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Cost–Utility Analysis of Pembrolizumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small Cell Lung Cancer With Different PD-L1 Expression Levels

Xiuhua Weng,^{*1} Shaohong Luo,^{*1} Shen Lin,^{*} Lixian Zhong,[†] Meiyue Li,^{*} Rao Xin,^{*} Pinfang Huang,^{*} and Xiongwei Xu^{*}

^{*}Department of Pharmacy, First Affiliated Hospital of Fujian Medical University, Taijiang, Fuzhou, P.R. China

[†]College of Pharmacy, Texas A&M University, College Station, TX, USA

To evaluate the cost–utility of pembrolizumab versus chemotherapy as the first-line setting for metastatic non-small cell lung cancer (NSCLC) from the US health care system perspective, a Markov model was developed to compare the lifetime cost and effectiveness of pembrolizumab versus chemotherapy for untreated metastatic NSCLC, based on the clinical data derived from phase III randomized controlled trial (KEYNOTE-042; ClinicalTrials.gov; NCT02220894). Weibull distribution was fitted to simulate the parametric survival functions. Drug costs were collected from official websites, and utility values were obtained from published literature. Total costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) were computed as primary output indicators. The impact of different PD-L1 expression levels on ICER was also evaluated. One-way and probabilistic sensitivity analyses were performed to assess the model uncertainty. Compared with chemotherapy, patients treated with pembrolizumab provided an additional 1.13, 1.01, and 0.59 QALYs in patients with PD-L1 expression levels of $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$, with corresponding incremental cost of \$53,784, \$47,479, and \$39,827, respectively. The resultant ICERs of pembrolizumab versus chemotherapy were \$47,596, \$47,184, and \$68,061/QALY, in three expression levels of PD-L1, respectively, all of which did not exceed the WTP threshold of 180,000/QALY. Probability sensitivity analysis outcome supported that pembrolizumab exhibited evident advantage over chemotherapy to be cost-effective. One-way sensitivity analysis found that ICERs were most sensitive to utility value of pembrolizumab in progression survival state. All the adjustment of parameters did not qualitatively change the result. For treatment-naïve, metastatic NSCLC patients with PD-L1⁺, pembrolizumab was estimated to be cost-effective compared with chemotherapy for all PD-L1 expression levels at a WTP threshold of \$180,000/QALY in the context of the US health care system.

Key words: Programmed cell death ligand 1 (PD-L1); Pembrolizumab; Non-small cell lung cancer (NSCLC); Cost–utility; Chemotherapy

INTRODUCTION

Lung cancer is the neoplasm with the highest incidence worldwide and is considered to be responsible for nearly 20% and ranked first in cancer-related deaths¹. Non-small cell lung cancer (NSCLC) accounts for approximately 80%–85% of all lung cancers². Over the past decade, platinum-based chemotherapy has remained the traditional mainstay of treatment for metastasis in NSCLC patients³, which is associated with modest efficacy and

has reached a plateau. Fortunately, the tremendous efforts in developing new drugs and profound research on potential biomarkers have promoted the emergency of immune checkpoint inhibitors (ICIs) that block the programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) pathway to treat NSCLC, showing considerable advantages^{4–6}.

Pembrolizumab (Keytruda), a humanized monoclonal antibody designed to block the PD-1 receptor, was approved by the Food and Drug Administration (FDA)

[†]These authors provided equal contribution to this work.

Address correspondence to Pinfang Huang, Department of Pharmacy, First Affiliated Hospital of Fujian Medical University, 20 ChaZhong Rd, Taijiang, Fuzhou, P.R. China. Tel: +13600898956; E-mail: 2363869908@qq.com or Xiongwei Xu, Department of Pharmacy, First Affiliated Hospital of Fujian Medical University, 20 ChaZhong Rd, Taijiang, Fuzhou, P.R. China. Tel: +8613600826726; E-mail: xxw0409@163.com

as the first-line treatment for metastatic NSCLC patients without an EGFR mutation or ALK translocation⁷⁻⁹. The use of pembrolizumab brings hopes to the treatment of metastatic NSCLC patients. New clinical outcomes have further proved that pembrolizumab survival benefits statistically compared to chemotherapy⁵. Taking the drug price into account, this could result in a significant rise of financial burden on the health care system, so it is necessary to conduct an economic analysis.

On the basis of survival data from a series of KEYNOTE trials, numerous economic appraisals of pembrolizumab have been carried out from different countries' perspective¹⁰⁻¹². However, there are still no relevant reports based on the KEYNOTE 042, which investigated the benefits of pembrolizumab monotherapy compared with chemotherapy in PD-L1 $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$ metastatic NSCLC patients, respectively, to evaluate the cost-utility of pembrolizumab. By reason of patients with a higher expression level of PD-L1 could achieve longer median survival time than that lower PD-L1 expression, the possibility of pembrolizumab to be cost saving might vary from different PD-L1 levels. Therefore, in this analysis, we sought to evaluate the cost-utility of pembrolizumab in metastatic NSCLC patients with different expression levels of PD-L1 in the context of the US health care system.

MATERIALS AND METHODS

Model Structure

A Markov model was developed to project expected costs and efficacy of pembrolizumab compared with chemotherapy, within three mutually exclusive health states: "progression-free survival (PFS)" (initial state of patient until progression), "progression survival (PS)" (state after disease progression), and "death" (absorbing state)

(Fig. 1). Eligible population in this model was based on the enrollment criterion of KEYNOTE-42 trial⁶, which was patients with locally advanced or metastatic NSCLC, previously untreated, and without EGFR mutation or ALK translocation. Pembrolizumab was administrated up to a maximum of 35 cycles, and platinum-based chemotherapy was continued for 4–6 cycles or until disease progression. As disease progressed, patients were allowed to receive subsequent treatment including chemotherapy, target therapy, immunotherapy, or two treatment options mentioned above simultaneously. The parametric survival curve fitting was performed in R software (version 3.5.1), and the Markov model was developed and run in TreeAge 2017.

The analysis was conducted from the perspective of the US health care system. The cycle was as 21 days, and the model was run until 99% of the patients enter death state with a time horizon of lifetime. The primary outputs of this model were lifetime health care costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). ICERs were compared with the willingness-to-pay (WTP) threshold of \$180,000/QALY in the US¹³ to estimate the cost-utility. Costs were discounted at an annual rate of 3%¹⁰.

Effectiveness Parameters

The model effectiveness parameters were obtained from KEYNOTE-042⁶. The survival functions, which were fitted according to the PFS and OS data from Kaplan–Meier (KM) curves, were used to calculate the transfer probability among the states. Both the Weibull and the log-logistic distributions were fitted, and the optimal survival function was employed. The fitting was conducted following UK National Institute for Health and

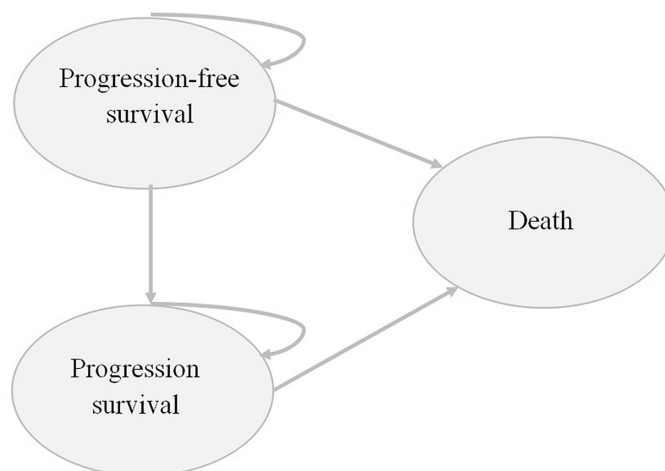


Figure 1. Model structure.

Care Excellence (NICE) Decision Support Unit (DSU) guidelines¹⁴. In adjusted R^2 of fit tests, the matching degree of extrapolation outcome and clinical data were considered in selecting the final distribution functions for the model. The background mortality rate for each age group was derived from published literature and adopted to estimate the transfer probability of PFS to death¹⁵. Finally, we fitted three series curves for patients with PD-L1 expressions of $\geq 50\%$, $\geq 20\%$ and $\geq 1\%$ according to KEYNOTE-042 setting (Table 1).

Utility value, which measures health-related quality of life (HR-QoL) in a range of 0–1, was obtained from published literature¹⁶ (Table 2). QALYs were computed by multiplying life-years by utility values.

Cost Inputs

Only direct medical costs were considered in the model. Cost components associated with cancer treatment included drug acquisition, follow-up, best support care (BSC), treatment of serious adverse events (SAEs), and terminal care.

Drug acquisition cost was based on the dosing schedule reported in KEYNOTE-042⁶. Pembrolizumab was administered at a dose of 200 mg every 3 weeks (q3w). The chemotherapy group regimens, namely, pemetrexed/paclitaxel + carboplatin, were administered q3w for 4 to 6 cycles depending on specific regimen choice, which was calculated based on the proportion of patients on each regimen according to the trial. As disease progressed, both groups of patients received one or more treatment regimens, so the drug cost for PS state was calculated and adjusted according KEYNOTE-042 trail. The patients' body surface area (BSA) and typical weigh were assumed to be 1.82 m² (17) and 71.4 kg¹⁸, respectively, to estimate the doses of chemotherapy agents as well as second-line drug therapy (nivolumab and bevacizumab). Unit prices

of drugs in the US were obtained from the website www.drugs.com.

Follow-up cost was counted from PFS state and throughout the treatment process, while BSC occurred in PS state after 5-month subsequent therapy on the basis of several articles about second-line treatment of NSCLC patients^{4,19}. Terminal care costs were also included as a one-time cost in the final state in the US²⁰. The above resource costs were obtained from previously published studies^{17,21,22}.

SAE-related costs were computed by multiplying the estimated incidence rates of per AEs by the corresponding unit treatment cost. Four SAEs with high incidence rates ($>1\%$) and expensive treatment expenditure were enrolled in this model, which were neutropenia, anemia, thrombocytopenia, and pneumonitis (Table 3). AE unit treatment costs were obtained from an analysis conducted in developed countries²³. All the unit costs used in the base analysis were presented as US dollars and are listed in Table 2.

Sensitivity Analyses

One-way deterministic sensitivity analysis (DSA) was conducted to evaluate the variation of the model result by changes in key parameters within the plausible ranges. To be specific, parameters were imposed lower and upper limits with mean \pm standard deviation obtained from the literature¹⁶ or a range of $\pm 20\%$ of the base case value¹⁵. Probabilistic sensitivity analysis (PSA) was carried out to test the alteration of the model with respect to uncertainty in model input parameters, performing Monte Carlo simulation with 1,000 iterations using different distributions such as log-normal for cost values and gamma for utility values. The ranges and distributions of parameters for sensitivity analyses are given in Table 2.

Table 1. Clinical Inputs: Weibull Survival Curve-Fitting Parameters

PD-L1 Expression	Regimen	Scale (λ)	Shape (γ)	Adjusted R^2
Overall survival				
$\geq 50\%$	Pembrolizumab	0.063985	0.796046	0.999902
	Chemotherapy	0.041061	1.089799	0.999146
$\geq 20\%$	Pembrolizumab	0.065791	0.816173	0.999862
	Chemotherapy	0.041653	1.066223	0.999218
$\geq 1\%$	Pembrolizumab	0.072141	0.8074439	0.999866
	Chemotherapy	0.04438	1.059809	0.999284
Progression-free survival				
$\geq 50\%$	Pembrolizumab	0.144153	0.769625	0.998946
	Chemotherapy	0.062074	1.232194	0.998621
$\geq 20\%$	Pembrolizumab	0.156777	0.770046	0.998626
	Chemotherapy	0.059433	1.226069	0.999018
$\geq 1\%$	Pembrolizumab	0.16432	0.79536	0.998187
	Chemotherapy	0.065666	1.197265	0.999148

PD-L1, programmed cell death ligand 1.

Table 2. Base Parameter Input to Model and Ranges of Sensitivity Analyses

Parameters	Base Value	Lower	Upper	Distribution	Source
Cost (\$)					
Pembrolizumab (200 mg)	9,180.80	7,344.64	11,016.96	Log-normal	15, www.drugs.com
Carboplatin (50 mg)	12.79	10.23	15.35	Log-normal	15, www.drugs.com
Paclitaxel (30 mg)	15.57	72.66	109.00	Log-normal	15, www.drugs.com
Pemetrexed (100 mg)	728.91	583.13	874.69	Log-normal	15, www.drugs.com
Nivolumab (40 mg)	1,119.90	895.92	1,343.88	Log-normal	15, www.drugs.com
Docetaxel (20 mg)	609.43	487.54	731.32	Log-normal	15, www.drugs.com
Gemcitabine (1000 mg)	782.50	626.00	939.00	Log-normal	15, www.drugs.com
Gefitinib (250 mg)	271.34	217.07	325.61	Log-normal	15, www.drugs.com
Crizotinib (250 mg)	293.48	234.78	352.18	Log-normal	15, www.drugs.com
Bevacizumab (100 mg)	840.51	672.41	1,008.61	Log-normal	15, www.drugs.com
Pneumonitis	6,491.17	5,192.94	7,789.40	Log-normal	15,23
Anemia	6,461.96	5,169.57	7,754.35	Log-normal	15,23
Neutropenia	104.48	83.58	125.38	Log-normal	15,23
Thrombocytopenia	232.55	186.04	279.06	Log-normal	15,23
Follow-up	3,785.00	3,028.00	4,542.00	Log-normal	15,17
Best support care	124.95	99.96	149.94	Log-normal	15,21
Terminal care	5,546.18	4,436.94	6,655.42	Log-normal	15,20
Utility values					
Pembrolizumab of PFS	0.71	0.47	0.95	gamma	16
Pembrolizumab of PS	0.67	0.47	0.87	gamma	16
Chemotherapy of PFS	0.68	0.44	0.92	gamma	16
Chemotherapy of PS	0.67	0.47	0.87	gamma	16
Body surface area (m ²)	1.82	1.52	1.92	Normal	17
Body weight (kg)	71.4	29	112	gamma	18
Discount rate (%)	3	0	5	Fixed	10,17

PFS, progression-free survival; PS, progression survival.

RESULTS

Base Case Results

Compared with chemotherapy, pembrolizumab yielded a gain of QALYs, along with an increase in total costs for treatment-naïve, metastatic NSCLC patients (Table 4). In this analysis, patients treated with pembrolizumab produced an additional 1.13, 1.01, and 0.59 QALYs more than chemotherapy in the cohorts with PD-L1 expression levels of $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$, respectively. From the US health care system perspective, the corresponding incremental costs over lifetime horizon spent for pembrolizumab in comparison to chemotherapy were \$53,784, \$47,479, and \$39,827. Consequently, ICERs were estimated to be \$47,596/QALY, \$47,184/QALY, and \$68,061/QALY in PD-L1 expression levels of $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$, respectively, all of which were within the WTP threshold of \$180,000/QALY.

Sensitivity Analyses

The results of one-way DSA are shown as the tornado diagrams (Fig. 2). It manifested that the utility value of pembrolizumab in PS state had the greatest impact on ICERs regardless of PD-L1 expression levels. The ICER varied from \$34,985 to \$76,420/QALY, \$32,804 to \$79,243/QALY, and \$45,498 to \$138,720/QALY in patients of PD-L1 $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$, respectively, both of which were far below the WTP (Fig. 2A–C). Other variables that considerably impacted the ICERs were the price of pembrolizumab, utility value of pembrolizumab in PFS state, and utility value of chemotherapy in the PS state. Taken together, varying the key parameters in a sensible range had limited impact on the results.

The PSA results are exhibited as the cost-effectiveness acceptability curve (Fig. 3). At the WTP of \$180,000/QALY, pembrolizumab showed an obvious advantage

Table 3. Treatment-Related Adverse Events

Adverse Event Rates ⁶	Pembrolizumab (%)	Chemotherapy (%)
Pneumonitis	20 (3%)	0
Anemia	4 (<1%)	80 (13%)
Neutropenia	1 (<1%)	46 (7%)
Thrombocytopenia	1 (<1%)	10 (2%)

Table 4. Base Case Results

	Pembrolizumab	Chemotherapy	Incremental
PD-L1 expression $\geq 50\%$			
QALY	1.87	0.74	1.13
Total cost	117,390	63,605	53,784
ICER			47,596
PD-L1 expression $\geq 20\%$			
QALY	1.78	0.77	1.01
Total cost	112,341	64,862	47,479
ICER			47,184
PD-L1 expression $\geq 1\%$			
QALY	1.37	0.78	0.59
Total cost	104,747	64,919	39,827
ICER			68,061

PD-L1, programmed cell death ligand 1; QALY, quality-adjust life years; ICER, incremental cost-effectiveness ratio.

over chemotherapy to be cost-effective, with 92.1%, 92.4%, and 82.3% of the 1,000 Monte Carlo simulations favored the outcome in patients of PD-L1 $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$, respectively.

DISCUSSION

The sharp rise in the cost of ICIs is a worldwide puzzle, and recently a lot of research has focused on their cost-effectiveness. Pembrolizumab, as a first-line therapy for metastatic NSCLC with PD-L1 expression level $\geq 50\%$, was previously evaluated in the US, France, and the UK^{11,16,24}. The analyses results revealed that in the US and France, pembrolizumab was considered a cost-effective strategy for treatment-naïve NSCLC patients with PD-L1 expression $\geq 50\%$ ^{11,24}, yet it was not a cost-saving regimen in the UK¹⁶. However, this research only covered the population with PD-L1 expression $\geq 50\%$ due to the clinical data limitation in KEYNOTE-024²⁵. KEYNOTE-042⁶, a further and enlarged research of KEYNOTE-024, revealed the different survival benefits for three levels of PD-L1 expression ($\geq 50\%$, $\geq 20\%$, and $\geq 1\%$). Given the different PFS and OS benefits associated with different PD-L1 expression levels, we specifically constructed a Markov model to evaluate the cost-effectiveness of pembrolizumab as first-line treatment for metastatic NSCLC patients in three levels of PD-L1 expression.

Base case results indicated that, compared to platinum-based chemotherapy, pembrolizumab provided the ICERs of \$47,596/QALY, \$47,184/QALY, and \$68,061/QALY at the PD-L1 expression levels of $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$, respectively. All ICERs were below the WTP threshold of \$180,000/QALY, which means the additional benefits associated with pembrolizumab is worth the extra costs in the context of the US health care system. Generally, the ICER decreased with the increase in PD-L1 expression along with more therapy efficiency. The higher the PD-L1 expression, the better the cost-effectiveness. We found that the ICER of expression

level $\geq 50\%$ close to that of expression $\geq 20\%$ may be due to the fact that in KEYNOTE-042 trial, the numbers of patients with expression level $\geq 50\%$ accounted for nearly 75% in the expression level $\geq 20\%$ group.

One-way DSA revealed that the main driver of the incremental cost was the utility value of pembrolizumab in the PS state. Because PS state occupies a longer duration in patients' overall survival time, a slight change in the utility value in the PS state could cause a significant impact on ICERs. However, the relationship between the ICERs and WTP remained unchanged in either lower or upper values of key parameters. According to the PSA results, the possibility of pembrolizumab over chemotherapy to be cost-effective at a WTP of \$180,000/QALY was 92.1%, 92.4%, and 82.3% in patients with PD-L1 $\geq 50\%$, $\geq 20\%$, $\geq 1\%$, respectively. Even if the WTP was lowered to \$100,100/QALY, pembrolizumab also surpasses chemotherapy to be cost saving. It signifies that pembrolizumab monotherapy is worth being widely used in clinics when both price and efficacy are taken into account simultaneously.

There are some strengths in our study. One major strength is that we used the most novel survival data from a randomized controlled trial, which directly compared pembrolizumab monotherapy with chemotherapy as first-line treatment for metastatic NSCLC patients with a median follow-up time of 12.8 months, especially 25.2 month for patients with PD-L1 expression level $\geq 50\%$. Nevertheless, the earlier pharmacoeconomic evaluations of pembrolizumab simulated patient survival based on the data with a shorter follow-up time of 11.2 months¹¹ and thus the model assumptions would have an impact on the results to a greater extent. These long-term data are likely to confirm robustness of extrapolations and reduce uncertainty around results. Another strength is that we evaluated the cost-effectiveness of pembrolizumab with different expression levels of PD-L1, and the outcomes suggest that the acceptability among patients with three

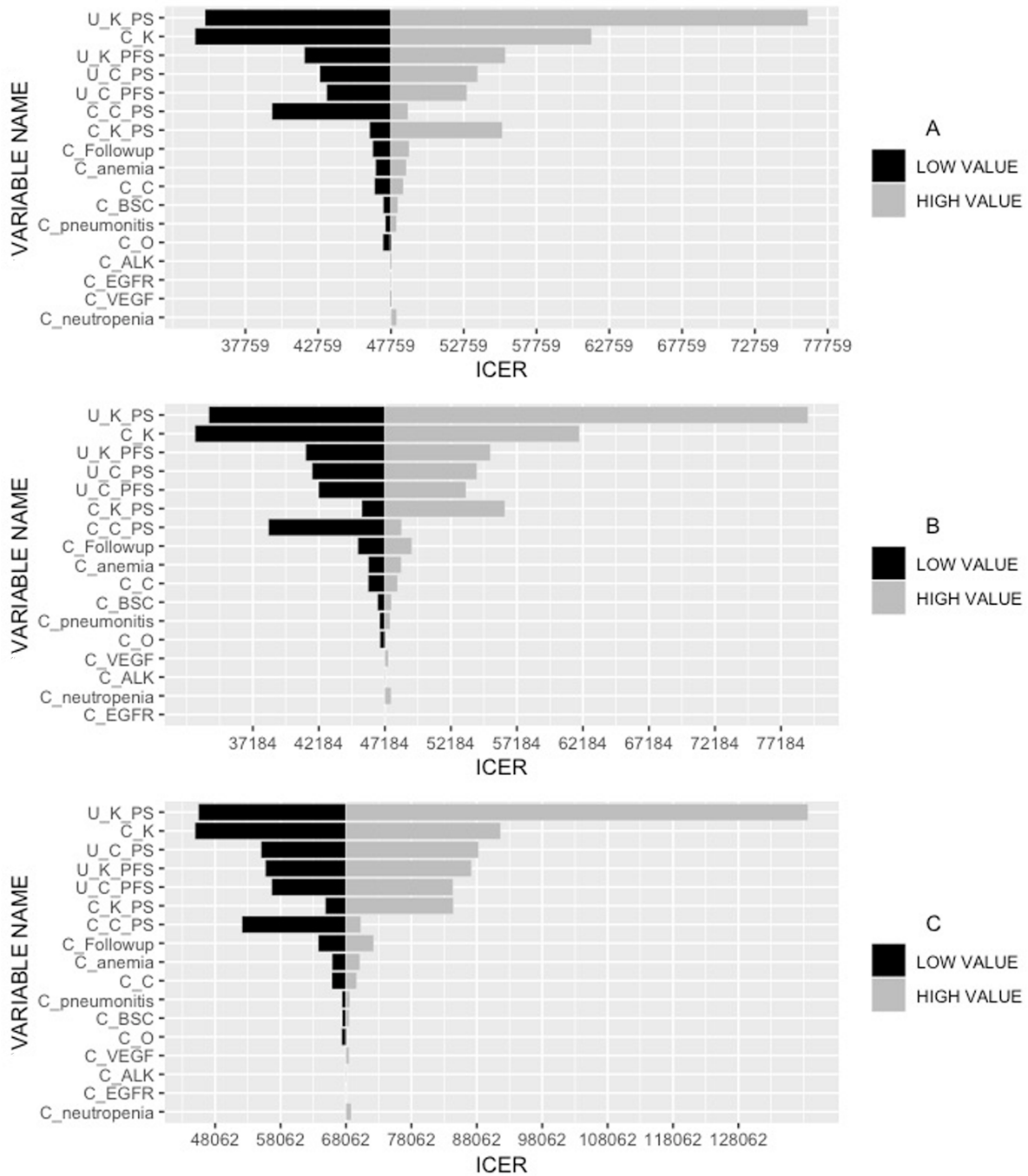


Figure 2. Tornado diagrams for one-way deterministic sensitivity analysis. U_K_PS, utility of pembrolizumab in progression survival state; C_K, cost of pembrolizumab; U_K_PFS, utility of pembrolizumab in progression-free survival state; U_C_PS, utility of chemotherapy in progression survival state; U_C_PFS, utility of chemotherapy in progression-free survival state; C_C_PS, cost of chemotherapy in progression survival state; C_K_PS, cost of pembrolizumab in progression survival state; C-BSC, cost of best support care; C_C, cost of chemotherapy; C_pneumonitis, cost of treatment in pneumonitis; C_O, cost of nivolumab; C_Followup, cost of follow-up; C_anemia, cost of treatment in anemia; C_VEGF, cost of bevacizumab; C_ALK, cost of crizotinib; C_neutropenia, cost of treatment in neutropenia; C_EGFR, cost of epidermal growth factor receptor inhibitors.

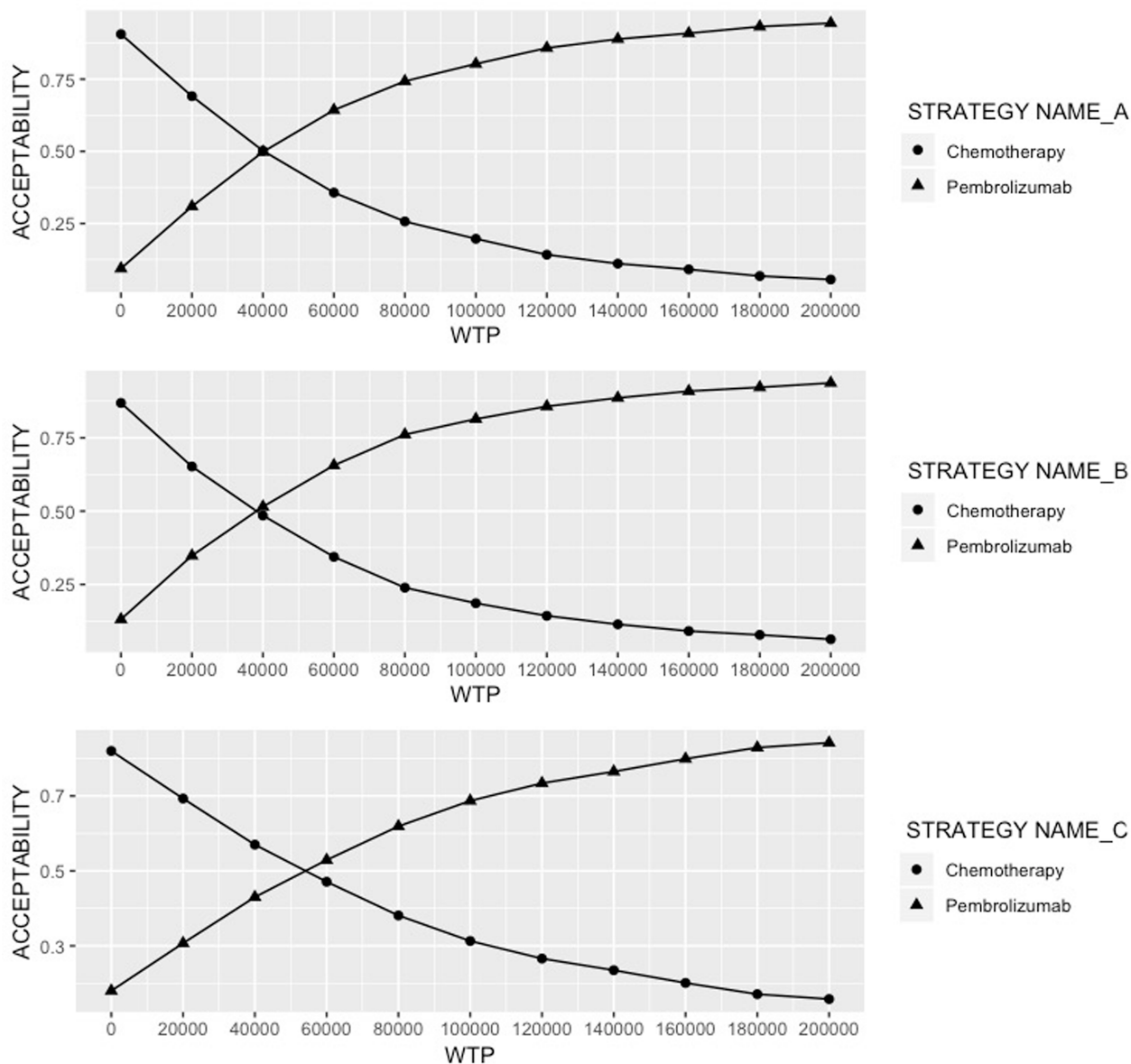


Figure 3. Cost-effectiveness acceptability curve. WTP, willingness-to-pay.

levels of expression of PD-L1 presented a similar result. Furthermore, our analysis chose two survival functions, Weibull and log-logistics distributions, that agree well with clinical data in previous publications¹⁵. By comparison of two fitted curves we selected Weibull distribution due to its higher adjusted R^2 , and the predicted data were in agreement with the trial results.

Some limitations also need to be pointed out, which are mainly governed by data availability and model assumptions. First, intangible cost such as pain and fear were included in utility weights; hence, they were not computed separately. Indirect costs, which were wage losses caused by suspension of school, work, early death,

etc., are difficult to estimate in most cases, so we did not incorporate this into the model. Although there was little difference between the regimens in intangible and indirect costs, further cost components need to be considered for an adequate assessment. Second, pseudoindividual patient data that could improve estimate accuracy of mean survival time were unavailable, and thus we adopted a Markov model that relied on the aggregate survival data reported from the clinical trial. We compared the overall survival curves simulated by the model with the KM curves of clinical trial using R software and confirmed that two groups of curves coincided. The cohort study results showed that the median overall survival of three

PD-L1 expression levels predicted by this model, which was 20.5, 17.2, and 18.0 months for pembrolizumab and 12.7, 13.5, and 12.7 months for chemotherapy, did accord with the data of clinical trial KEYNOTE-042. Furthermore, utility value reflects the HR-QoL, which is a subjective experience and may vary greatly among individuals, so it is difficult to provide an accurate value. In our study, utility values were derived from published literature¹⁶, which directly evaluate the utility of patients using pembrolizumab from the real world. The utility values were suitable for our study, and one-way DSA demonstrated that the variation of utility values did not qualitatively change the result.

CONCLUSION

From the perspective of US health care system, pembrolizumab is estimated to be cost-effective compared to chemotherapy for previously untreated NSCLC patients with different expression levels of PD-L1 at a WTP threshold of \$180,000/QALY.

ACKNOWLEDGMENTS: The authors gratefully acknowledge the financial support of the Natural Science Foundation of Fujian Province (2019J01446) and Startup Fund for Scientific Research, Fujian Medical University (Grant No.: 2018QH1091). All authors contributed to data analysis, drafting, and revising the article, and provided final approval of the version to be published. The authors declare no conflict of interest.

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