Original Article



# Cost-effectiveness of pembrolizumab versus docetaxel as second-line treatment of non-small cell lung cancer in China

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**Background:** Pharmacoeconomic information for pembrolizumab as a second-line lung cancer treatment is insufficient in China, so we aimed to assess its cost-effectiveness versus docetaxel as a second-line treatment for patients with non-small cell lung cancer (NSCLC) in China.

**Methods:** A partitioned survival model was developed to assess the cost-effectiveness of pembrolizumab versus docetaxel in the treatment of NSCLC patients. A phase III clinical trial (KEYNOTE-010) was used as the clinical data. Long-term survival data were extrapolated based on the clinical study data. Lifetime cost and utility were calculated with a discount set at 3%. One-way deterministic sensitivity analyses and probabilistic sensitivity analysis were used to test the robustness of incremental cost-effectiveness ratios (ICER).

**Results:** In the base-case scenario, the ICERs were $107,846/quality-adjusted life year (QALY) and $448,414/QALY for pembrolizumab (2 and 10 mg/kg) groups, respectively. Both ICER values were 3-fold higher than the threshold of China's per-capita GDP in 2019 ($30,055.01). One-way deterministic sensitivity analyses showed that the price of pembrolizumab is the main factor affecting the result of ICER. Median ICERs were $108,658/QALY ($107,005/QALY–$110,089/QALY) for the pembrolizumab 2 mg/kg group and $451,590/QALY ($443,685/QALY–$457,496/QALY) for the pembrolizumab 10 mg/kg group using the current price in China. For patients receiving regimens with 2 mg/kg pembrolizumab, the probabilities will be exceeding 95% when the price of pembrolizumab decreases by 25% in a high-income region (willing to pay setting as $71,406/QALY).

**Conclusions:** The results suggest that for it to become a second-line treatment of NSCLC in China, a reduction in the cost of pembrolizumab is needed.

**Keywords:** Cost-effectiveness; docetaxel; non-small cell lung cancer (NSCLC); pembrolizumab; second-line treatment

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## Introduction

According to the Global Cancer Statistics 2018 report, lung cancer (LC) is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths) around the world (1). In order of the number of cases and deaths, LC also ranks first in the incidence and death of malignant tumors in China. The number of new cases and deaths was 787,000 and 631,000, respectively, in China in 2015 (2). LC is a heterogeneous group of tumors, consisting of more

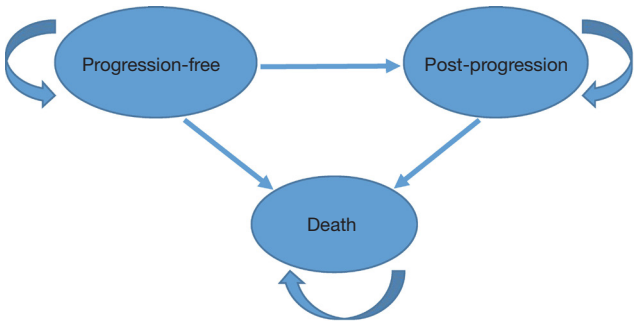


**Figure 1** Model structure.

than 50 histomorphological subtypes. Non-small cell LC (NSCLC) comprises approximately 80–85% of all LC, with adenocarcinoma (ADC, ~40–50% of cases) and squamous cell carcinoma (SCC, ~20–30% of cases) comprising the predominant histological subtypes of NSCLC. Clinically, only a small portion of NSCLC patients are diagnosed at an early stage (stage I or II), when the tumor can be treated by surgical resection (3). More than 60% of LC patients present with locally advanced or metastatic disease (stage III or IV) at the time of diagnosis. Within the past decade, based on genomic studies and analyses of molecular pathways in different subtypes of LC, both the development of targeted therapies and clinical trials have increased rapidly (4). Although targeted therapy has improved clinical outcomes in certain subsets of LC patients, the 5-year survival rate is still less than 20% (5,6). More recently, immunotherapies have transformed the management of patients with NSCLC, and are generally associated with improved overall survival (OS), lower toxicity, and better quality of life compared with chemotherapy (7).

Pembrolizumab is a humanized monoclonal IgG4 kappa anti-PD1 antibody (8). By blocking the binding of the PD-1 receptor and its ligand on the surface of T cells, their function can be partially restored and the tumor can be attacked. The efficacy and safety of pembrolizumab in treating advanced NSCLC have been demonstrated in several clinical trials, including the KEYNOTE-010, KEYNOTE-024 and KEYNOTE-042 (9-11). Pembrolizumab prolongs progression-free survival (PFS), OS, and has a favorable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced NSCLC. However, with the improvement in first-line treatment and supportive treatment for NSCLC, the number of patients entering second-line treatment continues to increase, which means that second-line therapy remains an important part of the overall management of cancer patients. The guidelines for China, the United Kingdom, the USA and Australia all contain recommendations for pembrolizumab as a second-line LC treatment (12), but pharmacoeconomic information for pembrolizumab as a second-line LC treatment is insufficient in China. Docetaxel, a chemotherapy drug, is considered the most adequate comparator for pembrolizumab because it has now become the standard comparator in multiple clinical trials and used for driving gene-negative non-SCC patients after first-line progression as class I recommended drug in China (13,14). In previous, pembrolizumab was evaluated as a cost-effective option compared with Docetaxel in the USA for previously treated PD-L1-positive advanced NSCLC patients (15), however, the conclusion could not be used in Chinese patients as the difference medical cost and willingness-to-pay. Economic evaluation of pembrolizumab is necessary for Chinese patients. Cost effectiveness analysis is a method of comparing decision alternatives in which both the costs and the effects are taken into account in a systematic way, which is widely used in the field of pharmacoeconomic study (16). Therefore, the purpose of this study was to evaluate the cost-effectiveness of pembrolizumab versus docetaxel as second-line treatment of patients with NSCLC from the perspective of the Chinese National Health Service.

We present the following article in accordance with the CHEERS reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4178).

## Methods

### *Model structure*

Based on data from clinical trial KEYNOTE-010, a partitioned survival model was developed and adapted for cost-effective analysis. The partitioned survival model was programmed and implemented using the 'heemod' package in R software (The R Project for Statistical Computing. https://www.r-project.org/). Patients were simulated in three states [PFS, post-progression (PP) and death] in the model (*Figure 1*). These three states are mutually exclusive, which means that one patient can only exist in one of three states at any given time. All patients start in the PFS state. Once the disease progresses, the patient moves from the PFS state to the PP state, from where they can progress to death or remain in PP; it is not allowed to return to the original PFS state from the PP state in the model. In addition, PFS could progress to death (terminal state) without going through the PP state. The proportion of patients in the PFS and terminal states at any time is determined directly from

 

the PFS and OS data; the proportion of patients in the PP state is calculated as OS minus PFS. In accordance with the schedules of pembrolizumab and docetaxel, the simulation was conducted on a 3-week cycle, with a time horizon of 630 cycles, during which time over 99% of the simulated patients would die, and represent the lifetime horizon for patients with advanced NSCLC (17). Because each health state has a specific cost and quality-of-life adjustment weight (or utility), the cumulative cost and quality-adjusted life years (QALYs) over the time range can be accessed by calculating the time duration of each state. Analyses were performed from the perspective of the health service system.

### *Model inputs*

#### Clinical data

The parameters of the model were mainly derived from the KEYNOTE-010 clinical trial, which was a phase II/III clinical trial conducted at 202 academic medical centers in 24 countries between August 28, 2013, and February 27, 2015, including 1,034 patients with locally advanced or metastatic NSCLC with positive tumor PD-L1 expression and who had received at least one previous chemotherapy regimen. Pembrolizumab and the chemotherapy drug docetaxel were compared in this trial. Patients were divided into three groups, given the standard dose of 2 mg/kg pembrolizumab, the high dose of 10 mg/kg pembrolizumab or 75 mg/m$^2$ docetaxel, respectively, all once every 3 weeks. Primary endpoints were OS and PFS. Definitions were based on the RECIST V1.1 criteria (18), with secondary endpoints of overall response rate and duration of response (9).

Kaplan-Meier (KM) data were used to estimate PFS and OS in the model until reaching the cutoff date of KEYNOTE-010. The time points for pembrolizumab and docetaxel in PFS were 218 and 157 weeks respectively, and in OS were 227 and 225 weeks respectively. After that time point, subsequent KM data of PFS are estimated by using a function fitting method. The best-fit parametric functions were chosen according to the Akaike information criterion and the Bayesian information criterion (Table S1). Because the 2 and 10 mg/kg pembrolizumab dose groups were pooled in the published long-term PFS and OS data, the estimated long-term PFS and OS for the two dose groups were split by applying a hazard ratio (HR) derived from KEYNOTE-010. Following long-term KM estimation of PFS and OS, the applied HR was also used in the best-fit parametric functions. As subsequent split and fitted data did not accurately come from the clinical data, we performed a sensitivity analysis of the HR and function parameters.

#### Utility score

Utilities for patients with NSCLC in China were mainly determined according to Nafees *et al.*'s study (19), in which the utilities were elicited from a societal perspective using the standard gamble method in several countries including China. As reported in the published study, the utility score of 0.804 for PFS state and 0.321 for PP state were used in our study, Adverse events (AEs) in the PFS state were also considered as disutilities in the model; the most five common AEs associated with KEYNOTE-010 patients were assigned disutility scores by applying the published data or consulting oncologists.

#### Costs

Only direct costs were considered in the model. Direct costs included the price of pembrolizumab and docetaxel in the PFS state, cost of follow-up in the PFS state, supportive treatment costs, treatment costs of serious AEs and end-stage palliative care expenses in the death state. Considering the different expenditures at different stages of the disease, the costs of treatment in the three stages [PFS, PP and death (terminal state)] were assessed separately. The prices of drugs were obtained from the Yaozhi network (20), which represent the drug prices in most Chinese hospitals. Others were based on the published literature. Cost of AEs and duration of AEs were estimated by a Delphi panel of 10 Chinese clinical experts (5 oncologists and 5 pharmacists), specializing in NSCLC treatment. All costs in this study were reported in US dollar ($).

The pembrolizumab price was derived from the retail price in Chinese public hospitals, whereas the docetaxel price was assessed from the average price of pharmaceutical purchases in various provinces across the country. Because the total doses and costs of pembrolizumab and docetaxel are related to body weight, the weight distribution in the Chinese National Health Survey was used for correction during the calculation.

The discount rate was setting as 3% according to Chinese guidelines for pharmacoeconomic evaluations (21). In accordance with the World Health Organization guidelines, willingness-to-pay (WTP) thresholds are set as 3-fold the per-capita gross domestic product ($30,055 for general regions, $14,376 for low-income regions and $71,406 for high-income regions) (22,23).

 

**Table 1** Parameters for base-case analysis, one-way DSA and PSA

| Parameters | Base case | Range for DSA | Parameters (or distribution) for PSA* | Reference |
|---|---|---|---|---|
| Cost ($) | | | | |
| Pembrolizumab/mg | 25.50 | 20.41–30.61 | Fixed | (20) |
| Docetaxel/mg | 10.6 | 8.5–12.7 | Gamma | (20) |
| PD-L1 test | 48.5 | 38.8–52.2 | Normal | (24) |
| Routine follow-up per cycle | 55.6 | 41.7–69.4 | Log-normal | (25) |
| Subsequent systemic therapy in PP state per cycle | 854.1 | 706.5–992.4 | Log-normal | (26) |
| Best supportive care per cycle | 337.5 | 158.7–793.7 | Log-normal | (25) |
| Terminal phase cost | 2627.8 | 2,291.8–2,966.6 | Log-normal | (26) |
| Neutropenia per event | 461.5 | 415.4–507.7 | Log-normal | (27) |
| Fatigue per event | 115.4 | 103.8–126.9 | Log-normal | (27) |
| Diarrhea | 150 | 100–200 | Log-normal | Local charge |
| Severe skin reaction | 248 | 200–296 | Log-normal | Local charge |
| Pneumonitis | 200 | 100–300 | Log-normal | Assumption |
| Utility | | | | |
| PFS | 0.804 | 0.643–0.881 | Beta | (19) |
| PP | 0.321 | 0.257–0.385 | Beta | (19) |
| Disutility | | | Beta | |
| Severe skin reaction | 0.30 | 0.10–0.40 | Beta | Assumption |
| Fatigue | 0.07 | 0.07–0.49 | Beta | (19) |
| Neutropenia | 0.20 | 0.15–0.50 | Beta | (19) |
| Diarrhea | 0.07 | 0.06–0.35 | Beta | (19) |
| Pneumonitis | 0.20 | 0.1–0.3 | Beta | Assumption |
| Duration of adverse events (weeks) | | | | |
| Severe skin reaction | 1 | Fixed | Fixed | Assumption |
| Fatigue | 1 | Fixed | Fixed | Assumption |
| Neutropenia | 1 | Fixed | Fixed | Assumption |
| Diarrhea | 1 | Fixed | Fixed | Assumption |
| Pneumonitis | 1 | Fixed | Fixed | Assumption |
| Patient weight (kg) | 65 | Fixed | Fixed | (25) |

*, the simulated parameters for probabilistic sensitivity analysis were set with the standard error at 20% of the base-case value. DSA, deterministic sensitivity analyses; PSA, probabilistic sensitivity analysis.

### *Sensitivity analysis*

One-way deterministic sensitivity analyses were performed on the key parameters to analyze the effect of changes on the results. The range of each parameter value was set to the base-case value ±20%, when the parameter value range was ambiguous. The minimum and maximum values of each parameter are shown in *Table 1*. A second-order Monte Carlo simulation was conducted for probabilistic sensitivity analysis. Uncertainty of parameters for PFS and OS in each

 

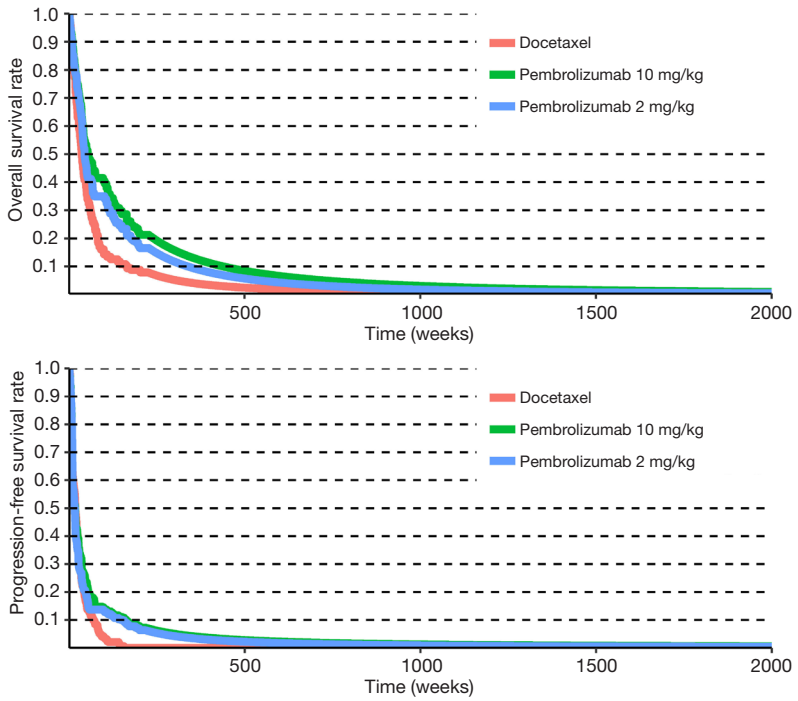


**Figure 2** Fitted overall survival curve and progression-free survival curve.

treatment group was assessed through a variance-covariance matrix assumed to be perfectly correlated. Based on the different assumptions of the distribution of each parameter (*Table 1*, Tables S2-S4), the sampling was repeated 1,000 times. The incremental cost-effectiveness ratios (ICER) values of each sample in the different groups were calculated and presented in a scatter plot. As medical reform continues to advance in China, the price of drug often decreases, so the influence of drug price decrease was also analyzed.

### *Statistical analysis*

The total cost, life years and QALY in each group were calculated in base-case scenario. The ICER values were calculated in base-case scenario and sensitivity analysis. All the statistical analyses were implemented in R software (http://www.r-project. org).

## Results

### *Base-case scenario*

Based on the clinical trial results in patients with NSCLC, pembrolizumab could significantly improve OS and PFS compared with docetaxel. The fitted OS and PFS curves for both pembrolizumab (log-logistic distribution for OS curve, and log-normal distribution for PFS) and docetaxel (log-logistic distribution for OS) are presented in *Figure 2*. The life years (2.5 life years, 3.3 life years) of the pembrolizumab groups (2, 10 mg/kg) were higher than those of the docetaxel chemotherapy group (1.4 life years), and the total QALYs (1.2 QALYs for pembrolizumab 2 mg/kg group, 1.45 QALYs for pembrolizumab 10 mg/kg group) were also higher than those of the docetaxel chemotherapy group (0.70 QALYs). The differences of QALYs in the non-progressive state was 0.4 in the pembrolizumab 2 mg group and 0.51 in the pembrolizumab 10 mg group compared with the docetaxel group, and the differences in the PP state were 0.1 QALYs (pembrolizumab 2 mg) and 0.23 (pembrolizumab 10 mg). Economic analysis showed that the costs of each cycle of treatment with pembrolizumab ($138.31 in the pembrolizumab 2 mg/kg group, $586.23 in the pembrolizumab 10 mg/kg group) were higher than with docetaxel ($52.52). The lifetime direct medical costs of pembrolizumab were $87,134.79 and $369,326.82, respectively, in the two dose groups (2 and 10 mg/kg), which were $54,047.98 and $336,240.02 higher than the docetaxel chemotherapy group ($33,086.8). The ICERs were $107,846/QALY and $448,414 QALY for pembrolizumab

 

**Table 2** Base-case scenario results

| | Life year (years) | Total cost ($) | Cost in PFS ($) | Cost in PP ($) | Cost in terminal ($) | QALY | QALY in PFS | QALY in PP | Increase cost-effectiveness ratio ($/QALY) |
|---|---|---|---|---|---|---|---|---|---|
| Discount =3% | | | | | | | | | |
| Docetaxel | 1.415569 | 33,086.801 | 16,584.98243 | 13,985.57082 | 2,516.248171 | 0.699023008 | 0.415285922 | 0.283737086 | |
| Pembrolizumab 2 mg/kg | 2.506085 | 87,134.788 | 65,950.3899 | 18,731.75113 | 2,452.646488 | 1.200180446 | 0.820153592 | 0.380026854 | 107,846.3214 |
| Pembrolizumab 10 mg/kg | 3.268327 | 369,326.82 | 341,301.0169 | 25,622.14013 | 2,403.662537 | 1.448864396 | 0.929046401 | 0.519817995 | 448,414.8563 |
| Discount =0 | | | | | | | | | |
| Docetaxel | 1.586283 | 35,962.074 | 16,848.39896 | 16,494.32379 | 2,619.351697 | 0.756516116 | 0.42188184 | 0.334634276 | |
| Pembrolizumab 2 mg/kg | 2.608329 | 100,049.463 | 75,925.75792 | 21,508.11567 | 2,615.589261 | 1.380579307 | 0.944226001 | 0.436353306 | 102,693.7485 |
| Pembrolizumab 10 mg/kg | 3.407474 | 433,056.416 | 399,721.7948 | 30,732.713 | 2,601.908083 | 1.71157748 | 1.088076977 | 0.623500503 | 415,778.8773 |

PFS, progression-free survival; PP, post-progression; QALY, quality-adjusted life year.

(2 and 10 mg/kg) groups. Both ICER values are higher than the threshold of WTP for the general region ($30,055.01). Detailed base-case scenario results are given in *Table 2*.

### *Sensitivity analysis*

*Figure 3* shows the effects of parameter changes on the results. It was observed that the model had excellent stability. Among all the parameters, the price of pembrolizumab and the utility of PFS were the main factors affecting the results of ICERs. In addition to those factors, the utility PS also had a minor effect on the results of ICER. The results of the probabilistic sensitivity analysis (PSA) were intuitively described by the scatter plot and cost-effectiveness acceptability curve (*Figures 4,5*). The median ICERs were $108,658/QALY ($107,005/QALY–$110,089/QALY) (number of simulation run was 1,000) for pembrolizumab 2 mg/kg group and $451,590/QALY ($443,685/QALY–$457,496/QALY) (number of simulation runs was 1,000) for the pembrolizumab 10 mg/kg group using the current price in China. The probability of being cost-effective was zero for both of the pembrolizumab groups at the set WTP threshold ($30,055 per QALY). A decrease in the pembrolizumab price could increase the probability of cost-effectiveness. For patients receiving a regimen with 2 mg/kg pembrolizumab, the probability will exceed 95% when the price of pembrolizumab decreases 25% in the high-income region (*Figure 6*).

## Discussion

Pembrolizumab as a better second-line treatment option for NSCLC was confirmed in KEYNOTE-010, but the economic evaluation for this treatment option is less reported. Huang *et al.* evaluated the cost-effectiveness of pembrolizumab versus docetaxel for the treatment of previously treated PD-L1-positive advanced NSCLC patients in the USA, for which, pembrolizumab was considered as a cost-effective option (15). Based on the latest data from a number of existing clinical studies, we used a partitioned survival model to analyze the cost-effectiveness of pembrolizumab and docetaxel in the treatment of Chinese NSCLC patients. The results indicated that pembrolizumab prolonged the life of NSCLC patients and increased the quality of life, but also increased the medical costs. The ICERs for the two dose groups of pembrolizumab were $107,846/QALY (pembrolizumab 2 mg/kg) and $448,414/QALY (pembrolizumab 10 mg/kg)

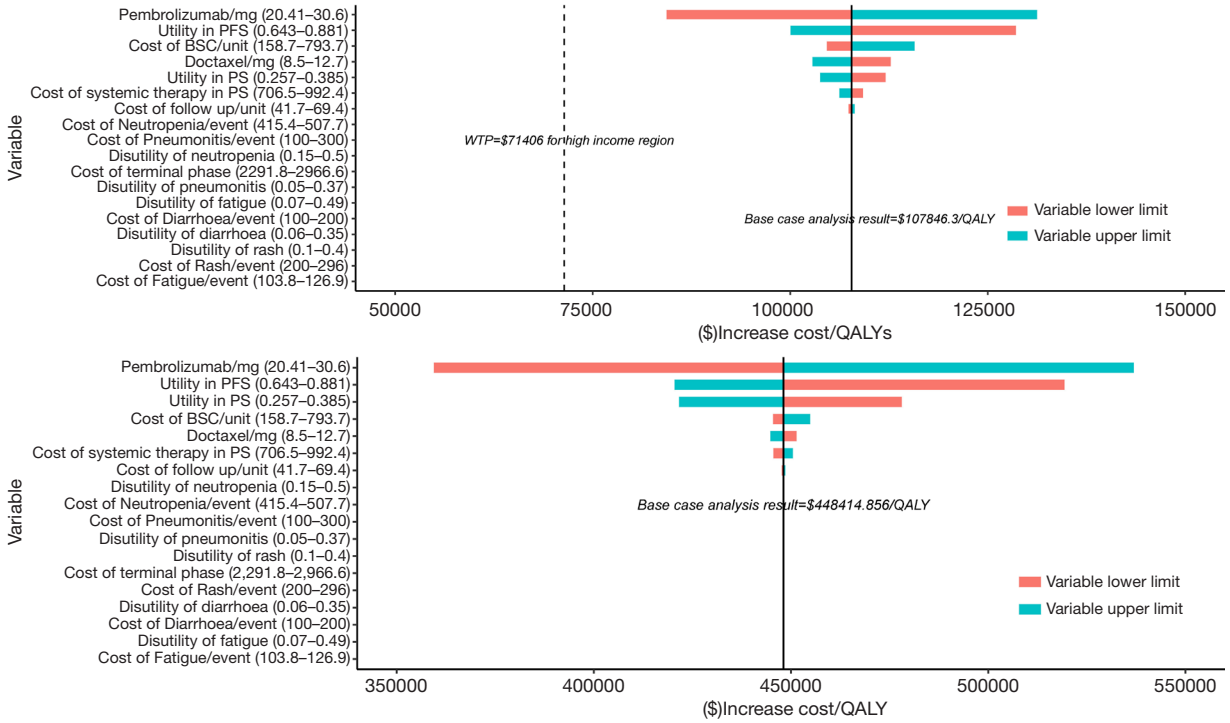


**Figure 3** Tornado diagram of the one-way sensitivity analysis. QALY, quality-adjusted life year.

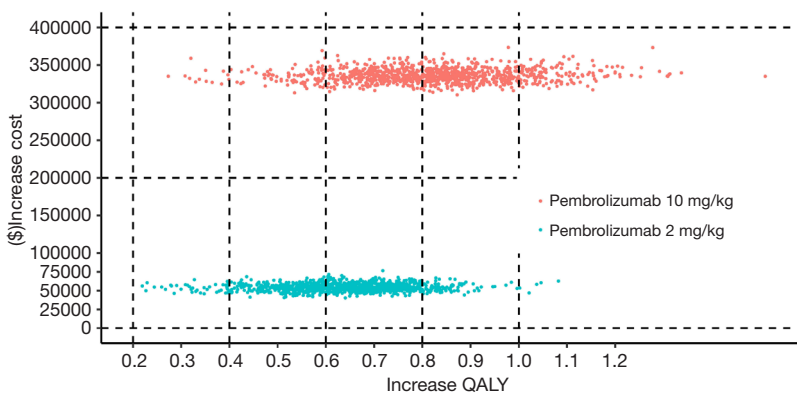


**Figure 4** Cost-effectiveness scatter plot of probabilistic sensitivity analysis. QALY, quality-adjusted life year.

versus docetaxel. Following Chinese guidelines for pharmacoeconomic evaluation, an acceptable ICER value should be less than 3-fold of the Chinese per-capita GDP, the use of pembrolizumab at both of the studied doses was not cost-effective compared with routine second-line treatment with docetaxel in China. Moreover, considering the unbalanced regional economic development in China, even for a high-income region (Beijing) with the WTP threshold set as $71,406/QALY, the pembrolizumab treatment regimens were not cost-effective.

To avoid bias, we conducted comprehensive sensitivity analyses including one-way deterministic sensitivity analyses and PSA. The cost-effectiveness results were robust to changing the inputs for most of the sensitivity analyses. A considerable effect on ICER was seen when changing the price of pembrolizumab or body weight. As a result, adjust the drug price could significant influence the cost-effective of pembrolizumab, higher price of pembrolizumab could

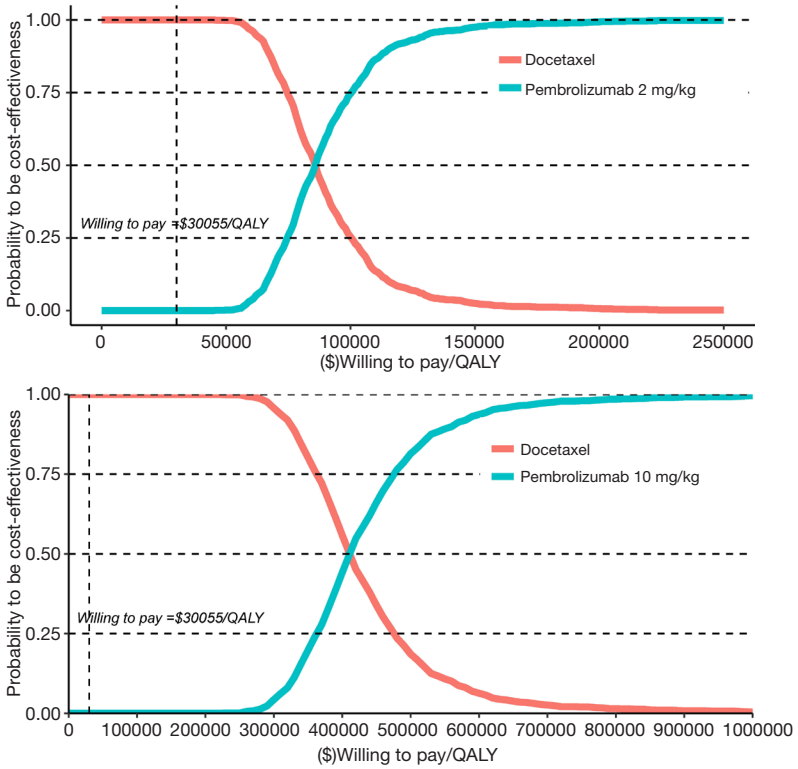


**Figure 5** Cost-effectiveness acceptability curve. QALY, quality-adjusted life year.

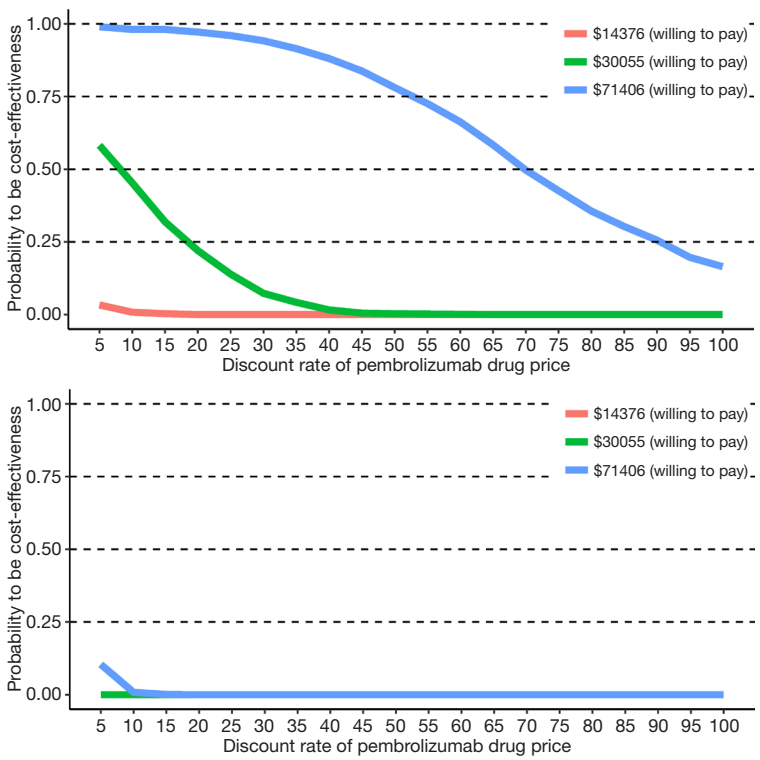


**Figure 6** Probability of cost-effectiveness curve for pembrolizumab at different discount rates of pembrolizumab price.

 

lower its cost-effectiveness, to improve the cost-effective probabilities for pembrolizumab requires a decrease in the drug price. In China a decrease in the drug price often occurs as medical reform continues to advance (26). As for pembrolizumab, the donation policy in China is also considered as a kind of drug price reduction strategy for first-line treatment of NSCLC. Therefore, we analyzed the influence of a drug price decrease on the result of the ICER. We found >95% probability of cost-effectiveness for pembrolizumab 2 mg/kg treatment regimen was reached with WTP set as $71,406/QALY when the price was 25% decreased.

The long-term PFS and OS outcomes are still an open question for the evaluation of anticancer drugs. In general, lifetime is thought to be the best for cost-effective evaluation, but the implementation of lifetime observation is impractical in the real world. Therefore, a cost-effective analysis often has to extrapolate from clinical study data to capture long-term effects. Even when the extrapolation is fitted by rigorous methodological approaches, there is still potential bias. In our study, we extrapolated the PFS and OS curves and analyzed the influence of the parameters changing. The results were robust when the parameters for extrapolation changed with a reasonable interval.

Of note, the effectiveness difference of the two dose groups for pembrolizumab was not significant. The ICER difference between the two dose groups was mainly associated with the cost of pembrolizumab; that is, patients given the high dose of pembrolizumab (10 mg/kg) would gain more unnecessary cost, which goes against the cost-effectiveness principle. Besides, the risk of AEs might be higher in the pembrolizumab high dose group (10 mg/kg) for real-world patients, even though the AE results in the clinical study were similar between the two dose groups (9).

### *Study limitations*

The data for the model construction and analysis were derived from a phase III randomized controlled trial (KEYNOTE-010), which was conducted mainly in Caucasians (~70%), so the patients enrolled in the clinical trials were not solely Chinese NSCLC patients. Effectiveness differences between races might affect the result. As there were no long-term follow-up data in this clinical trial, an extrapolation was performed with several criteria and the influence of fitted parameters was also tested in the sensitivity analyses. Considering the long-term biological effects of immune checkpoint inhibitors, applying long-term follow-up data to further validate this model is still needed. This study was based on the perspective of the health service system, so only direct medical costs were considered, which may lead to an underestimation of the overall benefits of therapy. The retail price was considered as the price of these two drugs, which might underestimate the total cost, as pretreatment were also need for cancer patients. There are currently no reports on the utility scores of related second-line treatment options for LC patients in China. The utility scores of the PFS and PP states were also not derived from Chinese NSCLC patients. Inputted literature scores and clinical experts' evaluated scores might not reflect the true value of the patients. Additionally, treatment in PP state is another limitation in relation to cost and utility; active treatment might be implemented in a real-world setting, which might make the model more complex and the data in the subsequent-line treatment insufficient to use.

## Conclusions

In summary, sensitivity analysis confirmed that the cost-effectiveness value estimated using the current model was reliable. Assuming a 3-fold China per-capita GDP as the WTP threshold, our study showed that both doses of pembrolizumab (2 and 10 mg/kg) are not cost-effective as second-line treatment of NSCLC in China; therefore, pembrolizumab is unlikely to be acceptable for the Chinese healthcare system. The results of our study suggest that to become a second-line treatment of NSCLC in China, a reduction in the price of pembrolizumab is needed.

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## Footnote

*Reporting Checklist:* The authors have completed the CHEERS reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-4178

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.

 

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*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. Informed consent from the patients was not required in this study because the research data is publicly available.



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## Supplementary

**Table S1** AIC and BIC goodness-of-fit statistics for PFS and OS curve distribution estimations

| | OS of pembrolizumab 2 mg | | PFS of pembrolizumab 2 mg | | OS of pembrolizumab 10 mg | | PFS of pembrolizumab 10 mg | | OS of pembrolizumab long | | PFS of pembrolizumab long | | OS of docetaxel long | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC | AIC | BIC |
| llogis | 1753.181 | 1760.862 | 1696.041 | 1703.722 | 1650.207 | 1657.9 | 1754.99 | 1762.683 | 5139.961 | 5149.034 | 4499.65 | 4508.723 | 2504.287 | 2511.963 |
| lnorm | 1752.948 | 1760.63 | 1700.309 | 1707.99 | 1647.265 | 1654.958 | 1756.052 | 1763.745 | 5135.918 | 5144.991 | 4500.397 | 4509.471 | 2511.068 | 2518.744 |
| weibull | 1772.871 | 1780.552 | 1782.791 | 1790.472 | 1664.729 | 1672.422 | 1812.754 | 1820.447 | 5197.835 | 5206.909 | 4693.218 | 4702.291 | 2559.955 | 2567.63 |
| exp | 1773.398 | 1777.239 | 1792.32 | 1796.16 | 1666.342 | 1670.189 | 1824.407 | 1828.253 | 5221.535 | 5226.07 | 4856.623 | 4861.16 | 2560.446 | 2564.283 |
| gamma | 1774.606 | 1782.287 | 1792.228 | 1799.909 | 1666.595 | 1674.288 | 1821.467 | 1829.16 | 5209.989 | 5219.062 | 4759.331 | 4768.405 | 2562.444 | 2570.12 |
| gompertz | 1754.771 | 1762.452 | 1716.258 | 1723.932 | 1648.974 | 1656.666 | 1769.829 | 1777.522 | 5151.048 | 5160.121 | 4545.172 | 4554.245 | 2530.551 | 2538.227 |

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

**Table S2** Adverse event rates in model

| Incidence rate | Incidence rate in pembrolizumab 2 mg/kg | Incidence rate in pembrolizumab 10 mg/kg | Incidence rate in docetaxel | Reference |
|---|---|---|---|---|
| Severe skin reaction | 0.0087 | 0.0087 | 0.0058 | KEYNOTE-010 |
| Fatigue | 0.0116 | 0.0173 | 0.0321 | KEYNOTE-010 |
| Neutropenia | 0 | 0 | 0.111 | KEYNOTE-010 |
| Diarrhea | 0.0058 | 0 | 0.0204 | KEYNOTE-010 |
| Pneumonitis | 0.0203 | 0.0202 | 0.0058 | KEYNOTE-010 |

**Table S3** Survival distribution estimation and distribution parameter variation in one-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA)

| Survival model | Distribution estimate from Keynote-010 | Range for DSA | Parameters for PSA |
|---|---|---|---|
| OS docetaxel (long term) | Log-logis | Shape (1.3946–1.6775)<br>Scale (10.6728–13.5470) | Generate numbers from correlated multivariate gamma distribution |
| OS pembrolizumab (long term) | Log-norm | Meanlog (2.7943–3.0077)<br>Sdlog (1.3189–1.4876) | Generate numbers from correlated multivariate gamma distribution |
| PFS pembrolizumab (long term) | Log-ogis | Shape (1.1664–1.3279)<br>Scale (5.5860–6.8824) | Generate numbers from multivariate gamma distribution correlated with OS curve parameters |

**Table S4** Reconstructed hazard ratio (HR) between pembrolizumab 10 mg/kg and pembrolizumab 2 mg/kg groups and HR variation in one-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA)

| Pembrolizumab 10 *vs.* 2 mg/kg | Constant | Range for DSA | Parameters for PSA |
|---|---|---|---|
| PFS | 0.898 | 0.7976–1.102 | Log-normal (mean =0.9375, sd =1.0859) |
| OS | 0.8512 | 0.7036–1.03 | Log-normal (mean =0.8512, sd =1.1021) correlated with HR for PFS |

OS, overall survival; PFS, progression-free survival.



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