Research Article

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Journal of **Comparative Effectiveness Research**

Cost–effectiveness of second-line nivolumab for platinum-treated advanced non-small-cell lung cancer

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Aim: To analyze the economic impact of nivolumab and chemotherapy in patients with non-small-cell lung cancer (NSCLC) who developed disease progression after platinum-containing dual-drug chemotherapy. **Materials & methods:** The partitioned survival model was used to analyze the cost-utility of two NSCLC treatments by nivolumab and docetaxel. The clinical data resulted from the Phase III clinical trial. The cost parameters were derived from our previous studies, and the utility parameters were derived from the literature. **Results:** The quality-adjusted life-years of nivolumab and docetaxel were 0.778 and 0.336. The lifetime direct medical expenses of nivolumab and docetaxel were US$44,707.17 and US$12,826.72. The incremental cost–effectiveness ratio was $72,127.71/quality-adjusted life-year. **Conclusion:** The combination of chemotherapy, nivolumab is not a cost-effective choice in the second-line treatment of NSCLC.

First draft submitted: 2 April 2020; Accepted for publication: 22 September 2020; Published online: 16 December 2020

Keywords: cost–effectiveness • nivolumab • non-small-cell lung cancer

Lung cancer is the malignant tumor with the highest morbidity and mortality in the world. GLOBOCAN data [1] revealed about 2 million new cases of lung cancer worldwide in 2018, accounting for 11.6% of all new cancer cases. About 1.8 million deaths occurred in 2018, accounting for 18.4% of all tumor deaths. Given the large population base in China, the number of new cases and deaths due to lung cancer far exceeds that of other countries. According to the China National Cancer Center, the incidence and mortality rate of lung cancer in China increased from 57.26/100,000 in 2015 and 45.87/100,000 in 2011, respectively [2,3]. Most primary lung cancer is non-small cell lung cancer (NSCLC), accounting for about 80% [4]. Most patients with NSCLC are advanced at the time of diagnosis, eliminating the opportunity for surgery [5,6]. Chemotherapy and radiotherapy have become their main treatment options.

Following the targeted therapy of tumors, immunotherapy drugs have provided new treatment options for NSCLC in recent years [7]. To date, the US FDA has approved four immunosuppressive agents for NSCLC: nivolumab and pembrolizumab, which target PD-1, and atezolizumab and durvalumab, which target PD-L1. In China, only nivolumab was approved in 2018 for the treatment of EGFR gene mutation-negative and ALK-negative patients with intolerable previously advanced or metastatic NSCLC who have undergone disease progression after platinum-containing chemotherapy. Nivolumab is a fully humanized IgG4 PD-1 inhibitor antibody. Its main function is to block the interaction with PD-L1 and PD-L2, as well as the immunosuppressive response mediated by PD-1 pathway, including antitumor immune response, so as to induce antitumor effect [8]. The recommended level of nivolumab monotherapy as a second-line treatment for NSCLC is in Category 1 in NCCN guidelines [9]. CheckMate017 [10,11] and CheckMate057 [11,12] demonstrated that nivolumab significantly prolongs the overall survival (OS) of patients with advanced nonsquamous and squamous NSCLC relative to chemotherapy.

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Figure 1. Markov model for non-small-cell lung cancer. A Markov model comprising three health states (progression-free survival, progressed survival and death) was built.

CheckMate078 [13] showed that nivolumab significantly prolongs survival compared with docetaxel in previously treated Chinese patients with advanced NSCLC, and their median survival is 12 (10.4–14) and 9.6 (7.6–11.2) months, respectively. The incidence of grade 3 or grade 4 adverse events is significantly lower than that of the control group (10 vs 48%).

Although nivolumab is a new treatment that can significantly improve the survival rate of patients with advanced NSCLC, the economic burden of treatment is also an important concern of the public. At present, there is no pharmacoeconomic study on nivolumab in the treatment of Chinese patients with NSCLC. A model was built based on the recommendations of the latest clinical guidelines, and recent clinical efficacy data were used to provide strong support for clinical decision-making through cost-benefit analysis to determine the economic impact of nivolumab as second-line treatment for advanced patients with NSCLC.

Materials & methods

Research object & intervention measures

Subjects were patients with advanced or metastatic squamous and nonsquamous NSCLC, excluding EGFR mutations in nonsquamous NSCLC or known ALK translocations. Patients (18 years or older) showed disease progression during or after treatment with a platinum-containing two-drug regimen and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients were selected regardless of the tumor's PD-L1 expression status. Baseline characteristics of patients were consistent with those in the clinical trial CheckMate078. Nivolumab (3 mg/kg) was administered once every 2 weeks, whereas docetaxel (75 mg/m^2) was administered every 3 weeks. Drug administration was continued until progression or intolerable toxicity.

Model structure

A model was developed based on a 'partitioned survival analysis' analytical framework to compare nivolumab and docetaxel on the basis of China's health service system. According to the current existing lung cancer-related pharmacoeconomic studies [14,15] and real-world situations, the structure of the model was divided into three different mutually exclusive health states. The model structure and transition between states are shown in Figure 1. All patients are in the initial state of progression-free survival (PFS) and their health status cannot be reversed. In the next cycle, some people will still be in PFS, and the rest will be in progressed survival (PS) depending on the transfer probability. Entering PS can only be in PS or into a state of death. Patients receive treatment until the disease progresses, and the patients enter the best support treatment after progression. The cycle time in the model was set to 21 days based on clinical research and treatment options. After 10 years of model operation, all patients were in a state of death. To fully present the lifelong benefits of the two treatment options, the study duration was set to 10 years.

Clinical data

Clinical efficacy data were derived from a Phase III randomized, open-label study (CheckMate-078) [13]. The efficacy and safety of nivolumab and docetaxel in patients with stage IIIb/IV NSCLC who developed disease after platinum-based dual-agent chemotherapy were compared through a Phase III clinical study of the first PD-1 inhibitor in the field of lung cancer in China. The research was mainly conducted in China, with research centers in Hong Kong, Singapore and Russia. The study population was mainly Chinese patients (n = 451) and a small number of Russian (n = 45) and Singapore (n = 8) patients. The trial enrolled 504 patients with squamous and nonsquamous NSCLC, including patients with PD-L1 expression levels <1 and $\geq 1\%$. The graphic digitization software GetData Graph Digitizer (version 2.25) was used to read the PFS and OS curve data of the CheckMate-078 trial nivolumab group and docetaxel group, respectively, to obtain the cumulative survival probability at each time point. The survival proportions in CheckMate 078 at the end of the study are close to zero, only one person and zero people survived at 24 months in the two groups. The long-term clinical outcome survival function came from the fitting and extrapolation of the K-M curve. The goodness-of-fit was based on a visual inspection, Akaike information criterion and Bayesian information criterion [16–18]. A Weibull distribution was fitted to the pseudo-

Table 1. Key clinical inputs.

Parameter	Value		PSA distribution	Ref.
	Nivolumab	Docetaxel		
Log-logistic survival model				
PFS	Scale = 0.222264; shape = 1.311032; r^2 = 0.9657941	Scale = 0.184894; Shape = 1.742256; r^2 = 0.9802700	Fixed	[13]
OS	Scale = 0.054293; shape = 0.836117; r^2 = 0.9896381	Scale = 0.067665; shape = 0.839898; r^2 = 0.9891647	Fixed	[13]
Quality of life				
Utility of PFS	0.784 (0.431–0.974)	0.784 (0.431–0.974)	Beta	[23,24]
Utility of PS	0.470 (0.184–0.773)	0.470 (0.184–0.773)	Beta	[23]
Disutility of toxicities				
Diarrhea	0.047 (0.016–0.077)	0.047 (0.016–0.077)	Beta	[24]
Neutropenia	0.09 (0.058–0.122)	0.09 (0.058–0.122)	Beta	[24]
Rash	0.032 (0.01–0.055)	0.032 (0.01–0.055)	Beta	[24]
Anemia	0.073 (0.037–0.11)	0.073 (0.037–0.11)	Beta	[24]
Cost data (US$)				
Cost of drug	2786.88 (2229.50–2786.88) per cycle	216.25 (173.00–216.25) per 20 mg	Fixed	Local charge
Cost of SAEs per unit	362 (272–453)	362 (272–453)	Gamma	[21]
Cost of follow-up per cycle	59.2 (44.4–74)	59.2 (44.4–74)	Gamma	[21]
Cost of supportive care per cycle	359 (169–845)	359 (169–845)	Gamma	[21]
Cost after disease progression cycle	866.45 (693.16–1,039.74)	866.45 (693.16–1039.74)	Gamma	[19,20]

OS: Overall survival; PFS: Progression-free survival; PS: Progressed survival; PSA: Probability sensitivity analysis; SAE: Serious adverse event (≥grade 3).

individual patient data as it provided the best fit among the gompertz, exponential, log-logistic and log-normal distribution.

Cost & utility

As this study was based on the perspective of health service system, only direct medical cost was considered. The direct medical costs in the model included drug costs, follow-up costs, costs for the treatment of severe adverse events, and costs for post-progression of the disease. The cost of disease progression was from our previously published literature [19] and the drug price was adjusted based on the price in China's latest National Food Protection Bureau's 4 + 7 City Drug Centralized Procurement Document [20]. This policy was a bargaining price under the group purchase model of public hospitals, and the price of medicines has dropped significantly. Other cost data were derived from published relevant literature [21].

According to the Nivolumab drug package insert and guidelines in China, the recommended dose for treating NSCLC is 3 mg/kg, delivered intravenously every 2 weeks. Although the FDA has approved a dosing regimen every 4 weeks, China has not yet approved this usage. Nivolumab (3 mg/kg) was intravenously injected every 2 weeks, and docetaxel (75 mg/m^2) was given intravenously every 3 weeks. We assumed that the patient entered the model with a body surface area of 1.6 m^2 and an average body weight of 60 kg. To avoid the impact of this hypothesis on the results, sensitivity analysis of body surface area and bodyweight was performed. The average exchange rate in 2018 was 6.6174 yuan to 1 dollar, and all costs were converted from RMB to USD [22].

The utility values for each state in this study were obtained from studies by Klazien [23], and the effect of two major adverse events above the third grade on utility values was considered [24]. The incidence rates of docetaxel-related neutropenia, rash, anemia were 19, 0 and 2%, respectively, and the incidence of nivolumab-related neutropenia, rash, anemia were 0.3, 1 and 0.3% [13]. Both cost and utility were discounted at a rate of 3%. The cost and utility values used in the model are shown in Table 1.

Basic analysis & sensitivity analysis

Basic analysis and sensitivity analysis were conducted through a model constructed by Treeage Pro 2015 software. A queue model was established to evaluate the quality-adjusted life-years (QALYs) and lifetime costs of patients

Table 2. Summary of cost and outcome results from a base-case analysis.

Strategy	Costs (US$)	QALY	LY	Medican PFS months	Median OS months	Δ Costs (US$)	Δ QALY	Δ LY	ICER (US$/QALY)
Nivolumab	44,707.17	0.778	1.417	3.3	12.0	31,880.45	0.442	0.856	72,127.71
Docetaxel	12,826.72	0.336	0.561	2.8	9.0	NA	NA	NA	NA

ICER: Incremental cost–effectiveness ratio; LY: Life year; OS: Overall survival; PFS: Progression-free survival; QALY: Quality adjusted life year.

with NSCLC. By calculating the incremental cost–effectiveness ratio (ICER), cost-utility analysis was carried out by comparing it with the threshold value. The threshold for patients with NSCLC in China remains undefined. According to Chinese pharmacoeconomics guidelines and WHO recommendations: ICER >three-times per capita GDP, the increased cost is not acceptable. In this study, the threshold is determined to be three-times of the national per capita GDP in 2018 [25,26]. Therefore, this study adopted the China's 2018 triple GDP per capita of US$29,306.37 as the threshold value.

In order to test the influence of the variables on the results of cost–effectiveness analysis, one-way sensitivity analysis was carried out for all the parameters of input model. The variation range of the parameters mainly came from the relevant research results, with 95% CIs or ± 20% changes. The discount rate was between 0 and 8%. Considering that the Chinese government is pushing forward the reform in the field of drugs and promoting the reduction of drug prices, it is unlikely that drug prices will increase in the short term. Therefore, the drug prices were only set to decline by 20%.

Probability sensitivity analysis (PSA) was repeated 1000 second-order Monte Carlo simulations to calculate the ICER based on each sampling of two different treatment schemes. The utility value was set to beta distribution and the cost was set to gamma distribution. This was mainly based on the suggestions from the the ISPOR-SMDM Modeling Good Research Practices Task Force [24,27]. The prices of nivolumab and docetaxel were fixed in PSA because they are branded drugs. The two treatment schemes were calculated based on the ICER value of each sample and presented in the form of a scatter plot.

Results

Basic analysis

Table 2 shows that the lifetime cumulative cost of nivolumab was US$44,707.17 (CNY 295,845), the cumulative utility was 0.778 QALYs, and the life year was 1.417 years. The lifetime cumulative cost of docetaxel was US$12,826.72 (CNY 84,879), the cumulative utility was 0.336 QALYs, and the life year was 0.561 years. Nivolumab had an ICER of US$72,127.71/QALY (CNY 477,297/QALY) compared with docetaxel. The ICER was much larger than the threshold set in this study (US$29,306.37).

Sensitivity analysis

One-way sensitivity analyses revealed that progressive quality of life, progression-free state quality of life, body weight and nivolumab's drug cost were the main influencing factors. These parameters may cause large changes in the ICER by adjusting their values. The cost of follow-up only slightly influenced the outcome. The results are presented in a tornado diagram in Figure 2. When these parameters fluctuated within their range, nivolumab still had a cost advantage over docetaxel. Therefore, the change in parameters did not affect the conclusion of the study, that is, docetaxel was economical. The results of the scatter plot are shown in Figure 3. All scatter points of nivolumab, compared with those of docetaxel, were above the willingness-to-pay (WTP) threshold line. Thus, under the threshold, the probability of docetaxel having a cost effect was 100%. The cost–effectiveness curve of PSA is shown in Figure 4. The cost-effective acceptable curve showed that the probability that nivolumab had a cost effect increased as the social average WTP increased. When WTP was US$80,000 (CNY 52,939), the acceptable probability of nivolumab was greater than that of docetaxel, that is, the probability of nivolumab exerting a cost effect was 59.9%. As the value of WTP increased, the probability that nivolumab was economical also increased. With a WTP was US$100,000 (CNY 66,174), the probability of nivolumab being most cost-effective was 78.9%.

Discussion

The pharmacoeconomic evaluation of nivolumab in the treatment of NSCLC in China is crucial. Nivolumab was just launched in China in mid-2018. China has a large population base and a large absolute number of patients with lung cancer. After the listing of nivolumab, it will impose a heavy economic burden on patients and the

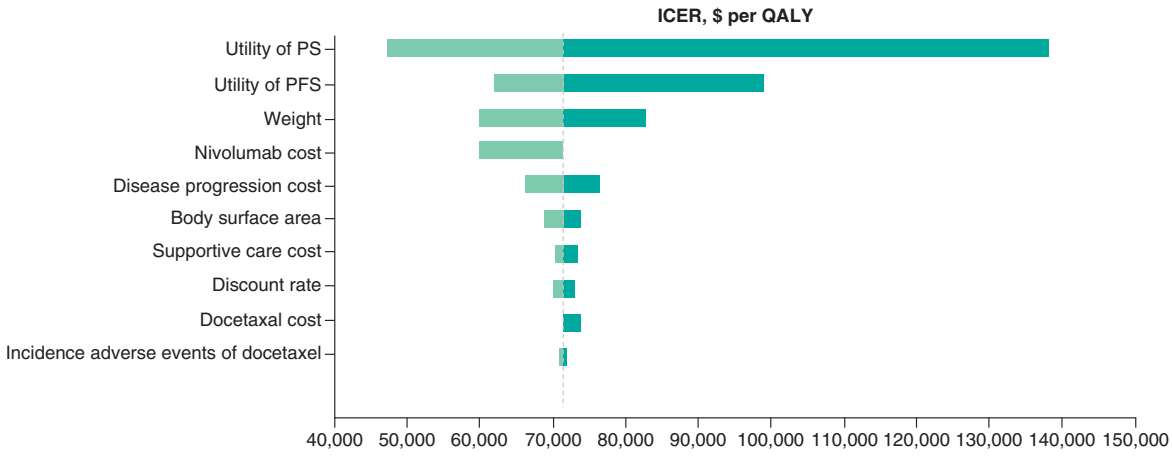

Figure 2. One-way sensitivity analysis. Tornado diagrams show the influence of factors on the Markov model. The factors are listed in descending order of the influence on ICER with variation of factor values.
ICER: Incremental cost–effectiveness ratio; PFS: Progression-free survival; PS: Progressed survival; QALY: Quality-adjusted life years.

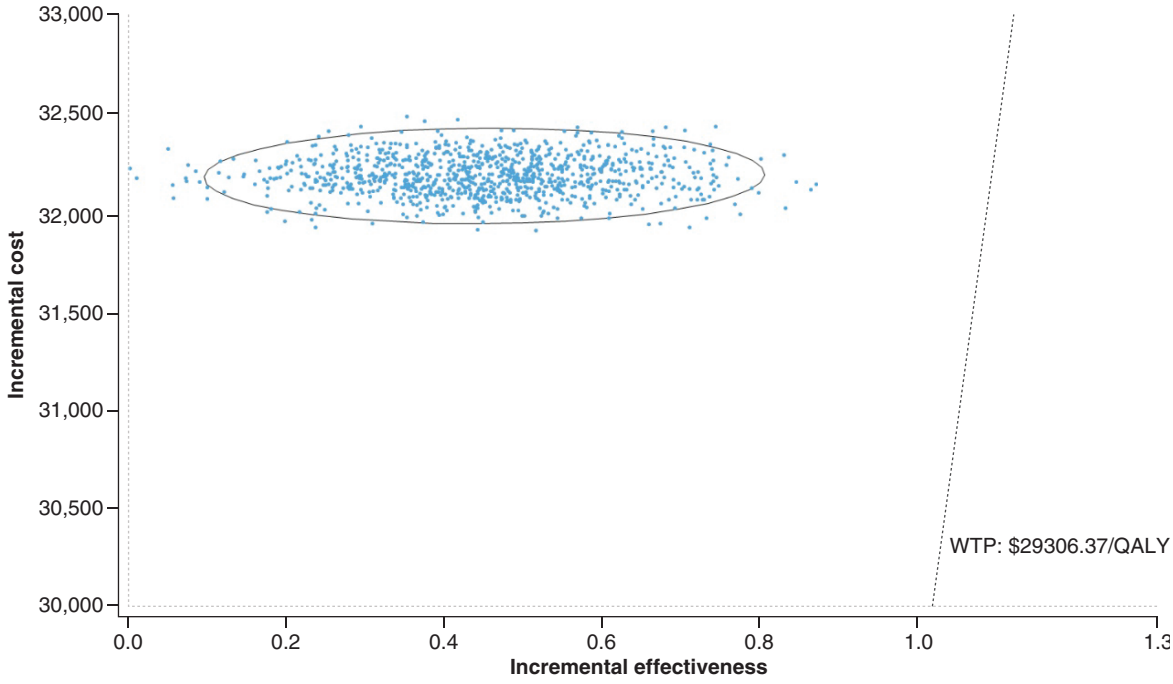

Figure 3. Probabilistic sensitivity analyses. The dot represents the result of the Monte Carlo simulation, and the ellipse represents the 95% CI. The diagonal line represents the WTP value, and the dot falls below the diagonal line to indicate that the test group has a cost effect compared with the corresponding control group.
QALY: Quality-adjusted life years; WTP: Willingness-to-pay.

medical insurance fund. Clinicians, healthcare and patients are extremely interested in the long-term economics of NSCLC. At present, there have been two economic studies on nivolumab compared with docetaxel, which are evaluated in the Switzerland and China. But these studies differ in perspective, model and data source. Matter-Walstra *et al.* studied the treatment of nonsquamous NSCLC in Switzerland [23]. When nivolumab has an ICER value of CHF124,891/QALY compared with docetaxel and exceeds the threshold of CHF100,000/QALY, no cost effect is observed. Although the results are consistent with our study, the medical costs and thresholds values of Switzerland and China are considerably different, which can not directly reflect the economic evaluation in China.

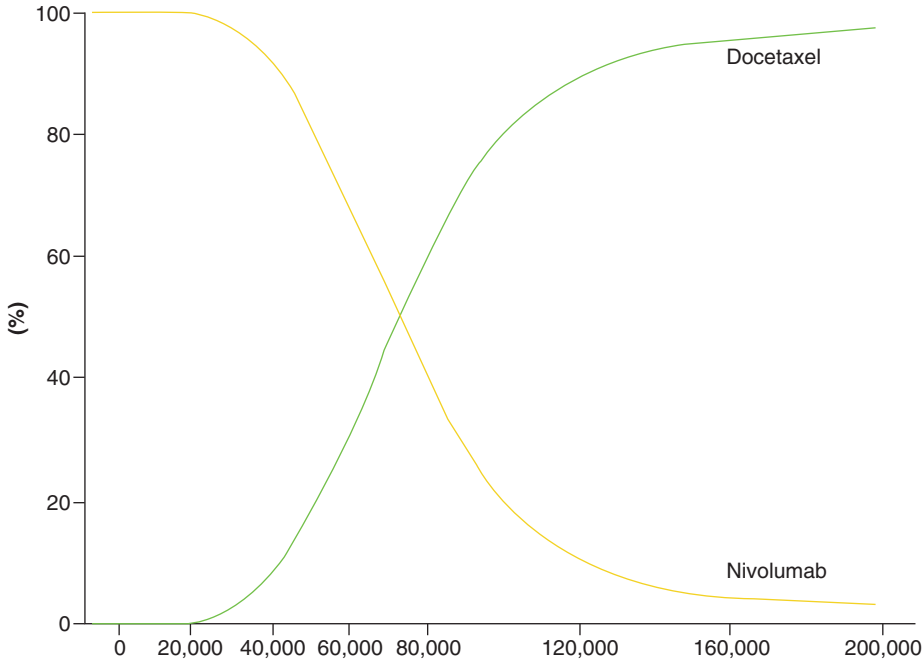

Figure 4. Cost–effectiveness acceptability curves. The cost–effectiveness acceptability curves reflected the results of probabilistic sensitivity analysis by estimating probabilities of different treatments being considered as optimal strategies at different WTP thresholds.
WTP: Willingness-to-pay.

Liu *et al.* established Markov model to evaluate the economics of nivolumab and docetaxel second-line treatment of NSCLC [28]. They found that nivolumab is unlikely to be cost-effective. Liu *et al.* and our study are both researched in China's geo-environment, but there are differences in the research perspective, model structure and PFS curve extrapolation methods. Therefore, there are some differences in cost-utility analysis results. For the nivolumab arm, Liu *et al.* used hazard ratio (HR) to adjust the Weibull parameters, but we fitted and extrapolated the K-M curves of PFS and OS were based on the CheckMate 078 trial. In addition, their model assumed that the patient's starting age was 60 years old, this is inconsistent with clinical trials. Participants in the CheckMate 078 trial and our model were 18 years of age and older. Their assumption would reduce the credibility of the results. The above study assessed the cost–effectiveness of nivolumab from different aspects and provided more comprehensive evidence for decision makers.

This study found that nivolumab works better and costs more than docetaxel, and ICER was significantly above the threshold. One-way sensitivity analysis showed that the quality of life and the cost of nivolumab were the most important sensitive parameters. In order to reduce the burden of patients' medical treatment, the Chinese medical insurance department will make dynamic adjustments to the medical insurance catalogue. Innovative targeted drugs will be negotiated nationally to determine whether they are reimbursed, and to determine payment criteria. Through equal negotiation and consultation between medical insurance and pharmaceutical enterprises, a relatively reasonable payment standard will be formulated [29]. The average decrease rate of drugs for cancer and diabetes is about 65% in 2019 Medical Insurance Catalogue [30]. In order to improve the economics of nivolumab, the national medical insurance department could reduce the price through medical insurance negotiations. Our research would improve the scientificity, standardization and effectiveness of nivolumab negotiations. Combining the level of China's per capita gross national income, exploring the reasonable medical payment standard of nivolumab will help further improve the utilization rate and accessibility of targeted drugs, enhance the quality of life, and decrease the patients' burden.

This study had some limitations. First, the CheckMate 078 trial was the only large-scale randomized controlled clinical trial that compared nivolumab with docetaxel in Chinese patients with NSCLC. However, our model depended on the validity and universality of the trial, and any deviations in the trial were reflected in our research. Second, the study hypothesized that patients enrolled did not require PD-L1 testing. This consideration was mainly

because the PFS and OS curves reported by the CheckMate 078 study included PD-L1 negative (<1%) and PD-L1 positive (≥1%) populations. In the CheckMate 078 study, a subgroup analysis of the effects of PD-L1 expression on OS was performed (pre-set subgroup). In patients with PD-L1 expression levels <1 and ≥1%, OS HR was 0.75 (95% CI: 0.52–1.09) and 0.62 (95% CI: 0.45–0.87). The PD-L1 negative (<1%) subgroup's OS benefit was slightly lower than that of the PD-L1 positive (≥1%) subgroup (effect value HR: 0.75 vs 0.62). Although the 95% CI upper limit of the PD-L1 negative subgroup exceeded 1, the benefit of the effector HR was significant. Compared with the control group of docetaxel monotherapy, nivolumab still improved the OS of patients with negative PD-L1 expression. Therefore, nivolumab poses varying degrees of survival benefit to patients with positive or negative PD-L1 expression, and patients with negative PD-L1 were not excluded in our model. Third, the CheckMate-078 study included some Russian and Singaporean populations, but nearly 90% of the population was Chinese. This clinical trial is believed to be a good representation of the Chinese population. Fourth, the utility values of PFS and PS status were not derived from Chinese NSCLC patients. One-way sensitivity analysis showed that the utility values of PFS and PS in both groups were the main influencing factors. The utility values of specific treatment schemes for Chinese lung cancer patients have not been retrieved from published literature, and the only measurement of the utility value of lung cancer patients in China is the patients with first-line treatment. Fifth, the use of nivolumab may change the clinical path of third-line drug treatment in patients with NSCLC, but we did not consider other individualized treatment decisions. Despite some limitations, the variables in the model did not affect the final result. Sensitivity analysis showed that probability, utility and cost data were unlikely to affect the final result.

Conclusion

Under the threshold of three-times GDP per capita in China, docetaxel is more economical than the nivolumab in the treatment regimen for patients with NSCLC and disease progression after platinum-based dual-agent chemotherapy. The Chinese government could try to reduce the price of nivolumab through medical insurance negotiations.

Summary points

- Nivolumab is not likely to be more cost-effective than chemotherapy in the second-line treatment of non-small-cell lung cancer in China.
- The Chinese government could try to reduce the price of nivolumab through medical insurance negotiations.

Author contributions

L Zhang contributed toward methodology, software, writing-original draft preparation and writing-review and editing. X Zeng contributed toward formal analysis, visualization, project administration and formal analysis. H Cai contributed toward conceptualization, methodology and supervision. N Li contributed toward writing-original draft preparation, and writing-review and editing. M Liu contributed toward methodology, supervision, project administration, resources. L Qiu contributed toward investigation, data curation, conceptualization. B Zheng contributed toward formal analysis and visualization.

Financial & competing interests disclosure

This study was supported by Fujian Provincial Department of Science & Technology (grant no. 2017Y0035) of the People's Republic of China and National Natural Science Foundation of China (grant no. 71804025). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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