was set to 6 weeks to simulate the patient's lifetime until 99% of patients died. The main outputs of the model were the cost, quality-adjusted life years (QALY) and incremental cost-utility ratio (ICUR). According to the China Guidelines for Pharmacoeconomics Evaluations (2020), both cost and utility used a discount rate of 5% annually and used 0% - 8% for deterministic sensitivity analysis [7]. What's more, three times the gross domestic product (GDP) per capita of China in 2020 (CNY 216,000) was used as the willing-to-pay (WTP) threshold [8].

2.3. Survival Extrapolation

During the trial follow-up period, the proportion of patients in each health state was obtained from Kaplan-Meier (KM) curves in CheckMate649, using GetData Graph Digitizer2.20. Beyond the trial period, extrapolation was constructed to estimate the proportion of patients by parameter method, using R4.1.2. Individual patient data were reconstructed by six distributions, including Exponential, Gamma, Gompertz, Weibull, Log-logistic and Log-normal distribution. The

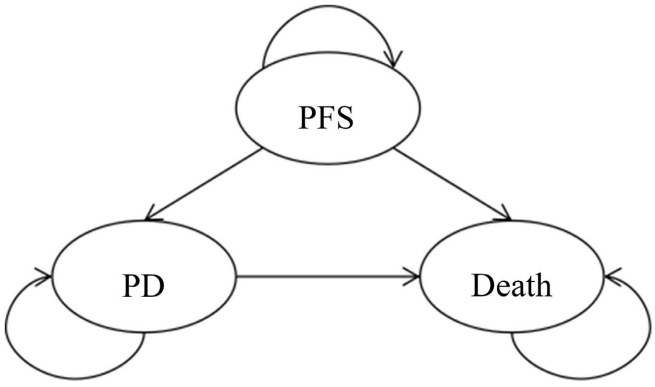

Figure 1. Partitioned survival model health state transitions. Notes. PFS: progression-free survival; PD: progressed disease.

proportion of patients calculated from PFS curve represented patients in PFS state. The proportion of patients calculated from OS curve represented all patients who are alive, including patients in PFS state and PD state.

Optimal survival distribution for extrapolation could be determined according to Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), combined with a visual inspection. As shown in Table 1, for OS curves, log-logistic distribution was used for both groups with the best AIC and BIC scores. For PFS curves, log-normal was used for the chemotherapy alone group and Log-logistic distribution was used for nivolumab plus chemotherapy group. The fitting curves could be drawn according to relevant parameters in Table 2. As depicted in Figure 2 and Figure 3, the fitting results were consistent with the original results, exhibiting high reproducibility.

2.4. Costs and Utilities

Only direct medical costs were included in this study, including the cost of drugs, disease management, subsequent therapies and the management of adverse events

Table 1. AIC and BIC values for different distributions.

OS Curves		Exponential	Gamma	Gompertz	Weibull	Log-logistic	Log-normal
Nivolumab + chemotherapy	AIC	4343.815	4284.142	4329.830	4294.939	4270.887	4276.096
	BIC	4348.485	4293.483	4339.171	4304.281	4280.229	4285.437
Chemotherapy alone	AIC	4459.273	4373.783	4433.650	4386.669	4365.079	4373.953
	BIC	4463.948	4383.132	4443.000	4396.019	4374.428	4383.302
PFS Curves							
Nivolumab + chemotherapy	AIC	3986.570	3934.857	3984.986	3951.199	3901.027	3901.208
	BIC	3991.241	3944.198	3994.328	3960.540	3910.369	3910.550
Chemotherapy alone	AIC	3680.134	3617.684	3678.556	3637.229	3586.524	3584.165
	BIC	3684.809	3627.033	3687.905	3646.578	3595.873	3593.515

Table 2. Optimal survival distribution and relevant parameters.

OS Curves	distribution		est	L95%	U95%	se
Nivolumab + chemotherapy	loglogistic	shape (γ)	1.7424	1.6235	1.8699	0.0628
		scale (λ)	0.0736	0.0791	0.0685	0.4979
Chemotherapy alone	loglogistic	shape (γ)	1.8735	1.7507	2.0049	0.0648
		scale (λ)	0.0881	0.0941	0.0825	0.3821
PFS Curves						
Nivolumab + chemotherapy	loglogistic	shape (γ)	1.7734	1.6564	1.8986	0.0617
		scale (λ)	0.1204	0.1293	0.1121	0.3038
Chemotherapy alone	lognormal	meanlog (μ)	1.8870	1.8147	1.9593	0.0369
		sdlog (σ)	0.9486	0.8940	1.0066	0.0287

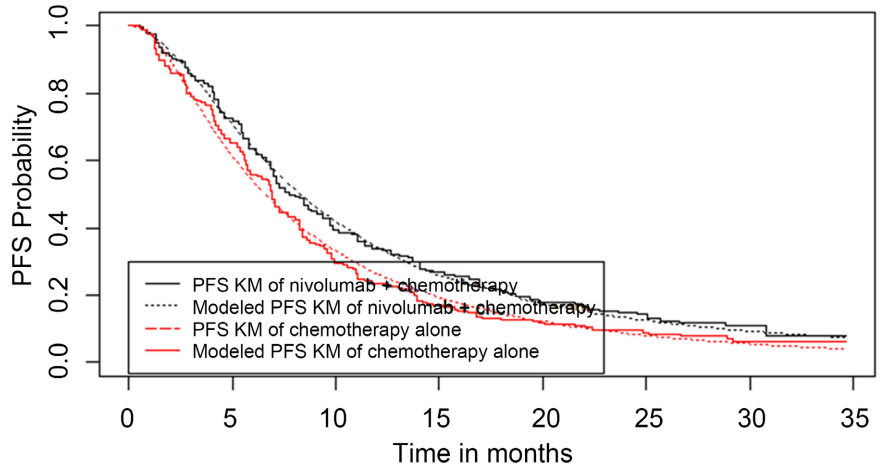

Figure 2. Kaplan-Meier survival curves for PFS.

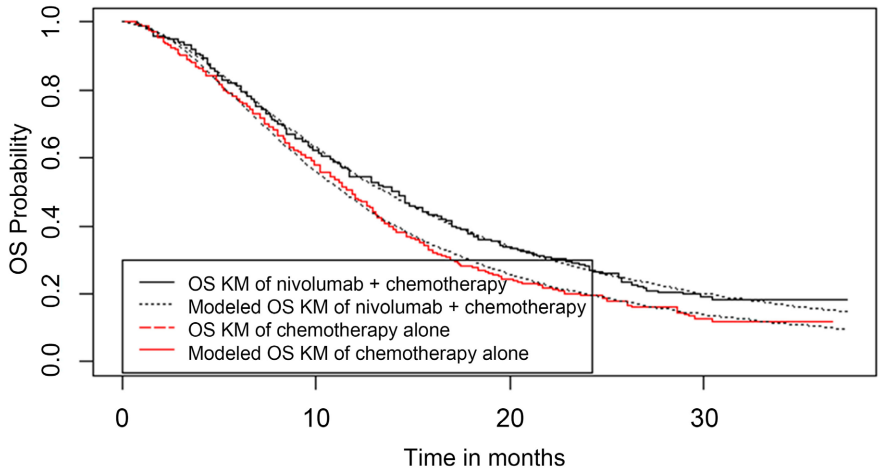

Figure 3. Kaplan-Meier survival curves for OS.

Table 3). It is assumed that the average body surface area and weight were 1.72 m^2 [9] and 65 kg [10] respectively. The prices of medicines were all sourced from MENET.

The disease management costs were sourced from HAN Jiaqi [11], including drug administration, hospitalization, imaging and PD-1 testing cost. The PD-1 testing, performed once before starting treatment, was considered a one-time cost for this study. The tumor imaging assessment was done every 6 weeks for the first 48 weeks and every 12 weeks thereafter.

Grade 3 or higher adverse events that occurred in ≥5% of patients in either treatment in CheckMate649 were included in the model and considered a one-time cost. As illustrated in Table 3, adverse events of the nivolumab group versus chemotherapy group were anemia (6.0% vs. 2.7%), neutrophil count decreased (25.7% vs. 20.9%), lipase increased (5.8% vs. 2.1%). The related costs were derived from other cost-utility analysis from the Chinese perspective [12] [13].

The costs of subsequent therapies could be calculated by costs from MENET and the proportion given in CheckMate649.

Table 3. Cost and utility data.

Parameter	Base-case value	Range	Distribution	Source
Treatment costs (CNY per cycle)				
Nivolumab	82561.32	66049.056 - 99073.584	GAMMA	MENET
XELOX	6681.99	5345.595 - 8018.392	GAMMA	MENET
FOLFOX	19024.40	15219.523 - 22829.285	GAMMA	MENET
Disease management costs				
Drug administration and hospitalization	402	321.6 - 482.4	GAMMA	Han Jia-qi *et al.*, [11]
Imaging examination (CT or MRI)	800	640 - 960	GAMMA	Han Jia-qi *et al.*, [11]
PD - L1 test	1410	1128 - 1692	GAMMA	Han Jia-qi *et al.*, [11]
Adverse event management costs (per event)				
Anemia	3789.40	3031.52 - 4547.28	GAMMA	Liu Guo-qiang *et al.*, [13]
Neutrophil count decreased	3381	2704.8 - 4057.2	GAMMA	Tan Chongqing *et al.*, [12]
Lipase increased	298	238.4 - 357.6	GAMMA	MENET
Incidence of adverse events in nivolumab plus chemotherapy group				
Anemia	0.06	0.048 - 0.072	BATA	CheckMate649 [6]
Neutrophil count decreased	0.257	0.206 - 0.308	BATA	
Lipase increased	0.058	0.046 - 0.069	BATA	
Incidence of adverse events in chemotherapy alone group				
Anemia	0.027	0.022 - 0.033	BATA	
Neutrophil count decreased	0.209	0.167 - 0.25	BATA	
Lipase increased	0.021	0.017 - 0.025	BATA	
The cost of Subsequent therapy				
In nivolumab plus chemotherapy group	17054.49	13643.596 - 20465.394	GAMMA	CheckMate649 [6]
In chemotherapy alone group	21582.01	17265.608 - 25898.412	GAMMA	
Health state utility values				
PFS	0.797	0.638 - 0.956	BATA	T Shiroiwa [14]
PD	0.577	0.462 - 0.692	BATA	
Discount rate	5%	0% - 8%	China Guidelines for Pharmacoeconomics Evaluations (2020) [7]	

Note. PFS: progress-free survival; PD: progressive disease.

The utility values of the three health states of PFS, PD and death in the model were 0.797, 0.577 and 0, respectively, and were sourced from published literature [14].

2.5. Sensitivity Analysis

Deterministic sensitivity analysis (DSA) was carried out to evaluate the influence of parameter changes within a certain range. The variation ranges of parameters

were 0% - 8% for the discount rate and ±20% of the base value for the other (as shown in Table 3). The analysis result is presented with a tornado diagram.

In addition, probabilistic sensitivity analysis (PSA) was conducted using 1000-times Monte Carlo simulation. The analysis result is presented in the form of a cost-effectiveness acceptability curve (CEAC) to evaluate the robustness of the model.

2.6. Scenario Analysis

According to the China Guidelines for Pharmacoeconomics Evaluations (2020), ICUR value between 1 time and 3 times the GDP per capita of China indicates that the regimen is economical, and ICUR lower than 1 times the GDP per capita of China indicates that the regimen is extremely economical.

Therefore, in this study, the WTP thresholds were set to be about 1 time and 3 times the GDP per capita of China, respectively, in order to provide a price reference for medical insurance negotiations.

3. Results

3.1. Base-Case Analysis

The results of the base-case analysis shown in Table 4 indicated that compared with the chemotherapy alone group, patients in the nivolumab plus chemotherapy group received more benefits but cost more. It is calculated that ICUR value was CNY 267498.67 per QALY, far more than 3 times the GDP per capita of China in 2020 (CNY 216,000). Thus, under 3 times the GDP per capita of China in 2020 as the WTP threshold, nivolumab plus chemotherapy was not a cost-effective option over chemotherapy alone.

3.2. Deterministic Sensitivity Analysis

According to tornado diagram depicted in Figure 4, the ICUR value was more sensitive to the utility value of PFS state, the cost of nivolumab, discount rate, the cost of subsequent therapy for nivolumab group and chemotherapy group, and the utility value of PD state, etc. In addition, the cost of testing and adverse event management had a weaker influence on the ICUR value. Generally speaking, the ICUR value ranged between CNY 216919.36/QALY and CNY 325246.55/QALY, all higher than 3 times the GDP per capita of China in 2020 (CNY 216,000).

Table 4. Cost-utility of nivolumab + chemotherapy vs chemotherapy alone.

	Costs (CNY)	Utilities (QALYs)
Nivolumab + chemotherapy	778470.78	10.08
Chemotherapy alone	204725.62	7.93
Difference	573745.16	2.14
ICUR (CNY/QALY)	267498.67	

Note. ICUR: incremental cost-utility ratio.

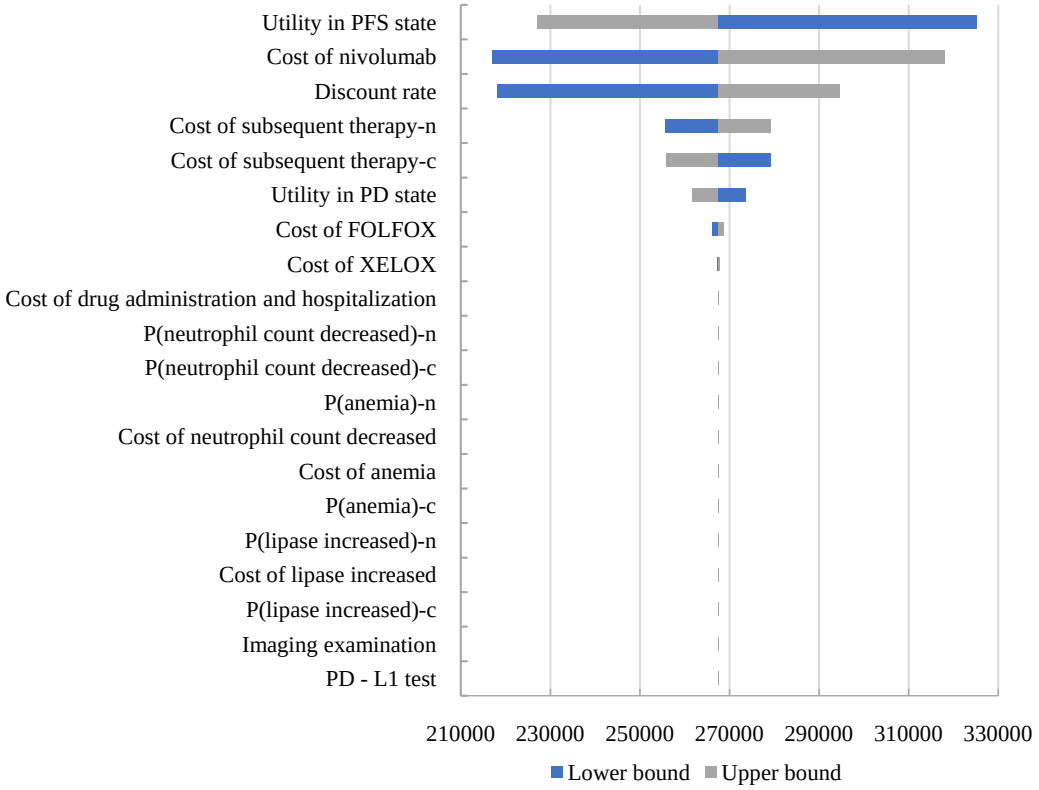

Figure 4. Tornado diagram for ICUR of nivolumab + chemotherapy vs chemotherapy. Note. PFS: progress-free survival; PD: progressive disease; P: probability; n: nivolumab plus chemotherapy group; c:chemotherapy alone group.

Therefore, nivolumab plus chemotherapy was not more cost-effective than chemotherapy alone.

3.3. Probabilistic Sensitivity Analysis

The results of the Monte Carlo simulation are shown in **Table 5**, compared with the results of the base-case analysis. The results showed that both mean and median ICUR value in the Monte Carlo simulation were high than 3 times the GDP per capita of China in 2020 (CNY 216,000), illustrating that nivolumab was not economical.

The results of probabilistic sensitivity analysis in the form of CEAC are depicted in **Figure 5**. Nivolumab plus chemotherapy group became more economical with an increase in the willingness-to-pay threshold. When the willingness-to-pay threshold reached CNY 216,000/QALY, the probability of cost-effectiveness of camrelizumab plus chemotherapy was approximately 29% was consistent with those of base-case analysis, proving that the results were robust. Under the WTP threshold of CNY 265,580/QALY, two curves intercross, which means that nivolumab plus chemotherapy has a 50% chance of being cost-effective compared to chemotherapy alone. Therefore, the results of probabilistic sensitivity analysis were basically consistent with those of the base-case analysis, proving that the results of base-case analysis were robust.

Table 5. Comparision between Monto Carlo simulation and base-case analysis.

		Base-case Analysis	Monte Carlo simulation	
			Mean	Median
Costs (CNY)	Nivolumab + chemotherapy	778470.78	777897.17	764293.86
	Chemotherapy alone	204725.62	206570.26	203128.18
Utilities (QALYs)	Nivolumab + chemotherapy	10.08	9.24	8.73
	Chemotherapy alone	7.93	7.17	6.55
ICUR (CNY/QALY)		267498.67	275160.04	256613.79

Note. ICUR: incremental cost-utility ratio.

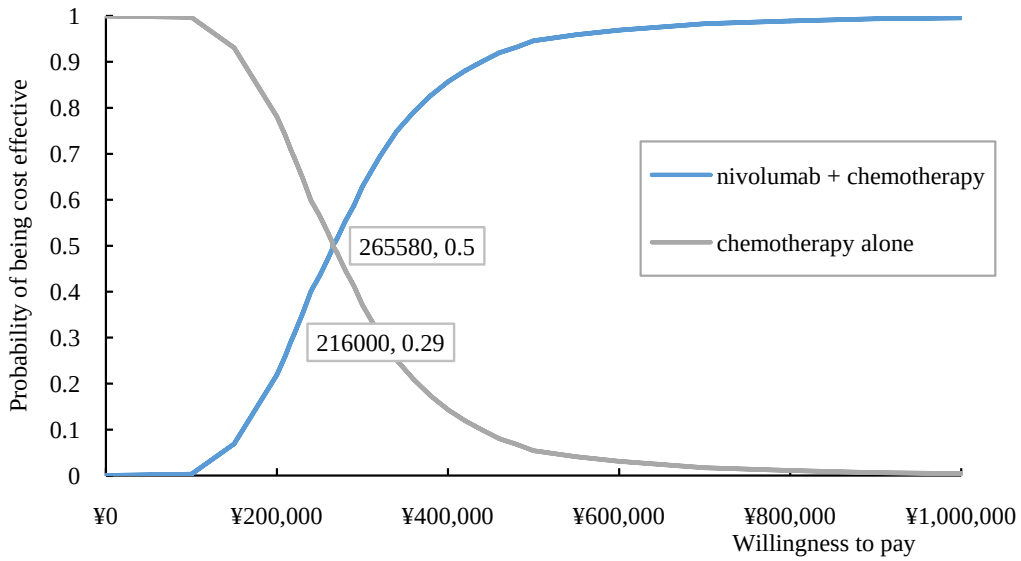

Figure 5. Cost-effectiveness acceptability curve of nivolumab + chemotherapy vs chemotherapy.

3.4. Scenario Analysis

As mentioned above, the cost of nivolumab had the greatest impact on ICUR value. Thus, further study was carried out to explore the price of nivolumab when it was economical.

According to Table 6, when the price of nivolumab (4 ml: 40 mg) was CNY 3652.71, the ICUR value was calculated to be CNY 215999.58/QALY, lower than 3 times the GDP per capita of China in 2020 (CNY 216,000), indicating that nivolumab was economic.

When the price of nivolumab (4 ml: 40 mg) was CNY 1041.01, the ICUR value was calculated to be CNY 71999.73/QALY, lower than 1 time the GDP per capita of China in 2020 (CNY 72,000), indicating that nivolumab was extremely economical.

4. Discussion

In Checkmate649, although grade 3 or higher treatment-related adverse events were more frequent with nivolumab plus chemotherapy alone compared with

Table 6. The result of scenario analysis.

The price of nivolumab	Nivolumab + chemotherapy		Chemotherapy alone		ICUR (CNY/QALY)
	Cost (CNY)	Utility (QALYs)	Cost (CNY)	Utility (QALYs)	
3652.71	664518.56	10.08	201231.35	7.93	215999.58
1041.01	345889.58	10.08	191460.79	7.93	71999.73

Note. ICUR: incremental cost-utility ratio.

chemotherapy alone group, nivolumab plus chemotherapy resulted in a 3.3-month improvement in median OS (14.4 months vs. 11.1 months) and a 1.7-months improvement in median PFS (7.7 months vs. 6.0 months). Based on significant clinical benefits in Checkmate649, nivolumab became the first and only PD-1 inhibitor to greatly improve median OS and PFS in the field of gastric cancer in China with acceptable safety. It was the first major breakthrough in this field for more than a decade and filled the gap in first-line treatment for advanced gastric cancer.

In this study, a three-state partitioned survival model was conducted to evaluate the cost-utility of nivolumab plus chemotherapy versus chemotherapy alone in the first-line treatment for GA, GEJA and EA. Compared with the Markov model, partitioned survival model can simulate disease events more directly and accurately because it can avoid some unnecessary assumptions without calculating the transition probability between states [15]. The results of the base-case analysis indicated that ICUR value was CNY 267498.67/QALY, more than 3 times the GDP per capita of China in 2020 (CNY 216,000). The results of deterministic sensitivity analysis indicated that the three parameters that most greatly impact on the ICUR value were the utility value of PFS state, the cost of nivolumab and the discount rate. The results of probabilistic sensitivity analysis illustrated a 29% probability of being lower than CNY 216,000/QALY, indicating the results of base-case analysis were robust and of practical significance. The scenario analysis indicated that economical price of nivolumab (4 ml: 40 mg) was CNY 3652.71.

Taking the charity drug donation policy into account, the total cost for nivolumab plus chemotherapy group would sharply decrease to CNY 496885.95, which was only CNY 292160.33 higher than that of the chemotherapy alone group. The ICUR value was calculated to be CNY 136214.66/QALY, below 3 times the GDP per capita of China in 2020 (CNY 216,000), indicating that the nivolumab plus chemotherapy group was more economical. Therefore, reducing the price of nivolumab can significantly raise the economic probability of the nivolumab group. Combined with the clinical benefit, it is suggested that nivolumab plus chemotherapy could be included in the medical insurance list to further improve the accessibility of drugs and alleviate the disease burden of patients.

208 Chinese patients were included in CheckMate649 and the proportion was the highest among all countries. Thus, the results could also be extrapolated to

the Chinese population. Presently, there are great economic differences among different regions in China. WTP threshold can be set under 3 times gross regional product per capita to judge whether nivolumab is economic among different regions in China. It was found that only in economically developed areas, such as Beijing, Tianjin, Shanghai, Jiangsu, etc., this treatment was considered a cost-effective option. What's more, the results can also apply to gastric cancer because 70% of patients suffer from gastric cancer.

However, this study has some limitations. First, like a majority of pharmacoeconomic evaluations, this study was modeled based on published clinical trial data, and the model parameters were derived from secondary literature. Secondly, the proportion of patients was directly exacted from the original curve in the first 25 cycle, and was extrapolated by parameter method. It was found that fitting data of the first 25 cycle were not significantly different from the original (difference < 5%). But it was bound to be different from the real-world situation, which would have a certain influence on the final research results. AIC and BIC values were relatively close, so log-normal distribution was used to supplement the results. It is displayed that the ICUR value was CNY 285,296.58/QALY, also more than 3 times the GDP per capita of China in 2020. Thus, the nivolumab plus chemotherapy group was also not economical, and the result was robust and practical. Lastly, utility values were not reported in CheckMate649, so those were derived from an economic evaluation for the treatment of advanced gastric cancer, which might not accurately reflect the state of all patients in the current model. But it was mentioned above that although utility values could have a great effect on ICUR value, nivolumab plus chemotherapy was always uneconomical within range of variation.

5. Conclusion

In general, under the willing-to-pay threshold of 3 times the GDP per capita of China in 2020, compared with chemotherapy alone, nivolumab plus chemotherapy is not a cost-effective option in China. The result is robust and of practical significance. When the price of nivolumab (4 ml: 40 mg) was reduced to CNY 3652.71, nivolumab plus chemotherapy was economical. These findings can provide a reference for local clinical decision-making and for medical insurance negotiations in China.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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