Original Article

The effect of PD-L1 categories-directed pembrolizumab plus chemotherapy for newly diagnosed metastatic non-small-cell lung cancer: a cost-effectiveness analysis

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Background: The effectiveness of adding pembrolizumab to chemotherapy improve outcomes in newly diagnosed metastatic non-small-cell lung cancer (NSCLC). We aimed to evaluate the economic outcomes of first-line treatment by adding pembrolizumab to chemotherapy with and without the use of PD-L1 testing for patient selection.

Methods: A decision-analytic model was adopted to project the disease course of newly diagnosed metastatic nonsquamous and squamous NSCLC without EGFR or ALK mutations. The efficacy and toxicity data were gathered from the KEYNOTE-189 and KEYNOTE-407 trials. Transition probabilities were estimated from the reported survival probabilities in each group. Cost and health preference data were derived from published economic evaluations. The incremental cost-effectiveness ratio (ICER) was measured, and subgroup, one-way and probabilistic sensitivity analyses (PSA) were performed for exploring the model uncertainties.

Results: In the US context, pembrolizumab plus chemotherapy is projected to increase quality-adjusted-life year (QALY) by 1.168 and 0.988 in comparison with chemotherapy and the ICERs were $122,248 and $121,375/QALY in the whole nonsquamous and squamous patients with unconfirmed PD-L1 tumor proportion scores (TPS), respectively. After the selection of patients by PD-L1 TPS by PD-L1 testing, the ICERs of adding pembrolizumab treatment for patients with confirmed PD-L1 TPS >1% and ≥50% were $143,282 and $127,661/QALY in nonsquamous disease, and $131,495 and $121,554/QALY in squamous disease, respectively. The ICERs of adding pembrolizumab treatment for Chinese patients were higher than $40,000/QALY regardless of the histology and TPS subgroups, which highly exceed the willingness-to-pay threshold of $29,196/QALY (three times of per capita gross domestic product of China in 2018) in China.

Conclusions: Pembrolizumab plus chemotherapy as first-line treatment for untreated metastatic NSCLC without EGFR or ALK mutations is a cost-effective option regardless of PD-L1 expression status in the US context, and not cost-effective in the Chinese context. However, PD-L1 categories-directed pembrolizumab could not increase the cost-effectiveness of immunotherapy.

Keywords: Cost-effectiveness; programmed cell death 1 ligand 1 (PD-L1); pembrolizumab; metastatic non-small-cell lung cancer (NSCLC)

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Introduction

The Global Burden of Disease Study revealed that lung cancer is one of the leading causes of non-communicable disease burden worldwide (1). Approximately 85% to 90% of lung cancers are non-small-cell lung cancer (NSCLC), including 65% to 75% locally metastatic or metastatic disease. Platinum-based chemotherapy has been the standard of care for the first-line treatment of metastatic NSCLC that lacks sensitizing EGFR or ALK mutations (2). However, the overall survival (OS) and progression-free survival (PFS) of chemotherapy are unsatisfied with metastatic NSCLC.

Recently, immune checkpoint inhibitors (ICIs) treatment that block the programmed cell death 1 ligand 1 (PD-L1) and programmed cell death 1 (PD-1) pathway has become to replace chemotherapy as the first-line regimen (3-5). The recent phase 3 KEYNOTE-189 and KEYNOTE-407 trials showed pembrolizumab plus chemotherapy provided longer OS and PFS in comparison with chemotherapy in patients metastatic NSCLC (6-8). Although the survival benefit associated with the pembrolizumab combination was observed in all subgroups of PD-L1 tumor proportion scores (TPS), the higher relative benefit was observed in the subgroup with a PD-L1 TPS of 1% to 49% and ≥50% than TPS of 1%. This finding was coherent with the recent trials that showed the PDL-1-expression category could predict the benefit of ICIs treatment, although patients with PD-L1 negative tumors also benefited from its treatment as compared to chemotherapy (9). However, due to the high cost of implementing pembrolizumab in the first-line setting that limited the widely prescription in clinical practice, the cost-effectiveness of first-line pembrolizumab plus chemotherapy need to be evaluated. Furthermore, despite the promising activity of pembrolizumab plus chemotherapy for metastatic NSCLC irrespective of PD-L1 expression, the following unclear question also needs to be elucidated: will the patient selection based on PD-L1 expression lead to improving the cost-effectiveness of adding pembrolizumab to chemotherapy? Is there a potential cut-point value of PD-L1 expression for pembrolizumab plus chemotherapy that is cost-effective?

For increasing adoption of expensive agents by rationalizing therapy from a clinical standpoint thus making treatment more cost-effective, health policymakers and payers would assess the clinical value of the drug in different subgroups with varying responses to immunotherapy (10). The present evaluation investigates the economic outcomes of first-line pembrolizumab plus chemotherapy treatment with and without patient selection using varied PD-L1 expression status in the US and Chinese context. We present the following article in accordance with the CHEERS Reporting Checklist (available at http://dx.doi.org/10.21037/tlcr-19-605).

Methods

Analytic overview

A mathematical model combining decision tree and Markov approach was established to measure the clinical and economic outcomes of adding pembrolizumab to chemotherapy for previously untreated metastatic nonsquamous and squamous NSCLC without EGFR or ALK mutations, which was similar with the KEYNOTE-189 and KEYNOTE-407 trials, respectively (7,8). For the whole patients with unconfirmed PD-L1 TPS, the decision trees included four competing strategies (*Figure 1A*): chemotherapy for all patients (reference strategy); pembrolizumab plus chemotherapy for all patients without determination of PD-L1 status (universal pembrolizumab strategy); pembrolizumab plus chemotherapy for patients with PD-L1 TPS of ≥50% and chemotherapy for other patients after PD-L1 TPS was determined (TPS50 pembrolizumab strategy), and pembrolizumab plus chemotherapy for patients with PD-L1 TPS of ≥1% and chemotherapy for other patients (TPS1 pembrolizumab strategy). For the three sub-populations with confirmed PD-L1 TPS ≥1%, 1% to 49% and ≥50%, chemotherapy and pembrolizumab plus chemotherapy would be the competing strategies (*Figure 1B*). A three-health-state Markov model was established to reflect the disease course, which included the following health states: progression-free disease (PFD), progressed disease (PD), and death. The Markov cycle length was 21-day in keeping with the treatment schedule reported by KEYNOTE-189 and KEYNOTE-407 trials (7,8), and the time horizon was 20 years as previous studies done (11,12). During each Markov cycle, the model redistributes the hypothetical patients among the three health states according to transition probabilities. The initial state is assumed to be PFD, and death is the absorbing state.

Clinical data inputs

PFS and OS for pembrolizumab plus chemotherapy and

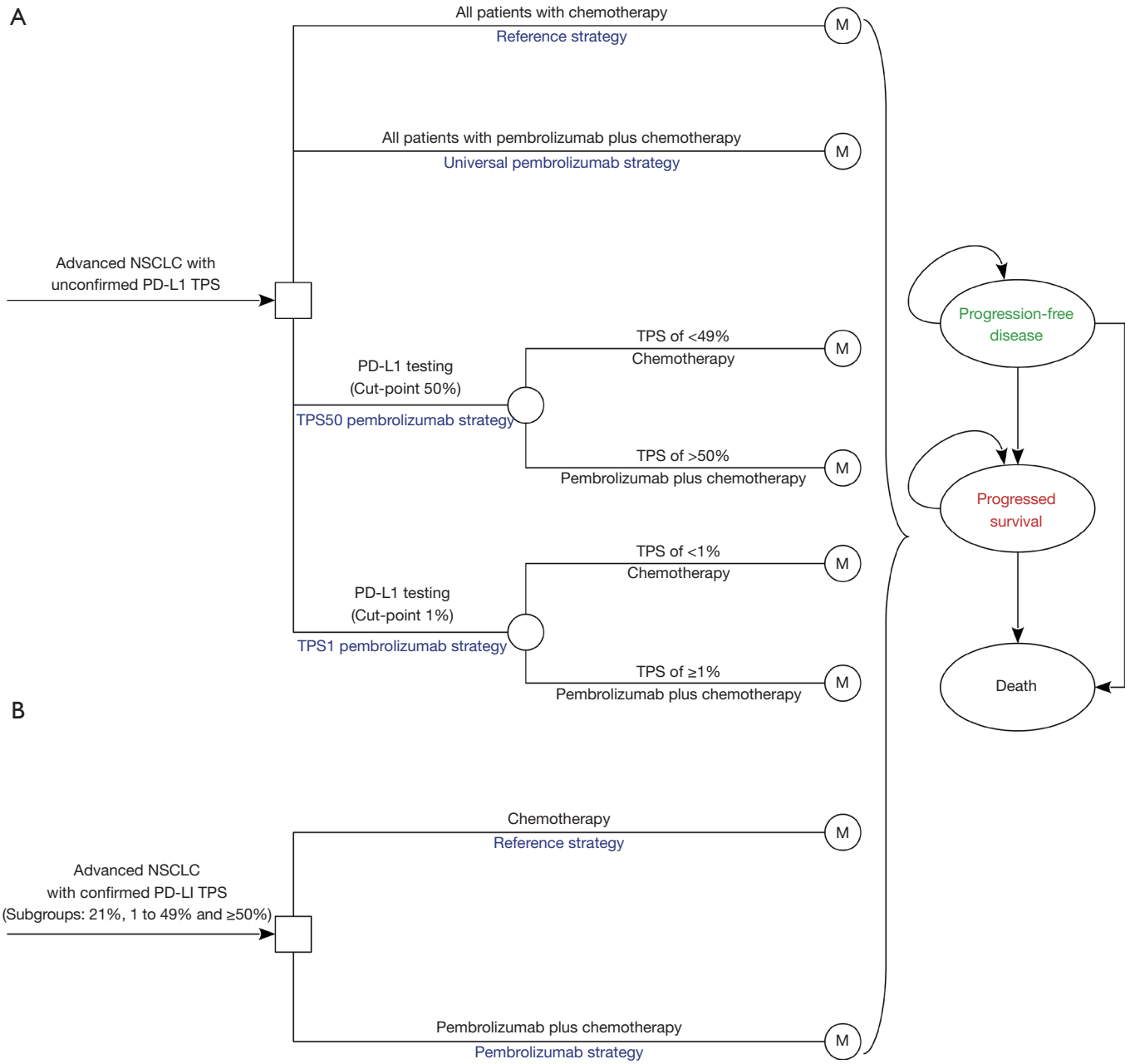

Figure 1 Model structure for previously untreated metastatic nonsquamous and squamous NSCLC without EGFR or ALK mutations. (A) The whole patients with unconfirmed PD-L1 TPS; (B) sub-populations with confirmed PD-L1 TPS ≥1%, 1% to 49% and ≥50%. NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death 1 ligand 1; TPS, tumor proportion score.

chemotherapy in metastatic nonsquamous and squamous NSCLC were informed by the results of KEYNOTE-189 and KEYNOTE-407 trials, respectively (7), which were extrapolated over the model time horizon using standard statistical analyses described by Guyot *et al.* (13). Graph Digitizer (version 2.26; http://getdata-graph-digitizer.com) was used to gather the data points from the PFS and OS curves, and these data points were then used to fit following parametric survival functions: Weibull, log-normal, log-logistic, exponential, generalized gamma, Gompertz and Royston/Parmar spline models (14). Goodness of fit was based on visual inspection and Akaike information criterion

(AIC). The adopted model and AIC value for the whole intention-to-treat population and three subgroups of PD-L1 TPS (TPS of <1%, TPS of 1% to 49% and TPS of ≥50%) were shown in *Table S1*. The modeled virtual patient-level data comprised event and censor times and were equal in number to the initial number at risk, which was closely reproduced the digitized Kaplan-Meier curves. The PFS and OS plots created by using the virtual patient-level data and the predicted curves by using parametric survival models are shown in *Figures S1-S4*.

Due to the shorter follow-up time of KEYNOTE-189 and KEYNOTE-407 trials than the KEYNOTE-042 trial, we pooled the OS data of three trials for exploring the survival rates of chemotherapy to avoid the uncertainty around the long-term survival. Although the histology and chemotherapy regimen of these three trials were discrepant, our approach could be supported by the fact that no notable impact of histologies of advanced NSCLC and carboplatin- versus cisplatin-based chemotherapy on OS (2,15). By using the virtual patient-level data, we also compared the OS of three trials in the chemotherapy arm, and no notable difference was found (*Figure S5*). For the whole population receiving chemotherapy, Royston/Parmar spline model was adopted for extrapolating the pooled OS data, and the log-normal and log-logistic model for the PFS data from KEYNOTE-189 and KEYNOTE-407 trials, respectively. The PFS and OS probabilities of chemotherapy in three subgroups with confirmed PD-L1 TPS <1%, 1% to 49% and ≥50% were calculated by multiplying the PFS and OS rates in the whole population receiving chemotherapy and the HRs of subgroups versus the whole population. The HRs were shown in *Table S2*, which were estimated by using the Cox proportional-hazards model after pooling the virtual patient-level data of the whole population and three subgroups receiving chemotherapy. The PFS and OS data for the whole population and three subgroups in pembrolizumab plus chemotherapy was estimated by multiplying the reported HRs and the PFS and OS rates in chemotherapy arms. The influences of HRs would be checked in sensitivity and subgroup analyses.

On the basis of the fitted PFS and OS model, denoted as P(t) and S(t), we computed the disease progression probability $Prob_{(PFS \rightarrow PD)}$ and cancer-specific mortality $Prob_{(PD \rightarrow Death)}$ at cycle t as: $Prob_{(PFS \rightarrow PD)} = [(P_{(t)} - P_{(t+1)}]/P_{(t)}$ and $Prob_{(PD \rightarrow Death)} = [(S_{(t)} - S_{(t+1)}]/[(S_{(t)} - P_{(t)}]$, respectively. After the disease progressed, the data of patients who received second-line active treatment was collected from the KEYNOTE-189 trial and KEYNOTE-407 trials, respectively (7,8). The key clinic inputs were summarized in *Table 1*.

The model includes risks of all-cause adverse events (AEs) of grade ≥3 reported by the KEYNOTE-189 and KEYNOTE-407 trials (7,8). The impact of less severe or common AEs on model results would be expected to be negligible. The modeled probabilities of these AEs is described in *Table 1*.

Cost and utility inputs

Only direct medical costs were considered and stated in reported in 2018 US dollars, including the drug acquisition costs, costs attributed to the patient's health state, costs for the management of AEs, and costs of end-of-life care (*Table 1*). The costs associated with health care services were inflated to 2018 values according to the US consumer price index (17). In China, the costs were translated into 2018 US dollars ($1 = CNY 6.8).

Based on the KEYNOTE-189 and KEYNOTE-407 trials, pembrolizumab was prescribed at a dose of 200 mg on day 1 for up to 35 cycles with the combination of chemotherapy. The prices of pembrolizumab in the US (average wholesale price) were collected from public databases and the literature (18). In the US, the price of pembrolizumab was discounted at 17% to account for contract pricing (19). For the first 4 cycles, the cost related to cytotoxic chemotherapy for untreated metastatic NSCLC were $24,437 per patient regardless of histology (20). For nonsquamous NSCLC, the cost related to maintenance chemotherapy was $5,887 per cycle (20). After disease progressed, 44.6% in chemotherapy and 30.5% in pembrolizumab plus chemotherapy arm received subsequent active therapy (7). The average 21-day costs of disease management (excluding drug, drug administration, and AE related costs) in the PFD and PD states are stratified by years 1, 2, 3, 4 to 5, and over 5 following first-line treatment initiation. The analysis included the costs related to managing grade ≥3 AEs. The costs related to subsequent therapies taken following discontinuation of initial trial treatments, managing grade ≥3 AEs, disease management and terminal care the last 30 days of life were extracted from literature (11,12), which estimated the health resource utilization based on the KEYNOTE-189 and KEYNOTE-407 trials. In TPS1 and TPS50 pembrolizumab strategy, PD-L1 testing cost was considered (21). The cost estimates in the Chinese setting were showed in *Table S3*.

Table 1 Model parameters: baseline values, ranges, and distributions for sensitivity analysis

Parameters	Nonsquamous non-small-cell lung cancer	Squamous non-small-cell lung cancer
Clinical inputs* (7,8,16)		
Survival model of chemotherapy		
Model for PFS	Log-normal, meanlog: 1.9509 (se: 0.0681), sdlog: 0.9444 (se: 0.0537)	Log-logistic, shape: 1.872 (se: 0.112), scale: 7.053 (se: 0.402)
Royston/Parmar spline model for OS (nonsquamous and squamous)	Gamma0: −4.1030 (se: 0.1603), gamma1: 1.0462 (se: 0.1886), gamma2: −0.2579 (se: 0.0632), gamma3: 0.3653 (se: 0.0818)	
HR of PFS of between pembrolizumab plus chemotherapy and chemotherapy	0.48 [range: 0.4–0.58, dist: lognormal (log-mean =−0.734, log-sd =3.081)]	0.56 [range: 0.45–0.7, dist: lognormal (log-mean =−0.58, log-sd =2.752)]
HR of OS of between pembrolizumab plus chemotherapy and chemotherapy	0.56 [range: 0.45–0.7, dist: lognormal (log-mean =−0.58, log-sd =2.752)]	0.64 [range: 0.49–0.85, dist: lognormal (log-mean =−0.446, log-sd =2.388)]
Probability of AEs		
Grade ≥3 AEs in chemotherapy treatment	0.658 [range: 0.494–0.823, dist: beta (α =5.5, β =2.8)]	0.682 [range: 0.512–0.853, dist: beta (α =5.1, β =2.4)]
Grade ≥3 AEs in pembrolizumab plus chemotherapy treatment	0.672 [range: 0.504–0.84, dist: beta (α =5.2, β =2.6)]	0.698 [range: 0.524–0.873, dist: beta (α =4.8, β =2.1)]
Utility inputs (time to death in days) (11,12)		
≥360	0.834 [range: 0.823–0.846, dist: beta (α =3,354, β =667.6)]	0.842 [range: 0.823–0.861, dist: beta (α =1,192, β =223.7)]
[180,360)	0.765 [range: 0.743–0.786, dist: beta (α =1,142.9, β =351.1)]	0.814 [range: 0.795–0.833, dist: beta (α =1,311.5, β =299.7)]
[30,180)	0.709 [range: 0.69–0.728, dist: beta (α =1,556.6, β =638.9)]	0.737 [range: 0.717–0.756, dist: beta (α =1,443.2, β =515)]
<30	0.563 [range: 0.461–0.665, dist: beta (α =51.1, β =39.7)]	0.568 [range: 0.481–0.655, dist: beta (α =70.7, β =53.8)]
Cost inputs (11,12)		
Pembrolizumab 200 mg	9,162 [range: 4,581–9,162, dist: fixed)	
Platinum-doublet chemotherapy per patient/ four 21-days cycles	24,437 [range: 18328–30547, dist: gamma (α =190,916, λ =0.128)]	
Maintenance chemotherapy with pemetrexed per cycle	5,887 [range: 4,415–7,359, dist: gamma (α =45,994, λ =0.128)]	–
Post-discontinuation treatment in pembrolizumab treatment	13,097 [range: 9,823–16,371, dist: gamma (α =52,388, λ =0.25)]	1,195 [range: 896–1,494, dist: gamma (α =4,780, λ =0.25)]
Post-discontinuation treatment in chemotherapy treatment	41,161 [range: 30,871–51,451, dist: gamma (α =164,644, λ =0.25)]	15,763 [range: 11,822–19,704, dist: gamma (α =63,052, λ =0.25)]
Disease management in PFD state per 21-days in 1st year	3,773 [range: 2,829–4,716, dist: gamma (α =15,090, λ =0.25)]	3,938 [range: 2,953–4,922, dist: gamma (α =15,752, λ =0.25)]
Disease management in PFD state per 21-days in 2nd year	1,736 [range: 1,302–2,170, dist: gamma (α =6,945, λ =0.25)]	2,088 [range: 1,566–2,611, dist: gamma (α =8,354, λ =0.25)]
Disease management in PFD state per 21-days in 3rd year	1,464 [range: 1,098–1,830, dist: gamma (α =5,855, λ =0.25)]	922 [range: 691–1,152, dist: gamma (α =3,687, λ =0.25)]

Table 1 (*continued*)

Table 1 (*continued*)

Parameters	Nonsquamous non-small-cell lung cancer	Squamous non-small-cell lung cancer
Disease management in PFD state per 21-days in 4th to 5th year	1,188 [range: 891–1,485, dist: gamma (α =4,753, λ =0.25)]	766 [range: 574–957, dist: gamma (α =3,074, λ =0.249)]
Disease management in PFD state per 21-days in over 5th year	441 [range: 331–551, dist: gamma (α =1,771, λ =0.249)]	337 [range: 253–421, dist: gamma (α =1,353, λ =0.249)]
Disease management in PD state per 21-days in 1st year	3,785 [range: 2,839–4,731, dist: gamma (α =15,139, λ =0.25)]	4,345 [range: 3,259–5,432, dist: gamma (α =17,381, λ =0.25)]
Disease management in PD state per 21-days in 2nd year	2,967 [range: 2,225–3,709, dist: gamma (α =11,869, λ =0.25)]	3,044 [range: 2,283–3,805, dist: gamma (α =12,175, λ =0.25)]
Disease management in PD state per 21-days in 3rd year	2,621 [range: 1,966–3,277, dist: gamma (α =10,485, λ =0.25)]	2,575 [range: 1,931–3,219, dist: gamma (α =10,301, λ =0.25)]
Disease management in PD state per 21-days in 4th to 5th year	2,462 [range: 1,846–3,077, dist: gamma (α =9,848, λ =0.25)]	2,453 [range: 1,840–3,066, dist: gamma (α =9,811, λ =0.25)]
Disease management in PD state per 21-days in over 5th year	2,456 [range: 1,842–3,070, dist: gamma (α =9,824, λ =0.25)]	2,453 [range: 1,840–3,066, dist: gamma (α =9,811, λ =0.25)]
Managing ADR (grade ≥3) per patient related to ICI treatment	2,020 [range: 1,515–2,525, dist: gamma (α =8,080, λ =0.25)]	1,499 [range: 1,124–1,874, dist: gamma (α =5,996, λ =0.25)]
Managing ADR (grade ≥3) per patient related to chemotherapy	1,573 [range: 1,180–1,966, dist: gamma (α =6,292, λ =0.25)]	1,259 [range: 944–1,574, dist: gamma (α =5,036, λ =0.25)]
Terminal care (last 30 days of life)	14,633 [range: 10,975–18,291, dist: gamma (α =58,532, λ =0.25)]	15,498 [range: 11,624–19,373, dist: gamma (α =61,992, λ =0.25)]
PD-L1 testing	111 [range: 83–138, dist: gamma (α =437, λ =0.253)]	111 [range: 83–138, dist: gamma (α =437, λ =0.253)]

*, the clinical inputs were based on the whole patients with unconfirmed PD-L1 TPS. AE, adverse event; HR, hazard ratio; PFS, progression-free survival; PFD, progression-free disease; PD, progressed disease; OS, overall survival.

As previous studies have done (11,12), a time-to-death approach, reflecting the decline in cancer patients' quality-of-life, is used for modeling utilities. The utility scores of the ≥360, 180 to <360, 30 to <180 and <30 day time-to-death in metastatic nonsquamous and squamous NSCLC were derived from published reports, which collected utility data by using EuroQOL-5D-3-level instrument in patients of the KEYNOTE-189 and KEYNOTE-407 trials (*Table 1*).

Analysis

In the base-case analysis, incremental cost-effectiveness ratio (ICER) was calculated as incremental cost per additional quality-adjusted life-year (QALY) gained between pembrolizumab plus chemotherapy and chemotherapy. Cost and QALYs were discounted at an annual rate of 3% in the US and 5% in the Chinese context, respectively (22). We also estimated the incremental net-health benefit (INHB) based on the following formula: $INHB(\lambda) = (\mu_{E1} - \mu_{E0}) - (\mu_{C1} - \mu_{C0})/\lambda = \Delta E - \Delta C/\lambda$, where μ_{Ci} and μ_{Ei} were the cost and effectiveness of pembrolizumab plus chemotherapy and chemotherapy (i=1) or chemotherapy and chemotherapy (i=0), respectively, and λ was the willingness-to-pay threshold of $150,000/QALY in the US (23,24) and $29,196/QALY (three times of per capita gross domestic product of China in 2018) in China. Subgroup analyses were performed in the prespecified subgroup as reported in the KEYNOTE-189 and KEYNOTE-407 trials by varying the HRs of OS between universal pembrolizumab and chemotherapy strategy in the whole patients with unconfirmed PD-L1 TPS, respectively (7,8). The Markov model and statistical analyses were implemented in R software (http://www.r-project.org). The data used in this analysis is anonymous and therefore no informed consent was needed.

To evaluate the robustness of the base-case result, one-

way and probabilistic sensitivity analyses (PSA) were conducted. One-way sensitivity analyses were conducted for all parameters, and the estimated range of each parameter was either based on the reported or estimated 95% confidence intervals in the referenced studies or determined by assuming a 25% change from the base-case value (*Table 1*). In the PSA, a Monte Carlo simulation of 1,000 iterations was generated by simultaneously sampling the key model parameters from the pre-specified distributions. Gamma distribution was selected for the cost parameters, log-normal distribution for hazard ratios, and beta distribution for probability, proportion and preference value parameters. Based on the data from 1,000 iterations, a cost-effectiveness acceptability curve (CEAC) was created to represent the likelihood that pembrolizumab plus chemotherapy would be considered cost-effective at various willingness-to-pay levels for health gains (QALYs).

Results

Base-case analysis and subgroup analyses

For metastatic nonsquamous NSCLC in the US context, universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategy provided an additional 1.168, 0.388 and 0.777 QALYs with an incremental cost of $142,773, $55,594 and $99,219 comparing with chemotherapy in the whole patients with unconfirmed PD-L1 TPS, which resulted in the ICER of $122,248, $143,282 and $127,661/QALY, respectively. The INHBs of universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategy over chemotherapy were 0.216, 0.017 and 0.116 QALYs at the threshold of $150,000/QALY, respectively (*Table 2*). The subgroup analysis by varying the HRs of OS found that universal pembrolizumab showed the trend of gaining health benefits in most of the subgroups except the male patients (*Figure 2*). The INHBs in the subgroups with the respect to the health benefit varied from –0.07 (range, –0.47 to 0.48, probabilities of cost-effectiveness: 25.7%) in male patients to 2.21 (range, 0.34 to 4.05, probabilities of cost-effectiveness: 100%) in never-smoking patients. In three subgroups with confirmed PD-L1 TPS <1%, 1% to 49% and ≥50%, the ICERs of pembrolizumab over chemotherapy strategy were $111,763, $112,088 and $142,997/QALY, respectively.

For metastatic squamous NSCLC in the US context, universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategy provided an additional 0.988, 0.272 and 0.667 QALYs with an incremental cost of $84,934, $1,175 and $46,045 comparing with chemotherapy in the whole patients with unconfirmed PD-L1 TPS, which resulted in the ICER of $121,375, $131,495 and $121,554/QALY, respectively. The INHBs of universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategy over chemotherapy were 0.195, 0.038 and 0.133 QALYs at the threshold of $150,000/QALY, respectively (*Table 2*). The subgroup analysis by varying the HRs of OS found that universal pembrolizumab showed the trend of gaining health benefits in most of the subgroups except the male patients (*Figure 2*). The INHBs in the subgroups with the respect to the health benefit varied from –0.12 (range, –0.47 to 0.50, probabilities of cost-effectiveness: 26.8%) in those age ≥65 years old to 0.88 (range, –0.23 to 2.4, probabilities of cost-effectiveness: 92.1%) in female patients. In three subgroups with confirmed PD-L1 TPS <1%, 1% to 49% and ≥50%, the ICERs of pembrolizumab over chemotherapy strategy were $121,326, $113,780 and $131,136/QALY, respectively.

For metastatic nonsquamous and squamous NSCLC in the Chinese context, the ICER of universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategies were all higher than $40,000/QALY in comparison with chemotherapy (*Table S4*).

Sensitivity analyses

The one-way sensitivity analyses revealed that the HR of OS between universal pembrolizumab and chemotherapy strategy played a vital role in model outcomes regardless of histology in the US context (*Figure 3*). When its upper boundaries were adopted, the ICERs would exceed the threshold of $150,000/QALY. Other parameters, such as the cost of post-discontinuation treatment and related disease management and utility values, had a medium or small impact on the outcome. In general, the model results were robust to the adjustment of parameters.

For metastatic nonsquamous NSCLC in the US context, the CEAC showed nearly 86%, 54% and 75% probabilities of universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategy being a cost-effective strategy compared with chemotherapy at the threshold of $150,000/QALY in the whole patients with unconfirmed PD-L1 TPS (*Figure 4A*), and 88%, 82% and 55% probabilities of pembrolizumab being a cost-effective strategy compared with chemotherapy in three subgroups

Table 2 Summary of cost ($) and outcome results in base-case analysis

Strategy	Cost	Progression-free LYs	Overall LYs	QALYs	Incremental cost per QALY*	INHB*
Nonsquamous non-small-cell lung cancer						
Whole patients with unconfirmed PD-L1 TPS						
Chemotherapy (reference strategy)	198,863	0.469	1.896	1.398	NA	NA
Universal pembrolizumab strategy	341,637	1.145	3.555	2.566	122,248	0.216
TPS50 pembrolizumab strategy	254,458	0.727	2.452	1.786	143,282	0.017
TPS1 pembrolizumab strategy	298,082	1.033	3.010	2.175	127,661	0.116
Subgroup with confirmed PD-L1 TPS of <1%						
Chemotherapy (reference strategy)	178,010	0.458	1.443	1.065	NA	NA
Pembrolizumab strategy	310,704	0.798	3.097	2.253	111,763	0.303
Subgroup with confirmed PD-L1 TPS of 1% to 49%						
Chemotherapy (reference strategy)	208,990	0.545	2.094	1.544	NA	NA
Pembrolizumab strategy	346,523	1.510	3.855	2.771	112,088	0.310
Subgroup with confirmed PD-L1 TPS of ≥50%						
Chemotherapy (reference strategy)	209,181	0.412	2.140	1.577	NA	NA
Pembrolizumab strategy	366,030	1.140	3.712	2.674	142,997	0.051
Squamous non-small-cell lung cancer						
Whole patients with unconfirmed PD-L1 TPS						
Chemotherapy (reference strategy)	159,481	0.496	1.796	1.362	NA	0
Universal pembrolizumab strategy	283,797	1.155	3.219	2.386	121,375	0.195
TPS50 pembrolizumab strategy	200,038	0.991	2.221	1.67	131,495	0.038
TPS1 pembrolizumab strategy	244,908	1.046	2.775	2.065	121,554	0.133
Subgroup with confirmed PD-L1 TPS of <1%						
Chemotherapy (reference strategy)	158,528	0.44	1.713	1.301	NA	NA
Pembrolizumab strategy	277,045	0.769	3.063	2.278	121,326	0.187
Subgroup with confirmed PD-L1 TPS of 1% to 49%						
Chemotherapy (reference strategy)	168,469	0.388	1.888	1.432	NA	NA
Pembrolizumab strategy	309,930	0.56	3.634	2.675	113,780	0.300
Subgroup with confirmed PD-L1 TPS of ≥50%						
Chemotherapy (reference strategy)	152,308	0.646	1.791	1.356	NA	NA
Pembrolizumab strategy	266,646	2.046	2.992	2.228	131,136	0.110

*, comparing with reference strategy. QALY, quality-adjusted-life year; PD-L1, programmed cell death 1 ligand 1; TPS, tumor proportion score.

with confirmed PD-L1 TPS <1%, 1% to 49% and ≥50% (*Figure 4B*).

For metastatic squamous NSCLC in the US context, the CEAC showed nearly 83%, 60% and 77% probabilities of universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategy being a cost-effective

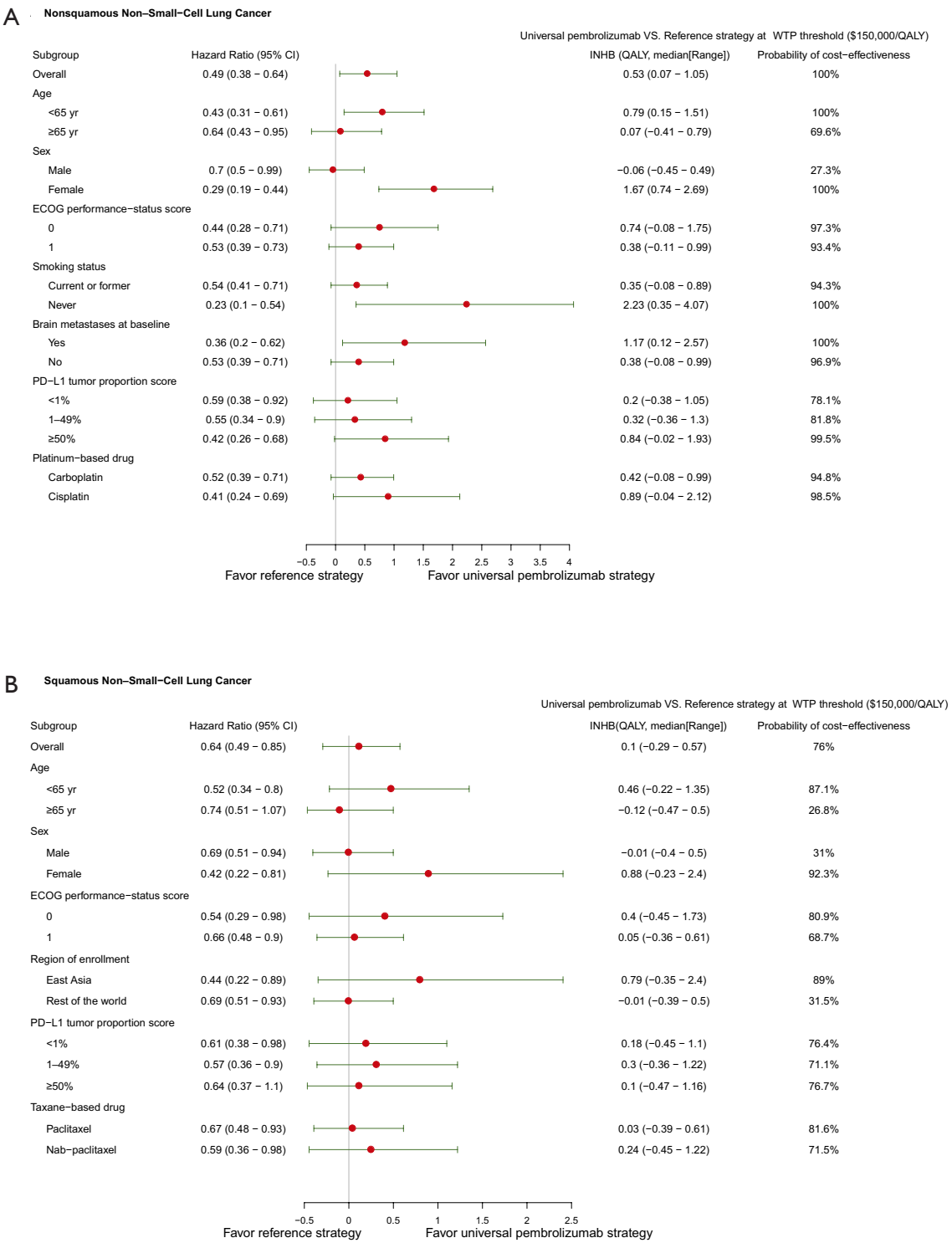

Figure 2 Subgroup analysis of incremental net health benefits (INHB) and probabilities of cost-effectiveness of universal pembrolizumab strategy versus reference strategy by varying the hazard ratios (HRs) of OS in whole patients with unconfirmed PD-L1 TPS metastatic nonsquamous NSCLC (A) and squamous NSCLC (B). The vertical line indicates the point of no effect (INHB =0), the red circle indicates the median INHB, and the green bar indicates the ranges of INHB adjusted by the HRs. OS, overall survival; PD-L1, programmed cell death 1 ligand 1; TPS, tumor proportion score; NSCLC, non-small-cell lung cancer.

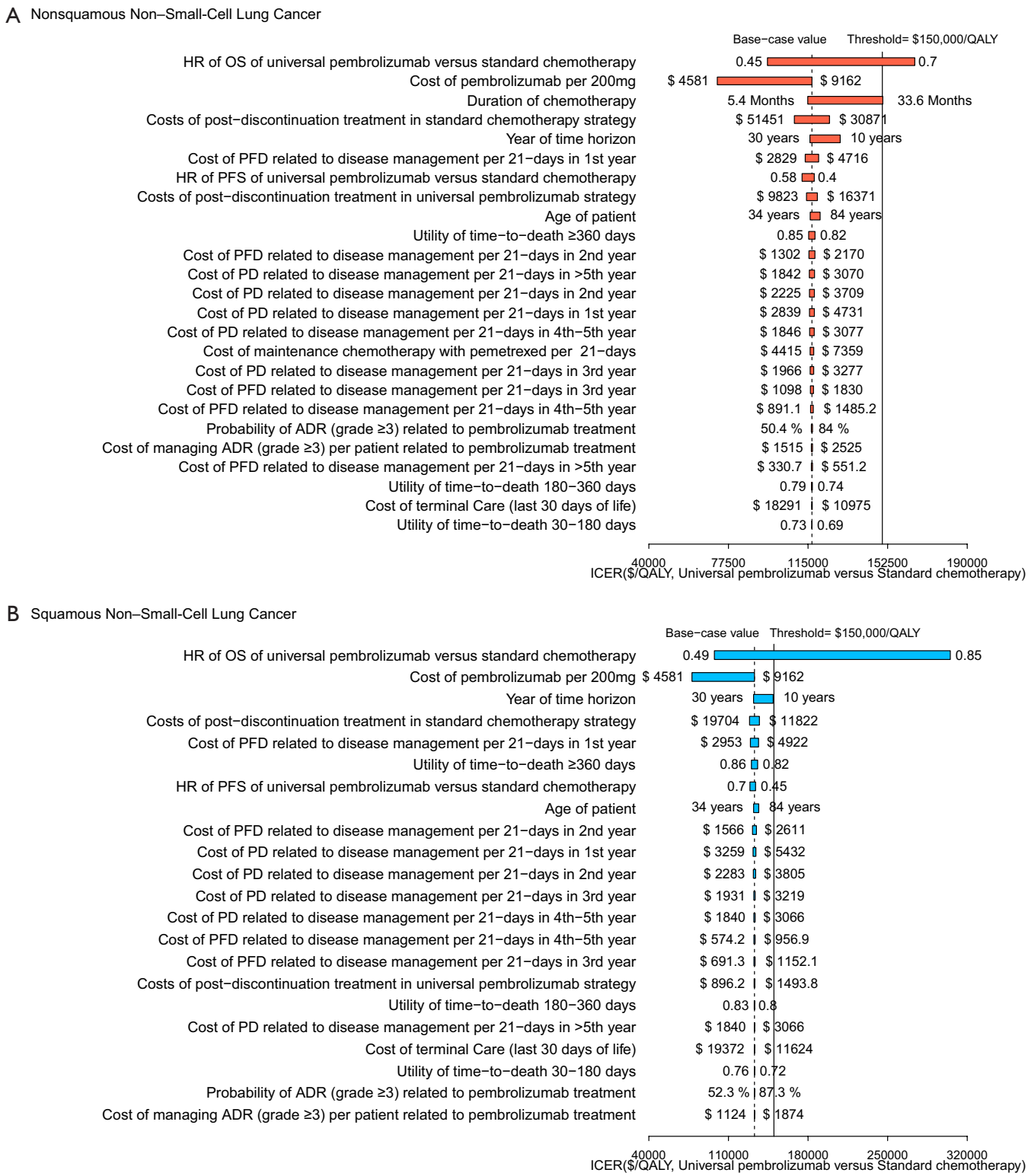

Figure 3 Tornado diagram of one-way sensitivity analyses of universal pembrolizumab versus chemotherapy (reference strategy) in the whole patients with unconfirmed PD-L1 TPS metastatic nonsquamous NSCLC (A) and squamous NSCLC (B). PD-L1, programmed cell death 1 ligand 1; TPS, tumor proportion score; NSCLC, non-small-cell lung cancer.

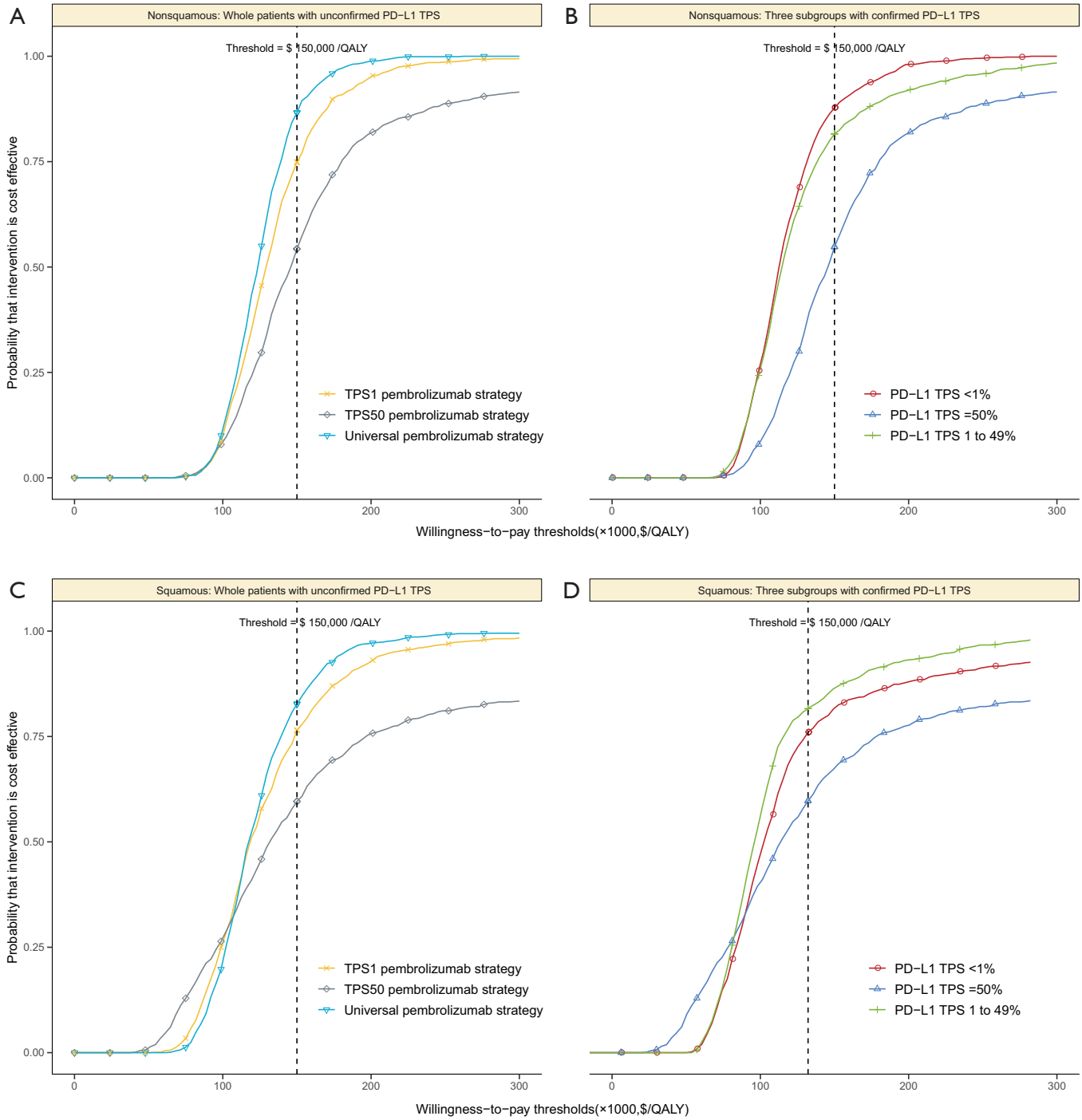

Figure 4 Cost-effectiveness acceptability curves of universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategy versus chemotherapy (reference strategy) for metastatic nonsquamous and squamous NSCLC in the whole patients with unconfirmed PD-L1 TPS (A and C), and pembrolizumab strategy versus chemotherapy (reference strategy) in three subgroups with confirmed PD-L1 TPS <1%, 1% to 49% and ≥50% (B and D). PD-L1, programmed cell death 1 ligand 1; TPS, tumor proportion score; NSCLC, non-small-cell lung cancer.

strategy compared with chemotherapy at the threshold of $150,000/QALY in the whole patients with unconfirmed PD-L1 TPS (*Figure 4C*), and 76%, 82% and 60% probabilities of pembrolizumab being a cost-effective strategy compared with chemotherapy in three subgroups with confirmed PD-L1 TPS <1%, 1% to 49% and ≥50% (*Figure 4D*).

For metastatic nonsquamous and squamous NSCLC in the Chinese context, the CEAC showed lower than 10% probabilities of universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategy being a cost-effective strategy compared with chemotherapy at the threshold of $29,196/QALY in the whole patients with unconfirmed PD-L1 TPS and three subgroups with confirmed PD-L1 TPS <1%, 1% to 49% and ≥50%.

Discussion

To our knowledge, this is the first analysis to address the unmet need for an economic assessment of PD-L1 categories-directed pembrolizumab treatment in the first-line setting. When treatment was guided according to the PD-L1 TPS after PD-L1 expression status was tested, adding pembrolizumab for only those with PD-L1 TPS ≥1% and ≥50% did not show the improvement of cost-effectiveness in comparison with routinely adding pembrolizumab treatment for all patients. Although the ICERs of universal pembrolizumab, TPS50 pembrolizumab and TPS1 pembrolizumab strategy versus chemotherapy were comparable, the universal pembrolizumab strategy gained the greatest incremental QALYs and INHB. The sensitivity analysis confirmed that these results are generally robust. These findings suggest that routinely adding pembrolizumab to chemotherapy without PD-L1 testing is a favorable option for previously untreated metastatic nonsquamous and squamous NSCLC without EGFR or ALK mutations. This finding could be supported by the results in the subgroups prespecified by the KEYNOTE-189 and KEYNOTE-407 trials (7,8), which showed the addition of pembrolizumab treatment are cost-effective in these subgroups. However, in the developing setting, adding pembrolizumab to chemotherapy is not a cost-effective option because its ICERs of pembrolizumab plus chemotherapy against chemotherapy were higher than $100,000/QALY regardless of the histology and TPS subgroups, which highly exceed the willingness-to-pay threshold of $29,196/QALY in the Chinese context.

Our finding was consistent with two recent economic analyses, which found that pembrolizumab plus chemotherapy generated an ICER of $104,823/QALY and $86,293/QALY comparing with chemotherapy strategy in the overall non-squamous and squamous NSCLC population from a US healthcare payer perspective, respectively (11,12). However, adding pembrolizumab to chemotherapy for non-squamous NSCLC with PD-L1 <1% is exceeding $150,000 per QALY, which is distinguished with our results. A possible explanation for this variation could be that the incremental health outcomes in Insinga's evaluation were lower than ours due to the different method of tracking the survival probabilities among three subgroups, where the same estimation in Insinga's evaluation was applied for three subgroups and the full trial population (12). As shown by the results of KEYNOTE-189 trial, health outcomes in PD-L1 ≥50% subgroup receiving chemotherapy is superior to the PD-L1 <1% subgroup. However, Insinga's evaluation showed the PD-L1 <1% subgroup had the longer life-years and QALYs than the PD-L1 ≥50% subgroup (12), which in turn had an underestimation effect of pembrolizumab plus chemotherapy on the incremental health outcomes in PD-L1 <1% subgroup. By using the estimated HRs of PFS and OS between three subgroups and the whole patients, our analysis captured the distinguishable health outcomes among three subgroups.

One recent economic evaluation found that the use of PD-L1 expression as a biomarker increases the cost-effectiveness of immunotherapy for second-line treatment of metastatic/metastatic NSCLC from a US healthcare payer perspective (10), which is coherent with our finding in the squamous NSCLC. However, it is discordant with the nonsquamous NSCLC that adding pembrolizumab for all patients without PD-L1 testing was more cost-effective than the PDL1-directed pembrolizumab treatment, which might be explained by the fact that the PD-L1 <1% subgroup in nonsquamous NSCLC had the more favorable economic outcomes than those with PD-L1 TPS ≥50%. The potential reason is that the lower incremental cost and higher incremental health outcomes of pembrolizumab versus chemotherapy strategy in PD-L1 <1% subgroup than those with PD-L1 TPS ≥50%, which was yielded by the relatively higher HR of PFS and lower OS of pembrolizumab versus chemotherapy strategy in PD-L1 <1% subgroup (6). The higher HR of PFS led to the shorter duration and lower cost of pembrolizumab treatment.

The nature of pembrolizumab plus chemotherapy to prolong the OS was a major driver of economic outcomes.

The results of one-way sensitivity analysis revealed that the HR of OS is a substantial model input, which suggested that the addition of pembrolizumab would become more cost-effective in patients with more favorable HR of OS, such as the female patients and age <65 years old. However, in some patients with more unfavorable HR of OS who have a high risk of death, such as those aged ≥65 years, the addition of pembrolizumab might be less cost-effective. The cost of pembrolizumab was also found to be a considerable influential factor. When the cost of pembrolizumab decreased by 50%, the ICER for the addition of pembrolizumab decreased to be close to $50,000/QALY. Recently, the US government has proposed indexing the prices that Medicare pays for drugs to those paid by health systems in other developed countries, to help bring down the relatively high prices paid by US patients (25). Once it is enacted or implemented, the initiative might lead to a reduction in the price of pembrolizumab and achieving a more favorable economic outcome.

There are several weaknesses with the analysis. Firstly, due to the lack of head-to-head data, the discrepancy of trial design and different techniques of biomarker testing, we did not include other ICIs regimens, such as nivolumab plus ipilimumab and atezolizumab plus chemotherapy, which have also shown favorable health benefits in the first-line setting for metastatic NSCLC (26,27). Secondly, health benefits beyond the observation time of the KEYNOTE-189 and KEYNOTE-407 trials were assumed through the fitting of parametric distributions to the reported PFS and OS data, which might result in uncertainty in the model outputs although the predicted and observed data were validated. Thirdly, we did not measure the budget impact of adding pembrolizumab on society, which usually performed in addition to a cost-effectiveness analysis for estimating the financial consequences of adopting a new intervention (28). For example, because about annually 64,901 new NSCLC patients would be eligible for 17.9 first-line treatment cycles of pembrolizumab (29), wide first-line prescription of pembrolizumab might intensively raise the financial burden. However, because the findings of this evaluation reflected the general clinical conditions of managing metastatic NSCLC, it might be a valuable reference for physicians and policy-makers.

These estimates demonstrated that adding pembrolizumab to chemotherapy as a first-line strategy was the cost-effective option in the US, and could be directly administered for treating metastatic nonsquamous and squamous NSCLC harboring no EGFR or ALK mutations and without PD-L1 expression information. However, pembrolizumab plus chemotherapy is not a cost-effective option in the Chinese context. Reducing the price of pembrolizumab could improve the economic outcomes. These findings might contribute to aiding clinicians in making the optimal decision for the treatment of metastatic NSCLC.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/tlcr-19-605

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-19-605). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was based on a literature review and modeling techniques; this study did not require approval by an institutional research ethics board.

References

1. Anonymous. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries

and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1859-922.
2. Griesinger F, Korol EE, Kayaniyil S, et al. Efficacy and safety of first-line carboplatin-versus cisplatin-based chemotherapy for non-small cell lung cancer: A meta-analysis. Lung Cancer 2019;135:196-204.
3. Zhou Y, Chen C, Zhang X, et al. Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: a systematic review and meta-analysis. J Immunother Cancer 2018;6:155.
4. Gubens MA, Davies M. NCCN Guidelines Updates: New Immunotherapy Strategies for Improving Outcomes in Non-Small Cell Lung Cancer. J Natl Compr Canc Netw 2019;17:574-8.
5. Peters S, Reck M, Smit EF, et al. How to make the best use of immunotherapy as first-line treatment of advanced/metastatic non-small-cell lung cancer. Ann Oncol 2019;30:884-96.
6. Gadgeel SM, Garassino MC, Esteban E, et al. KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. J Clin Oncol 2019;37:9013.
7. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. New Engl J Med 2018;378:2078-92.
8. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
9. Vecchiarelli S, Passiglia F, D'Incecco A, et al. Circulating programmed death ligand-1 (cPD-L1) in non-small-cell lung cancer (NSCLC). Oncotarget 2018;9:17554-63.
10. Aguiar PN, Perry LA, Penny-Dimri J, et al. The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC. Ann Oncol 2017;28:2256-63.
11. Insinga RP, Vanness DJ, Feliciano JL, et al. Cost-effectiveness of pembrolizumab in combination with chemotherapy versus chemotherapy and pembrolizumab monotherapy in the first-line treatment of squamous non-small-cell lung cancer in the US. Curr Med Res Opin 2019;35:1241-56.
12. Insinga RP, Vanness DJ, Feliciano JL, et al. Cost-effectiveness of pembrolizumab in combination with chemotherapy in the 1st line treatment of non-squamous NSCLC in the US. J Med Econ 2018;21:1191-205.
13. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data:reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.
14. Ouwens MJNM, Mukhopadhyay P, Zhang Y, et al. Estimating Lifetime Benefits Associated with Immuno-Oncology Therapies: Challenges and Approaches for Overall Survival Extrapolations. Pharmacoeconomics 2019;39:1129-38.
15. Treat J, Edelman MJ, Belani CP, et al. A retrospective analysis of outcomes across histological subgroups in a three-arm phase III trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. Lung Cancer 2010;70:340-6.
16. Mok TSK, Wu Y, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819-30.
17. Anonymous. US Department of Labor. Calculators. Available online: https://www.bls.gov/data/inflation_calculator.htm. [Accessed January 5, 2019].
18. Anonymous. RED BOOK Online. Available online: http://www.micromedexsolutions.com. [Accessed 24 March 2019].
19. Hornberger J, Hirsch FR, Li Q, et al. Outcome and economic implications of proteomic test-guided second- or third-line treatment for advanced non-small cell lung cancer: extended analysis of the PROSE trial. Lung Cancer 2015;88:223-30.
20. Yu TM, Morrison C, Gold EJ, et al. Budget Impact of Next-Generation Sequencing for Molecular Assessment of Advanced Non-Small Cell Lung Cancer. Value Health 2018;21:1278-85.
21. Criss SD, Weaver DT, Sheehan DF, et al. Effect of PD-L1 testing on the cost-effectiveness and budget impact of pembrolizumab for advanced urothelial carcinoma of the bladder in the United States. Urol Oncol 2019;37:180.e11-8.
22. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA 2016;316:1093-103.
23. Craig BA, Black MA. Incremental cost-effectiveness ratio and incremental net-health benefit:two sides of the

same coin. Expert Rev Pharmacoecon Outcomes Res 2001;1:37-46.
24. Stinnett AA, Mullahy J. Net health benefits:a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998;18:S68-80.
25. Dyer O. US drug prices should be tied to foreign prices to tackle "global freeloading," says Trump. BMJ 2018;363:k4542.
26. Hellmann MD, Ciuleanu T, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. New Engl J Med 2018;378:2093-104.
27. West H, Mccleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:924-37.
28. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health 2014;17:5-14.
29. Goldstein DA, Gordon N, Davidescu M, et al. A Phamacoeconomic Analysis of Personalized Dosing vs Fixed Dosing of Pembrolizumab in Firstline PD-L1-Positive Non–Small Cell Lung Cancer. JNCI 2017;109.

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Supplementary

Table S1 Survival model parameters fitting to the PFS and OS data from KEYNOTE-189 and KEYNOTE-407 trials

Trials and populations	PFS			OS		
	Model	Parameter	AIC	Model	Parameter	AIC
KEYNOTE-189 trial						
Whole patients with unconfirmed PD-L1 TPS						
Pembrolizumab plus chemotherapy	Gamma	Shape =1.4661; rate =0.0904	1873.05	Mixed cure model with Gompertz	Theta =0.6019; shape =0.0894; rate =0.0346	1241.31
Chemotherapy	Log-normal	Meanlog =1.9509; sdlog =0.9444	1083.14	Mixed cure model with Weibull	Theta =0.4023; shape =1.5979; scale =11.1068	897.70
Subgroup with confirmed PD-L1 TPS of <1%						
Pembrolizumab plus chemotherapy	Log-normal	Meanlog =2.1661; sdlog =0.9333	639.15	Exp	Rate =0.0264	456.18
Chemotherapy	Log-normal	Meanlog =1.956; sdlog =0.8955	351.90	Log-normal	Meanlog =2.749; sdlog =1.2256	291.22
Subgroup with confirmed PD-L1 TPS of 1% to 49%						
Pembrolizumab plus chemotherapy	Log-logistic	Shape =1.6079; scale =13.5793	550.35	Mixed cure model with Weibull	Theta =0.6321; shape =1.4845; scale =13.4376	363.45
Chemotherapy	Log-logistic	Shape =2.1047; scale =8.4391	291.20	Mixed cure model with Gompertz	Theta =0.4666; shape =0.1891; rate =0.0208	241.85
Subgroup with confirmed PD-L1 TPS of ≥50%						
Pembrolizumab plus chemotherapy	Log-normal	Meanlog =2.7938; sdlog =1.3274	573.49	Mixed cure model with Exp	Theta =0.4777; rate =0.0356	343.80
Chemotherapy	Gompertz	Shape =0.0029; rate =0.1024	369.26	Mixed cure model with Weibull	Theta =0.4403; shape =1.6597; scale =10.0783	298.21
KEYNOTE-407 trial						
Whole patients with unconfirmed PD-L1 TPS						
Pembrolizumab plus chemotherapy	Royston/Parmar spline	Gamma0 =-3.9141; gamma1 =0.6845; gamma2 =−0.907; gamma3 =1.2688	1149.42	Royston/Parmar spline	Gamma0 =-5.0944; gamma1 =0.2873; gamma2 =0.0969; gamma3 =−0.228	811.27
Chemotherapy	Log-logistic	Shape =1.8725; scale =7.0535	1294.25	Mixed cure model with Gompertz	Theta =0.3285; shape =0.0871; rate =0.0363	1014.34
Subgroup with confirmed PD-L1 TPS of <1%						
Pembrolizumab plus chemotherapy	Weibull	Shape =1.3007; scale =14.1579	403.01	Gompertz	Shape =0.0577; rate =0.016	279.48
Chemotherapy	Log-logistic	Shape =2.1166; scale =6.6265	508.39	Mixed cure model with Gompertz	Theta =0.3034; shape =0.1604; rate =0.0196	363.49
Subgroup with confirmed PD-L1 TPS of 1% to 49%						
Pembrolizumab plus chemotherapy	Log-logistic	Shape =1.4189; scale =11.4898	425.05	Mixed cure model with Gompertz	Theta =0.0035; shape =0.0634; rate =0.0139	302.59
Chemotherapy	Weibull	Shape =1.6288; scale =9.7936	489.05	Exp	Rate =0.0373	379.33
Subgroup with confirmed PD-L1 TPS of ≥50%						
Pembrolizumab plus chemotherapy	Weibull	Shape =1.5796; scale =14.3775	299.79	Mixed cure model with Exp	Theta =0.0033; rate =0.0263	217.50
Chemotherapy	Weibull	Theta =0.0781; shape =1.5134; scale =6.3663	345.17	Exp	Rate =0.0383	249.26

PFS, progression-free survival; OS, overall survival; AIC, Akaike information criterion; PD-L1, programmed cell death 1 ligand 1; TPS, tumor proportion score.

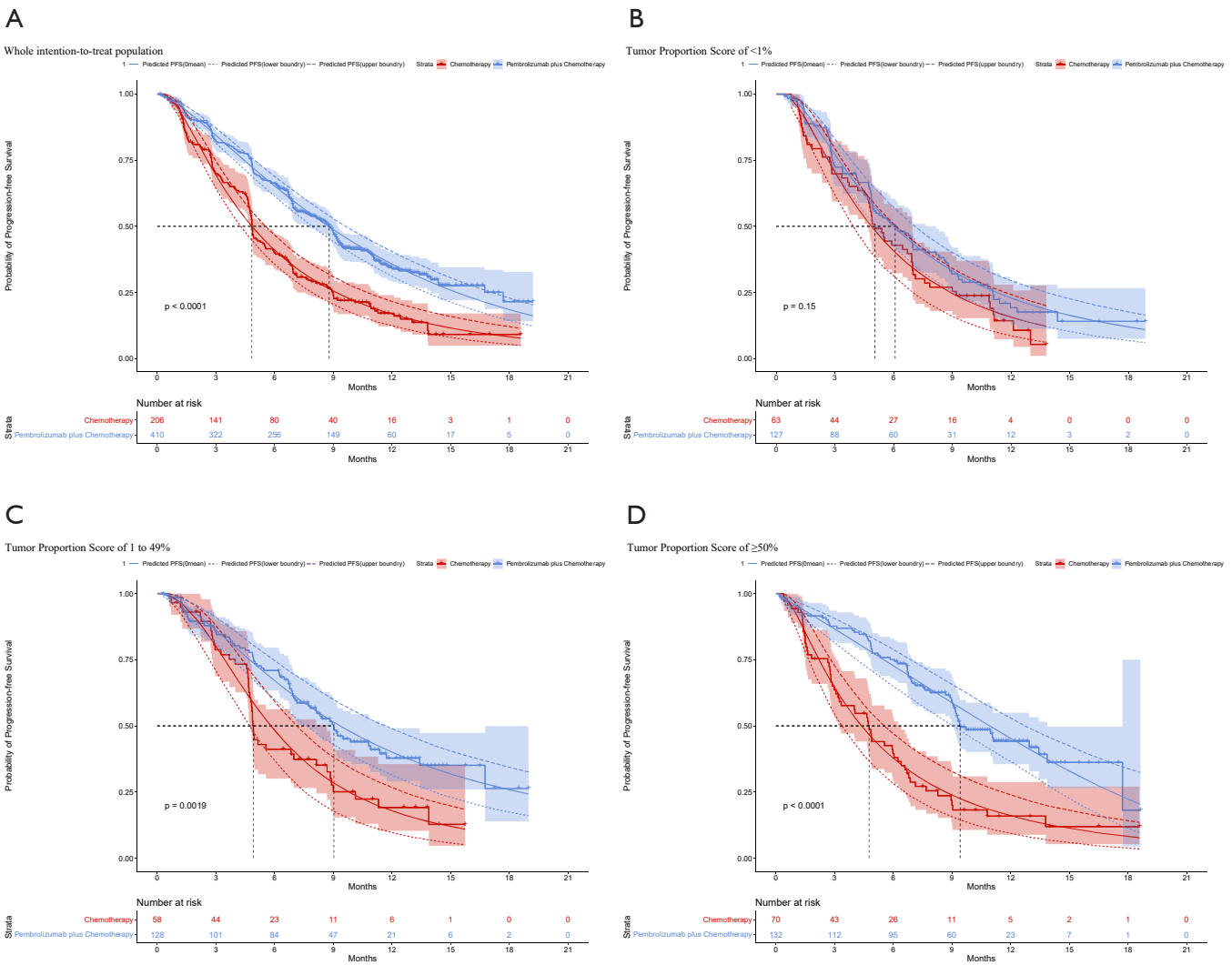

Figure S1 The replicated Kaplan-Meier PFS curves of standard chemotherapy (red) and pembrolizumab plus standard chemotherapy (blue) in KEYNOTE-189 trial. The smooth lines indicated the survival curves predicting their corresponding best survival distributions. The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI. PFS, progression-free survival.

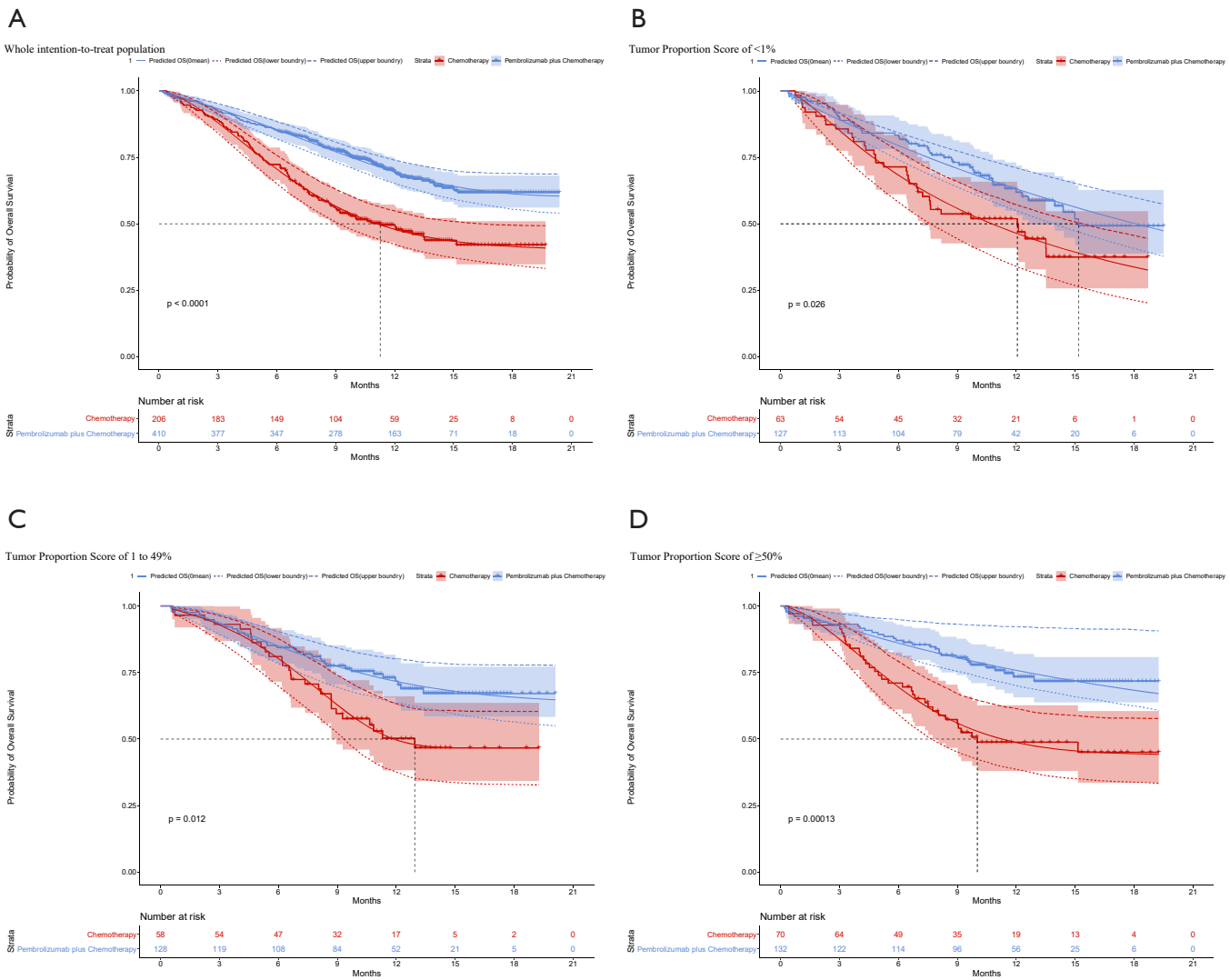

Figure S2 The replicated Kaplan-Meier OS curves of standard chemotherapy (red) and pembrolizumab plus standard chemotherapy (blue) in KEYNOTE-189 trial. The smooth lines indicated the survival curves predicting their corresponding best survival distributions. The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI. OS, overall survival.

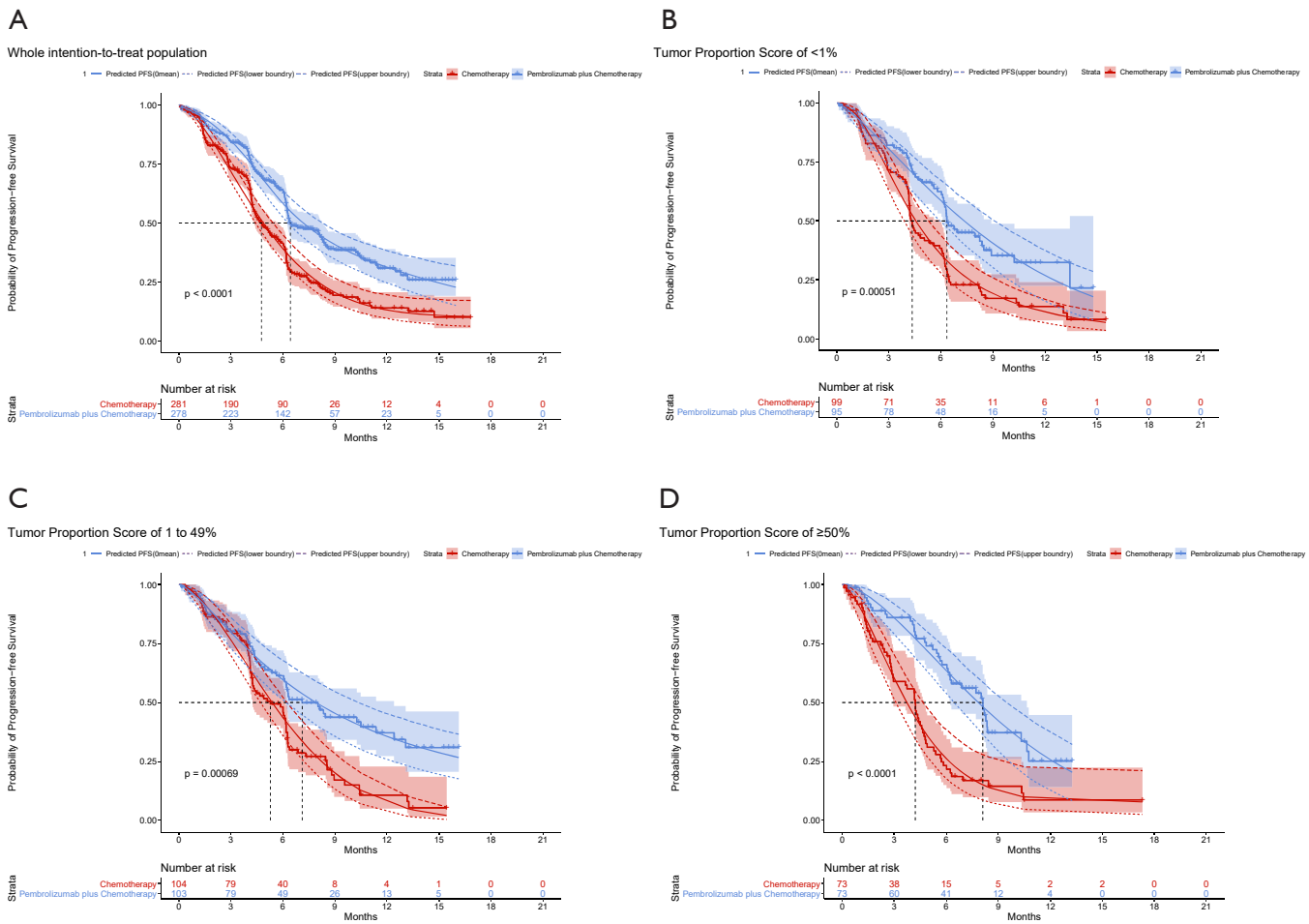

Figure S3 The replicated Kaplan-Meier PFS curves of standard chemotherapy (red) and pembrolizumab plus standard chemotherapy (blue) in KEYNOTE-407 trial. The smooth lines indicated the survival curves predicting their corresponding best survival distributions. The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI. PFS, progression-free survival.

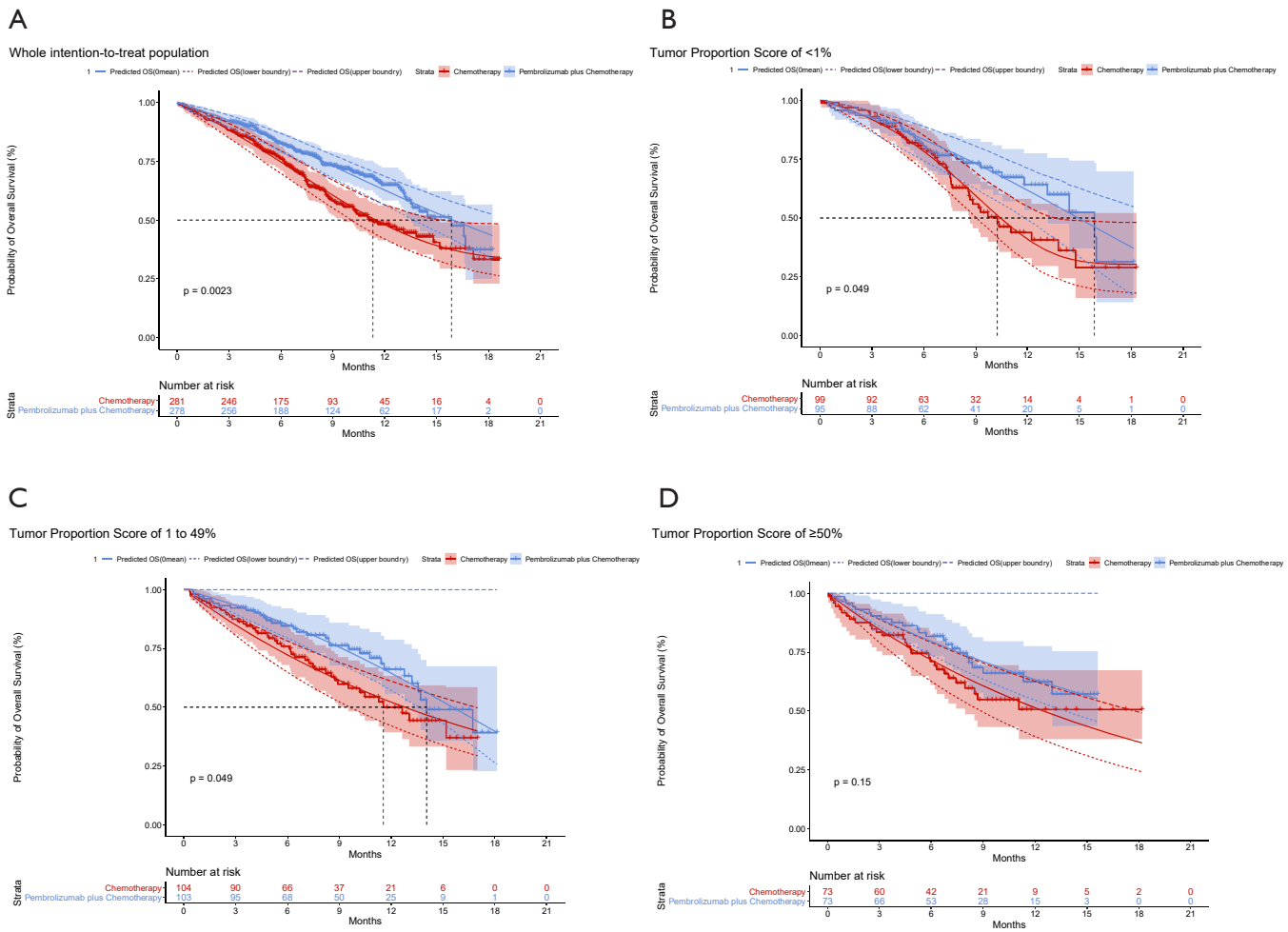

Figure S4 The replicated Kaplan-Meier OS curves of standard chemotherapy (red) and pembrolizumab plus standard chemotherapy (blue) in KEYNOTE-407 trial. The smooth lines indicated the survival curves predicting their corresponding best survival distributions. The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI. OS, overall survival.

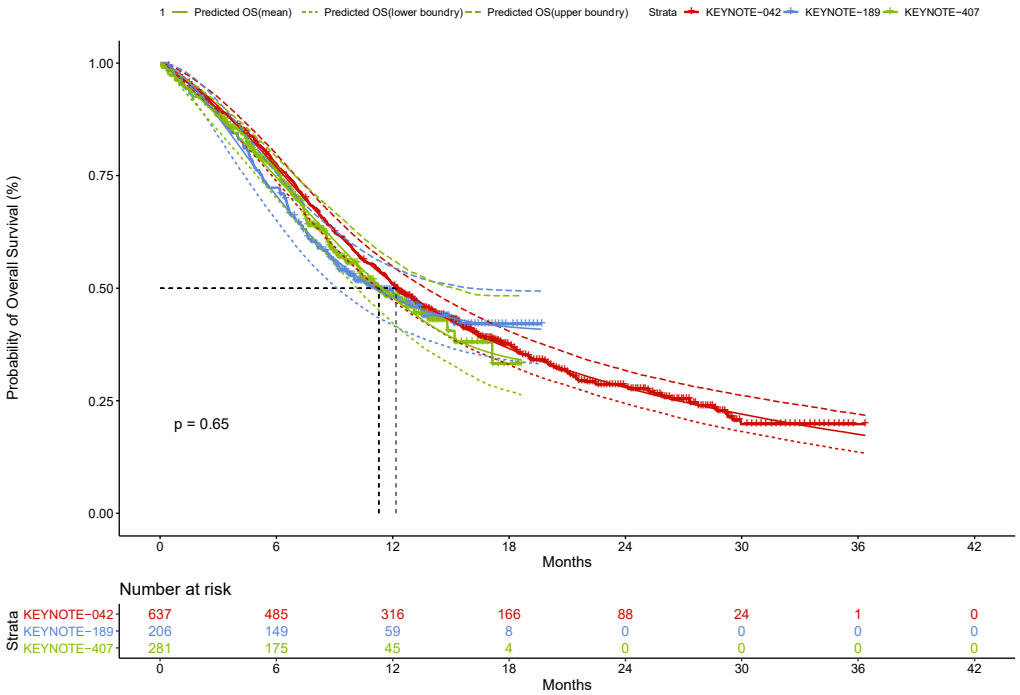

Figure S5 The replicated Kaplan-Meier OS curves of standard chemotherapy in KEYNOTE-042, 189 and 407 trials. The smooth lines indicated the survival curves predicting their corresponding best survival distributions. The smoothly solid, dashed and dotted lines indicated the mean, upper boundary and lower boundary lines of 95% CI. OS, overall survival.

Table S2 Hazard ratios of subgroups with confirmed PD-L1 TPS versus whole patients with unconfirmed PD-L1 TPS in chemotherapy arms

Trials and populations	PFS			OS		
	Expected value	Lower limit of 95% CI	Upper limit of 95% CI	Expected value	Lower limit of 95% CI	Upper limit of 95% CI
KEYNOTE-189 trial						
Subgroup with confirmed PD-L1 TPS of <1%	1.29	1.07	1.56	1.22	0.95	1.57
Subgroup with confirmed PD-L1 TPS of 1% to 49%	0.87	0.71	1.07	0.89	0.67	1.17
Subgroup with confirmed PD-L1 TPS of ≥50%	0.88	0.72	1.07	0.87	0.67	1.14
KEYNOTE-407 trial						
Subgroup with confirmed PD-L1 TPS of <1%	1.09	0.89	1.33	1.05	0.81	1.37
Subgroup with confirmed PD-L1 TPS of 1% to 49%	0.98	0.8	1.19	0.97	0.74	1.26
Subgroup with confirmed PD-L1 TPS of ≥50%	1.13	0.9	1.41	1.02	0.75	1.39

PFS, progression-free survival; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; TPS, tumor proportion score.

Table S3 Cost estimates in the Chinese setting

Strategy	Cost	Progression-free LYs	Overall LYs	QALYs	Incremental cost per QALY*	INHB*,#
Nonsquamous non-small-cell lung cancer						
Whole patients with unconfirmed PD-L1 TPS						
Standard chemotherapy (reference strategy)	52,327	0.479	1.822	1.304	NA	NA
Universal pembrolizumab strategy	104,925	1.317	3.554	2.416	47,328	–0.739
TPS50 pembrolizumab strategy	73,008	0.742	2.350	1.640	61,686	–0.392
TPS1 pembrolizumab strategy	88,934	1.050	2.880	1.976	54,536	–0.617
Subgroup with confirmed PD-L1 TPS of <1%						
Standard chemotherapy (reference strategy)	47,933	0.468	1.387	1.005	NA	NA
Pembrolizumab strategy	92,081	0.814	2.968	2.054	42,085	–0.505
Subgroup with confirmed PD-L1 TPS of 1% to 49%						
Standard chemotherapy (reference strategy)	55,717	0.556	2.012	1.435	NA	NA
Pembrolizumab strategy	105,925	1.527	3.684	2.495	47,400	–0.707
Subgroup with confirmed PD-L1 TPS of ≥50%						
Standard chemotherapy (reference strategy)	53,375	0.421	2.056	1.465	NA	NA
Pembrolizumab strategy	111,204	1.164	3.549	2.413	61,018	–1.088
Squamous non-small-cell lung cancer						
Whole patients with unconfirmed PD-L1 TPS						
Standard chemotherapy (reference strategy)	41,084	0.526	1.819	1.338	NA	NA
Universal pembrolizumab strategy	85,967	1.311	3.058	2.157	54,805	–0.761
TPS50 pembrolizumab strategy	59,920	1.050	2.247	1.624	65,920	–0.377
TPS1 pembrolizumab strategy	75,129	1.108	2.802	1.984	52,719	–0.552
Subgroup with confirmed PD-L1 TPS of <1%						
Standard chemotherapy (reference strategy)	41,146	0.466	1.736	1.282	NA	NA
Pembrolizumab strategy	83,163	0.813	3.094	2.185	46,548	–0.576
Subgroup with confirmed PD-L1 TPS of 1% to 49%						
Standard chemotherapy (reference strategy)	43,535	0.411	1.912	1.405	NA	NA
Pembrolizumab strategy	91,485	0.594	3.663	2.540	42,242	–0.553
Subgroup with confirmed PD-L1 TPS of ≥50%						
Standard chemotherapy (reference strategy)	38,829	0.685	1.812	1.331	NA	NA
Pembrolizumab strategy	91,443	2.167	3.022	2.139	65,136	–1.044

*, comparing with reference strategy; #, three times of Chinese gross domestic product (GDP) per capita in 2018 ($28,410) was adopted as the willingness-to-pay threshold. QALY, quality-adjusted-life year; INHB, incremental net-health benefit; PD-L1, programmed cell death 1 ligand 1; TPS, tumor proportion score.

Table S4 Summary of cost ($) and outcome results in base-case analysis in Chinese setting

Strategy	Cost	Progression-free LYs	Overall LYs	QALYs	Incremental cost per QALY*	INHB*,#
Nonsquamous non-small-cell lung cancer						
Whole patients with unconfirmed PD-L1 TPS						
Standard chemotherapy (reference strategy)	52,327	0.479	1.822	1.304	NA	NA
Universal pembrolizumab strategy	104,925	1.317	3.554	2.416	47,328	–0.739
TPS50 pembrolizumab strategy	73,008	0.742	2.350	1.640	61,686	–0.392
TPS1 pembrolizumab strategy	88,934	1.050	2.880	1.976	54,536	–0.617
Subgroup with confirmed PD-L1 TPS of <1%						
Standard chemotherapy (reference strategy)	47,933	0.468	1.387	1.005	NA	NA
Pembrolizumab strategy	92,081	0.814	2.968	2.054	42,085	–0.505
Subgroup with confirmed PD-L1 TPS of 1% to 49%						
Standard chemotherapy (reference strategy)	55,717	0.556	2.012	1.435	NA	NA
Pembrolizumab strategy	105,925	1.527	3.684	2.495	47,400	–0.707
Subgroup with confirmed PD-L1 TPS of ≥50%						
Standard chemotherapy (reference strategy)	53,375	0.421	2.056	1.465	NA	NA
Pembrolizumab strategy	111,204	1.164	3.549	2.413	61,018	–1.088
Squamous non-small-cell lung cancer						
Whole patients with unconfirmed PD-L1 TPS						
Standard chemotherapy (reference strategy)	41,084	0.526	1.819	1.338	NA	NA
Universal pembrolizumab strategy	85,967	1.311	3.058	2.157	54,805	–0.761
TPS50 pembrolizumab strategy	59,920	1.050	2.247	1.624	65,920	–0.377
TPS1 pembrolizumab strategy	75,129	1.108	2.802	1.984	52,719	–0.552
Subgroup with confirmed PD-L1 TPS of <1%						
Standard chemotherapy (reference strategy)	41,146	0.466	1.736	1.282	NA	NA
Pembrolizumab strategy	83,163	0.813	3.094	2.185	46,548	–0.576
Subgroup with confirmed PD-L1 TPS of 1% to 49%						
Standard chemotherapy (reference strategy)	43,535	0.411	1.912	1.405	NA	NA
Pembrolizumab strategy	91,485	0.594	3.663	2.540	42,242	–0.553
Subgroup with confirmed PD-L1 TPS of ≥50%						
Standard chemotherapy (reference strategy)	38,829	0.685	1.812	1.331	NA	NA
Pembrolizumab strategy	91,443	2.167	3.022	2.139	65,136	–1.044

*, comparing with reference strategy; #, three times of Chinese gross domestic product (GDP) per capita in 2018 ($28,410) was adopted as the willingness-to-pay threshold. QALY, quality-adjusted-life year; INHB, incremental net-health benefit; PD-L1, programmed cell death 1 ligand 1; TPS, tumor proportion score.