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Cost-effectiveness analysis of pembrolizumab plus chemotherapy for previously untreated metastatic non-small cell lung cancer in the USA

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ABSTRACT

Objectives Evaluating the cost-effectiveness of pembrolizumab plus standard chemotherapy in the first-line setting for patients with metastatic non-small cell lung cancer (NSCLC) from the US payer perspective.

Design A Markov model was constructed to analyse the cost-effectiveness of pembrolizumab plus chemotherapy in the first-line treatment of metastatic NSCLC. Health outcomes were estimated in quality-adjusted life-years (QALYs). The cost information was from Medicare in 2018. One-way and probabilistic sensitivity analyses examined the impact of uncertainty and assumptions on the results.

Setting The US payer perspective.

Participants A hypothetical US cohort of patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations.

Interventions Pembrolizumab plus chemotherapy versus chemotherapy.

Primary outcome measures Costs, QALYs, incremental cost-effectiveness ratio (ICER) of pembrolizumab plus chemotherapy expressed as cost per QALY gained compared with chemotherapy

Results The base case analysis demonstrated that pembrolizumab plus chemotherapy provided an additional 0.78 QALYs at incremental cost of $151 409, resulting in an ICER of $194 372/QALY. ICER for pembrolizumab plus chemotherapy was >$149 680/QALY in all of our univariable and probabilistic sensitivity analyses.

Conclusions Pembrolizumab in addition to chemotherapy provides modest incremental benefit at high incremental cost per QALY for the treatment of previously untreated metastatic NSCLC.

Strengths and limitations of this study

- ► The study strengths of this model-based economic assessment include that it is based on rigorous randomised controlled trials.
- ► From a US payer perspective, the cost and outcome data included in the model are collected for analysis.
- ► The limitation of this study is that because of the limited time scale of the model and the lack of long-term data, not all potential outcomes are included.

INTRODUCTION

Globally, lung cancer had an incidence rate of 27.4 per 100 000 and a mortality rate of 23.1 per 100 000 in 2018,[1] and non-small cell lung cancer (NSCLC) accounted for the vast majority of these cases.[2] Multiple drug regimens are available for the treatment of advanced NSCLC, including platinum-based combination chemotherapy, anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI), epidermal growth factor receptor (EGFR)TKI and immune checkpoint inhibitors.[2] Immune checkpoint inhibitors showed higher efficacy and less toxicity compared with other therapies.[3]

A new era of treating advanced NSCLC is upon us after the emergence of immunosuppressive agents.[4] Immune checkpoint inhibitors improve antitumor immunity by inhibiting programmed death 1 (PD-1) receptor or programmed cell death ligand 1 (PD-L1).[2 5–7] Pembrolizumab, a PD-1 inhibitor, was approved by the US Food and Drug Administration (FDA) for treatment of advanced NSCLC in 2015.[8 9]The Keynote-189 clinical trial showed pembrolizumab in combination with pemetrexed plus carboplatin or cisplatin could extend progression-free survival (PFS) by 3.9 months for patients with metastatic NSCLC without sensitising ALK or EGFR mutations.[10]

Although pembrolizumab plus chemotherapy improved survival significantly, the additional cost was notably high. Therefore, it is worth discussing whether pembrolizumab plus chemotherapy is a cost-effective regimen. The goal of this study was to analyse the cost-effectiveness of pembrolizumab plus chemotherapy for previously untreated metastatic NSCLC without ALK or EGFR mutations from the US payer perspective.

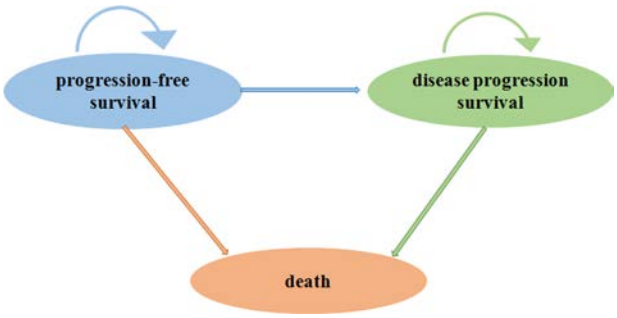

Figure 1 State transition diagram. The three circles show three main health states. Patients can transition from 'progression-free survival' to 'disease progression survival' or 'death'

MATERIAL AND METHODS

Decision model

A Markov model was built to simulate the flow process of patient morbidity, treatment and survival for previously untreated metastatic NSCLC, using three states, namely PFS state, disease progression survival state and death (figure 1). All patients entranced the model in the PFS state, with the treatment of pemetrexed combined platinum plus pembrolizumab or placebo. Patients who experienced progression could receive carboplatin plus pemetrexed, docetaxel plus ramucirumab, docetaxel monotherapy, nivolumab or pembrolizumab, because these regimens were used most in the Keynote-189 trial.[10] All patients were assumed to receive end-of-life care before death.

Each health state was assigned a health utility from published studies. Only direct costs were considered and adapted for 2018 US dollars using the Medical Care Consumer Price Index. All costs and health outcomes were discounted at an annual discount rate of 3%.[11] The model simulated a 20-year period and each model cycle represented 21 days because in the clinical trial patients received pembrolizumab plus chemotherapy every 3 weeks.[10] The primary outputs of the Markov model included cost and quality-adjusted life years (QALYs), which were applied to estimate the incremental cost-effectiveness ratio (ICER). All analyses were performed in TreeAge pro 2018 software (https://www.treeage.com).

Model probabilities

The probability of transition of disease progression and from any state to death were from the survival curve of pembrolizumab or placebo combined with chemotherapy in the keynote-189 trial.[10] We used the GetData Graph Digitizer software (V.2.25) to extract the data points of the Kaplan-Meier curves. According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC), the PFS data points were fitted by a Weibull distribution, and overall survival (OS) data points were fitted with an exponential distribution.[12] The distribution parameters were calculated using the method of Hoyle *et al*.[12] Finally, the PFS and OS rates of each cycle were estimated by exp $(-\lambda t^{\gamma})$ and exp$(-\lambda t)$, respectively, where λ is the scale parameter, γ is the shape parameter and t is survival time (table 1 near here).

Costs

Only direct costs, including the costs of the drug, premedication, administration and management of serious adverse events (AEs) (table 1 near here), were considered in our evaluation. In the PFS state, the cost of the intravenous drug for 3-week cycle was based on the following doses: pembrolizumab 200 mg/cycle, pemetrexed 500 mg/m^2, cisplatin 75 mg/m^2 and carboplatin 400 mg/m^2.

The model considered the hospitalisation cost of patients with AE ≧ grade 3, and the incidence rate exceeded 5% because these AEs were of great concern to clinicians.[13] And then the incidence rates of neutropenia and pneumonia from the Keynote-189 trial were used to calculate the cost of AEs treatments.[10]

Based on the Keynote-189 trial,[10] 30.5% of the patients in the pembrolizumab plus chemotherapy group and 46.6% in the placebo plus chemotherapy group received subsequent therapy after disease progression. Among patients in the pembrolizumab plus chemotherapy group, 3% received carboplatin plus pemetrexed, 2.3% received docetaxel plus ramucirumab, 17.8% received docetaxel, 4% received nivolumab and 3.4% received continuation maintenance treatment of pembrolizumab; among patients in the placebo plus chemotherapy group, 1.7% received docetaxel, 7.8% received nivolumab and 38% received crossover treatment with pembrolizumab. Patients who died accrued the cost of terminal care, including hospitalisation, palliative chemotherapy, doctor consultation, laboratory and diagnostic tests, according to the published literature.[14]

The mean value of a body surface area and body weight are 1.84 m^2 and 82 kg, respectively.[13 15] The drug costs were taken from the Centers for Medicare and Medicaid Services.[16] Administration costs were calculated according to the Medicare physician fee schedule for 2018.[17] The costs of AEs and end-of-life care were derived from the published literature.[13]

Outcome measures

The outcome indicator of the study was QALYs, which is defined by the patient's life years and health utility. In accordance with the approach of Anna Oh *et al*,[18] we also considered the disutility of AE. Baseline utility and disutility values were referenced in the published literature (table 1 near here).[19 20]

Analysis

The uncertainty of the parameters was evaluated by one-way sensitivity analysis and probabilistic sensitivity analysis, through the use of tornado diagrams and Monte Carlo simulation, respectively. The beta distribution was applied for the utilities, and the lognormal distribution was applied for the cost. Utilities were varied over their 95% CIs. In general, the upper and lower limits of the

Table 1 Parameters for cost effectiveness model

Parameter	Pembrolizumab Value	Pembrolizumab Ranges	Placebo Value	Placebo Ranges	Distribution
Probabilities					
PFS (Weibull)					
Scale(λ)	0.0448		0.0876		
Shape(γ)	1.2675		1.2312		
OS(exponential)					
Scale(λ)	0.0290		0.0586		
Costs ($)					
Pembrolizumab/mg[16]	48.57	+/-25%	48.57	+/-25%	Lognorm
Pemetrexed/mg[16]	6.75	+/-25%	6.75	+/-25%	Lognorm
Cisplatin/mg[16]	0.20	+/-25%	0.20	+/-25%	Lognorm
Carboplatin/mg[16]	0.06	+/-25%	0.06	+/-25%	Lognorm
Chemotherapy infusion 1 hour[16]	145	+/-25%	145	+/-25%	Lognorm
Chemotherapy infusion additional hour[16]	32	+/-25%	32	+/-25%	Lognorm
Subsequent therapies/cycle[16]	1160	+/-25%	4394	+/-25%	Lognorm
End-of-life care[14]	33 009	+/-25%	33 009	+/-25%	Lognorm
AE hospitalisation cost[13]	3538	+/-50%	3005	+/-50%	Lognorm
Baseline utilities					
PFS[19]	0.71	0.67–0.76	0.71	0.67–0.76	Beta
disease progression survival[19]	0.67	0.59–0.75	0.67	0.59–0.75	Beta
Disutilities					
Neutropenia[20]	0.09	0.060–0.119	0.09	0.060–0.119	Beta
Pneumonia[20]	0.09	0.059–0.121	0.09	0.059–0.121	Beta

AE, adverse effect; OS, overall survival;PFS, progression-free survival.

parameters were taken from the literature, and if otherwise, upper and lower limits of 25% were set. All baseline values and ranges for variables are shown in table 1.

Patient and public involvement

No patients or public were involved in the study.

RESULTS

Base case analysis

Weibull and exponential models used to fit the survival curves from the clinical trial (online supplementary appendix 1), which show that the decision analysis model established in this study can reflect the clinical effects very well. In the base case analysis, the lifetime cost of using pembrolizumab plus chemotherapy was $288 532 compared with $137 123 for placebo plus chemotherapy. When considering effectiveness, the pembrolizumab plus chemotherapy strategy yielded 1.61 QALYs, compared with 0.83 QALYs for the placebo plus chemotherapy strategy. The ICER of pembrolizumab plus chemotherapy was calculated as $194 372/QALY compared with the placebo plus chemotherapy. When pembrolizumab cost $12.05 and $31.38/mg, the ICERs approximated the WTP thresholds of $100 000 and $150 000/QALY, respectively (table 2).

Sensitivity analysis

The tornado diagrams present the results of one-way sensitivity analyses. Obviously, the cost of pembrolizumab, the cost of subsequent treatment in the placebo-combination group and baseline utility values of OS were the most relatively sensitive parameters, and the ICER range was

Table 2 Pembrolizumab plus chemotherapy cost-effectiveness at additional modelled price points

Parameter	Base case model analysis*	
WTP value, $/QALY	100 000	15 000
Nivolumab cost, $/mg	12.05	31.38
Total cost, $	176 197	235 651
QALYs	1.61	1.61
ICER, $/QALY	99 915	149 907

*Only the cost of pembrolizumab was varied.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, Willingness-to-pay.

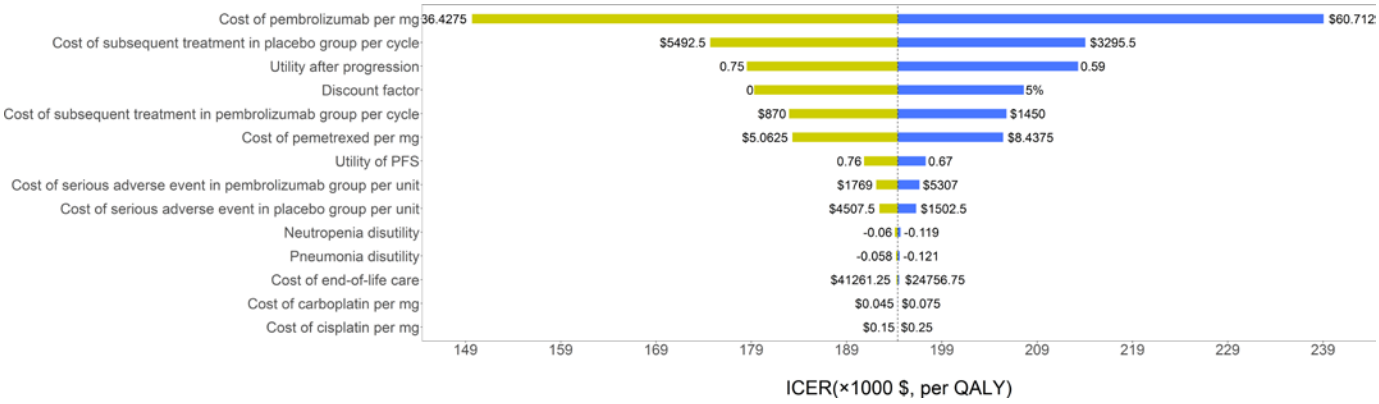

Figure 2 Tornado diagrams. The graphic shows the impact of varying individual model inputs on the cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER, incremental cost-effectiveness ratio; nSCLC, non-small cell lung cancer.

from \$149 680/QALY to \$239 065/QALY (figure 2). The discount rate, the cost of subsequent treatment in the pembrolizumab-combination group, the cost of pemetrexed, the baseline utility value of PFS and the cost of AE management had little impact on the model.

The cost-effectiveness acceptability curve shows the probabilistic sensitivity analysis results of different willingness-to-pay (WTP) thresholds (figure 3). The probability that pembrolizumab combined with chemotherapy is cost-effective increased as WTP increased. The results showed that the probability of pembrolizumab plus chemotherapy being cost-effective was 0% at a WTP threshold of \$130 000/QALY. If WTP threshold is \$192 000/QALY, the pembrolizumab plus chemotherapy strategy show a 50% chance cost-effectiveness (figure 3).

The results of the subgroup analysis showed that pembrolizumab combined with chemotherapy was the most cost-effective (36%) for patients who had never smoked at a WTP threshold of \$100 000. When the WTP threshold was \$150 000, the probability of pembrolizumab combined with chemotherapy being cost-effective in the subgroup of never-smoking and female patients was 100% (see online supplementary appendix 2).

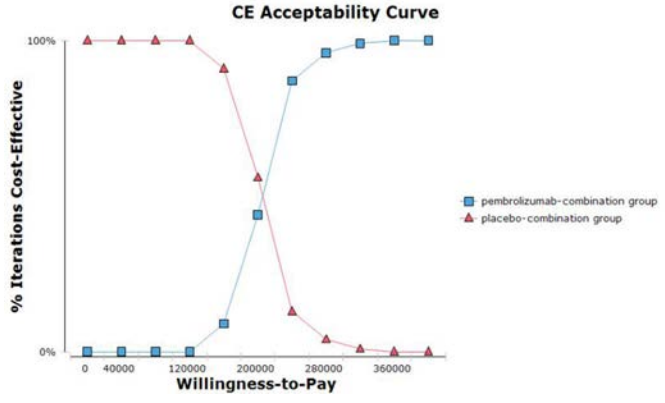

Figure 3 Cost-effectiveness (CE) acceptability curve. This plot represents the results of a probabilistic sensitivity analysis (for details, see Methods) comparing the cost-effectiveness of pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastaticnon-small cell lung cancer (NSCLC).

DISCUSSION

We performed a cost-effectiveness analysis of pembrolizumab in addition to chemotherapy in previously untreated metastatic NSCLC. Based on our model, the ICER for pembrolizumab plus chemotherapy was estimated as \$194 372/QALY compared with the placebo plus chemotherapy. The results showed that the probability of pembrolizumab plus chemotherapy being cost-effective was 0% at a WTP threshold of \$130 000/QALY.

There are many other studies that have analysed the cost-effectiveness of pembrolizumab for advanced NSCLC in different setting.[13 14 21–24] In the KEYNOTE-024 trial, pembrolizumab demonstrated the incremental survival benefits and better safety profile versus chemotherapy for first-line treatment of PD-L1 -positive (≥50%) metastatic NSCLC patients,[25] Based on the KEYNOTE-024 trial, a US-based study found that pembrolizumab was cost-effective, with an ICER of \$97 621/QALY,[14] a study by Georgieva *et al* demonstrated that pembrolizumab monotherapy was cost-effective in the USA but not the UK,[24] a study by Hu *et al* conducted in the UK demonstrated that pembrolizumab plus chemotherapy was not cost-effective, with an ICER of £86 913/QALY,[23] and a French study found that pembrolizumab appears cost-effective.[22] Our results differ from the above results may be due to different health systems and costs in different countries, which leads to different cost-effectiveness conclusions. Based on the KEYNOTE-010 trial, a study analysed the cost-effectiveness of pembrolizumab and docetaxel as second-line treatment for PD-L1 positive advanced NSCLC from the US third-party payer perspective. The results showed that the ICER was \$168 619/QALY, which was cost-effective at a threshold of three times GDP per capita (\$171 660).[13] These data provide reference value for evaluating the total cost of therapy and the value of regimens for advanced NSCLC.

Our one-way sensitivity analysis revealed that the cost of pembrolizumab had a great influence on the results of the study. High drug prices are the result of the monopoly of pharmaceutical companies and restrictions on the negotiating power of the payer.[26] This can be addressed by providing more meaningful price negotiation opportunities for payers and providing more evidence of a cost-effectiveness comparison of treatment regimens.[26] We can also reduce the cost of administration by using personalised dosing. Recent study has shown that personalised dosing (2 mg/kg) and fixed dosing (200 mg) of pembrolizumab have equivalent efficacy.[27] Avoiding drug waste is extremely important in an era of value-based cancer therapy.[27] When our study used 2 mg/kg of pembrolizumab based on the average weight of 82 kg,[15] the ICER was reduced to $171 751. We believe that manufacturers are responsible for providing multiple sizes of vials to minimise the chance of wastage.

However, there are few limitations to our study that deserve consideration. First, we used cost parameters provided by Medicare, which may be lower than private insurers.[28] Second, the health utility values were taken from other data sources instead of patients who participated in the Keynote 189 trial, which limits the accuracy of our results. Unfortunately, the clinical trial did not report the quality of life. Third, our analysis did not estimate the costs for all AEs in the PFS state, which may lead to underestimation of AEs costs. However, considering the low incidence, we expect the inclusion of all AEs would not change the conclusions of the present analysis. In addition, our model applied sensitivity analysis to a wide variation of these parameters, and it does not affect the results. Fourth, our analysis was based on the Keynote 189 trial, which excluded patients with sensitising EGFR or ALK translocation, because they usually used targeted agents as first-line treatment. However in the real-world setting, these patients with unknown EGFR or ALK translocation were also likely to be received PD-L1 testing and treated with pembrolizumab. Finally, our study directly compared pembrolizumab plus chemotherapy with chemotherapy according to the KEYNOTE-189 trial. Although there are other potential first-line treatments for advanced non-small cell lung cancer, our study did not indirectly compare them because of the lack of convincing trial data and robust head-to-head trial data.

Overall, the combination of pembrolizumab and chemotherapy for patients with metastatic NSCLC that we studied has high incremental cost and modest incremental benefit. New treatment technology for tumour is continuously undergoing development, but the price of tumour drugs is also rising dramatically. Based on our analysis, pembrolizumab offers lower value at current cost. The provision of cost-effective care requires new pricing and payment systems to support. The process for approving new drugs and the process of incorporating them into the guidelines must balance costs and benefits, and our research can offer decision-making information for this purpose.

Contributors Study concepts and design: CT; Clinical program: FM; Analysis and interpretation of the data: LP, YP, QL; The drafting and revising of the paper: XZ and XW; Final approved of manuscript: All authors; all authors agree to be accountable for all aspects of the work.

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