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

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Abstract

Objectives: We evaluated 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. **Methods**: We constructed a Markov model 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. **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 incremental cost-effectiveness ratio (ICER) of $194,372/QALY. The 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.

Keywords: Lung cancer, cost-effectiveness analysis, pembrolizumab, immunotherapy, quality-adjusted life years, sensitivity analysis.

Article Summary

1. The study strengths of this model-based economic assessment include that it is based on rigorous randomized controlled trials.
2. From a US payer perspective, the cost and outcome data included in the model are collected for analysis.
3. 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.

1 Introduction

Globally, lung cancer had an incidence rate of 27.4per 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 to other [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 ratified 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 extended progression-free survival (PFS) by 3.9 months for patients with metastatic NSCLC without sensitizing 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.

2 Material and methods

2.1 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 (Fig.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).

2.2 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 (version 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).

2.3 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 200mg/cycle, pemetrexed 500mg/m^2, cisplatin 75 mg/m^2 and carboplatin 400 mg/m^2.

The model considered the hospitalization cost of patients with AE $\geqq$ 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 hospitalization, 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 1.84m^2 and 82kg, 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].

2.4 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].

2.5 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 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.

3 Results

3.1 Base case analysis

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.

3.2 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 from $149,680/QALY to $239,065/QALY (Fig.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 (Fig.3). The probability that pembrolizumab combined with chemotherapy is cost-effective increased as WTP increased. These results showed that the cost-effectiveness probability of pembrolizumab plus chemotherapy was 0% under the condition of 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 (Fig.3).

4 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 of probabilistic sensitivity analysis suggested that the cost-effectiveness probability of pembrolizumab plus chemotherapy was 0% under the condition of a WTP threshold of $130,000/QALY.

There were many published study estimated the cost-effectiveness of pembrolizumab monotherapy as first-line setting for advanced NSCLC across multiple countries, with ICERs ranging from $52,000/QALY to $110,000/QALY [14 21-24], and if pembrolizumab monotherapy was used as a second-line treatment, the ICER was $168,619/QALY compared with docetaxel [13]. As a second-line treatment compared with docetaxel, the value of another immunosuppressive agent (nivolumab) was also evaluated to have the ICERs of A$220,029/QALY, CHF177,478/QALY and $15,229/QALY, from the perspective of Australia, Swiss and Canada, respectively [25-27]. Obviously the ICER we gained is comparable with the previous published studies of immunosuppressive agents used for second-line treatment [13 25-27]. 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 [28]. 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 [28]. We can also reduce the cost of administration by using personalized dosing. Recent study has shown that personalized dosing (2mg/kg) and fixed dosing (200mg) of pembrolizumab have equivalent efficacy [29]. Avoiding drug waste is extremely important in an era of value-based cancer therapy [29]. 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 minimize 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 [30]. 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 sensitizing 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.

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.

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Author Contributions: Study concepts and design: Chongqing Tan; Clinical program: Fang Ma; Analysis and interpretation of the data: Liubao Peng, Ye Peng, Qiao Liu; The drafting and revising of the paper: Xiaohui Zeng and Xiaomin Wan; Final approved of manuscript: All authors; all authors agree to be accountable for all aspects of the work.

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Table 1 Parameters for Cost Effectiveness Model

Parameter	Pembrolizumab		Placebo		Distribution
	Value	Ranges	Value	Ranges	
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]	33009	+/- 25%	33009	+/- 25%	Lognorm
AE hospitalization cost [13]	3538	+/- 50%	3005	+/-50%	Lognorm
Baseline utilities					
PFS [19]	0.71	0.67–0.76	0.71	0.67–0.76	Beta
OS [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

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

Fig.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"

Fig.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

Fig.3 Cost-effectiveness 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 metastatic NSCLC. CE: cost-effectiveness. NSCLC: non-small cell lung cancer

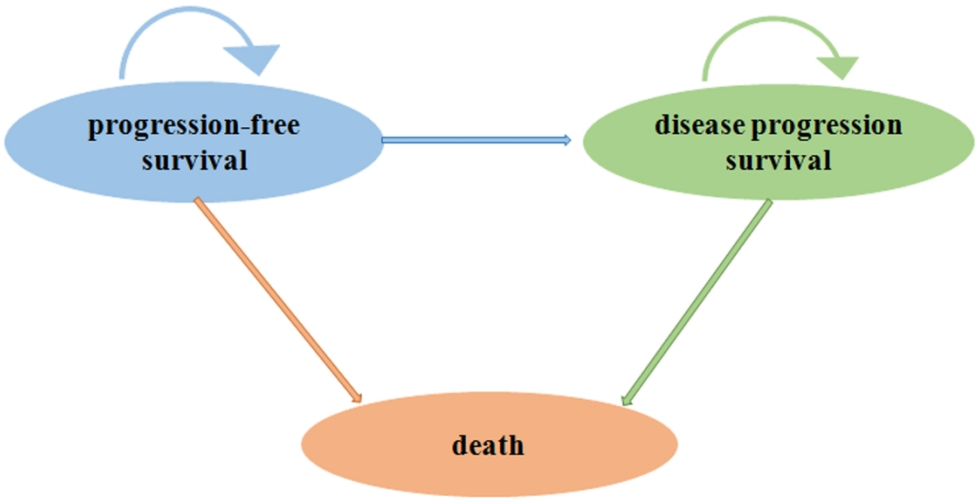

Fig.1 State transition diagram. The three circles show three main health states. Patients can transition from "progression-free survival" to "disease progression survival" or "death"

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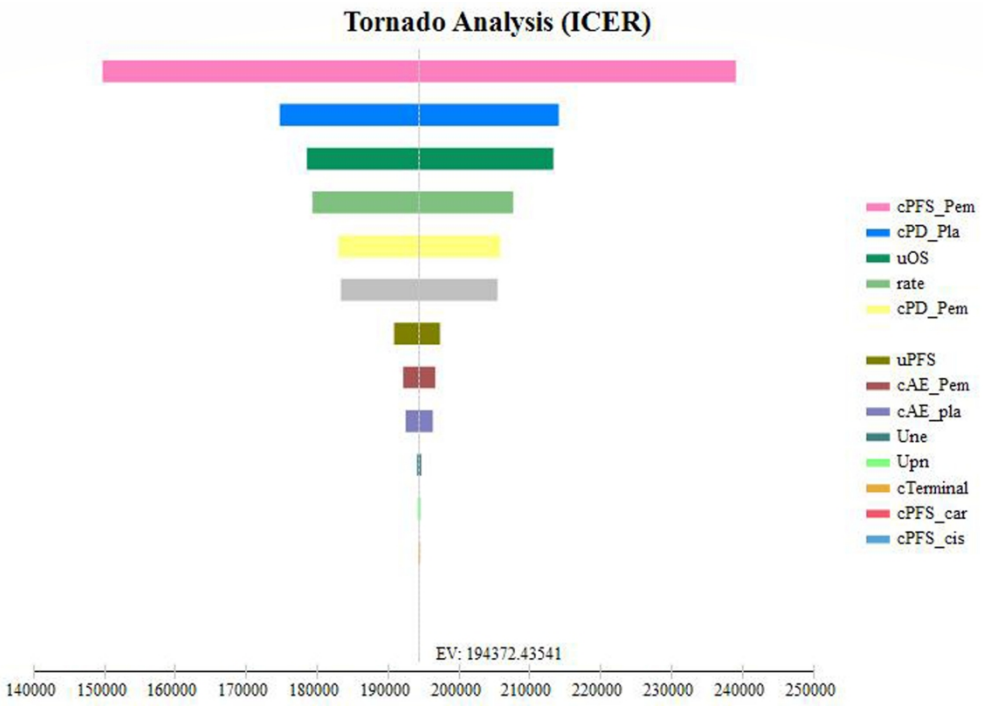

Fig.2 Tornado diagrams. The graphic shows the impact of varying individual model inputs on the cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental cost-effectiveness ratio. NSCLC: non-small cell lung cancer

1574x1111mm (96 x 96 DPI)

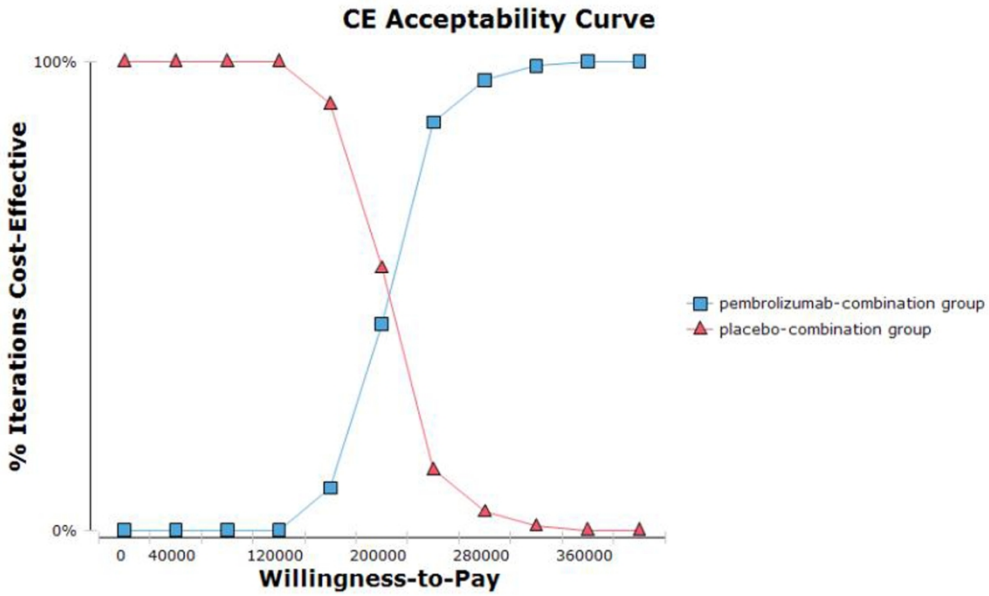

Fig.3 Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity analysis (for details, see Methods) comparing the cost-effectiveness of pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE: cost-effectiveness. NSCLC: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

169x104mm (600 x 600 DPI)

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section	Item No	Recommendation	Reported on page No/line No
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	P1/ L1-2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	P2/L33-45
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	P2-3/L58-76
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	P3/L79-80
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	P3/L81-85
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	P3/L76
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	P3/L82
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	P3/L88-89
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	P3/L88
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	P3/L90-91
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single	

		study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	P5/L126-130
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P4-5/L104-125
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P3/L86-87
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	P3/L79
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	P3/L80-85
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P5/L131-137
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	P12/L321
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If	P5/L139-144

		applicable, report incremental cost-effectiveness ratios.	

Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	P6/L145-157
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P6-P8/L158-202
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	P8/L210-212
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	P8/L213

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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

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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.

Intervention 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 anICER of $194,372/QALY. The 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.

Article Summary

1. The study strengths of this model-based economic assessment include that it is based on rigorous randomized controlled trials.
2. From a US payer perspective, the cost and outcome data included in the model are collected for analysis.
3. 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.

1 Introduction

Globally, lung cancer had an incidence rate of 27.4per 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 to 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 extended progression-free survival (PFS) by 3.9 months for patients with metastatic NSCLC without sensitizing 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.

2 Material and methods

2.1 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 (Fig.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).

2.2 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 (version 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).

2.3 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 200mg/cycle, pemetrexed 500mg/m^2, cisplatin 75 mg/m^2 and carboplatin 400 mg/m^2.

The model considered the hospitalization cost of patients with AE $\geqq$ 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 hospitalization, 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 1.84m^2 and 82kg, 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].

2.4 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].

2.5 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 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.

2.6 Patient and public involvement

No patients or public were involved in the study.

3 Results

3.1 Base case analysis

Weibull and exponential models used to fit the survival curves from the clinical trial (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 (Table2).

3.2 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 from $149,680/QALY to $239,065/QALY (Fig.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 (Fig.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 (Fig.3).

4 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 analyzed 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 US but not the UK[24], a study by Hu X 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 personalized dosing. Recent study has shown that personalized dosing (2mg/kg) and fixed dosing (200mg) 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 minimize 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 sensitizing 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.

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Table 1 Parameters for Cost Effectiveness Model

Parameter	Pembrolizumab		Placebo		Distribution
	Value	Ranges	Value	Ranges	
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]	33009	+/- 25%	33009	+/- 25%	Lognorm
AE hospitalization 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

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

Table 2 Pembrolizuman plus Chemotherapy Cost-Effectiveness at Additional Modeled Price Points

Parameter	Base-Case Model Analysis*	
WTP value, $/QALY	100000	15000
Nivolumab cost, $/mg	12.05	31.38
Total cost, $	176197	235651
QALYs	1.61	1.61
ICER, $/QALY	99915	149907

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; WTP: Willingness-to-pay.

* Only the cost of pembrolizumab was varied.

Fig.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"

Fig.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

Fig.3 Cost-effectiveness 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 metastatic NSCLC. CE: cost-effectiveness. NSCLC: non-small cell lung cancer

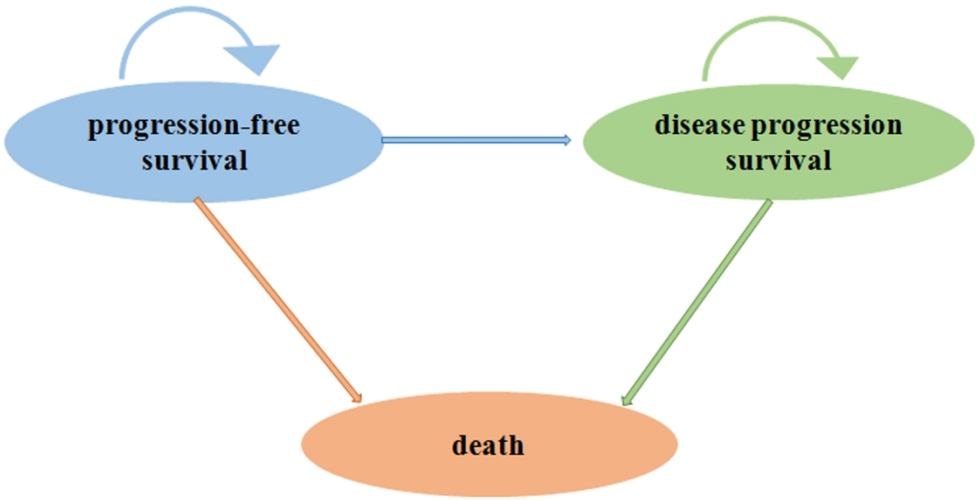


Fig.1 State transition diagram. The three circles show three main health states. Patients can transition from "progression-free survival" to "disease progression survival" or "death"

82x45mm (600 x 600 DPI)

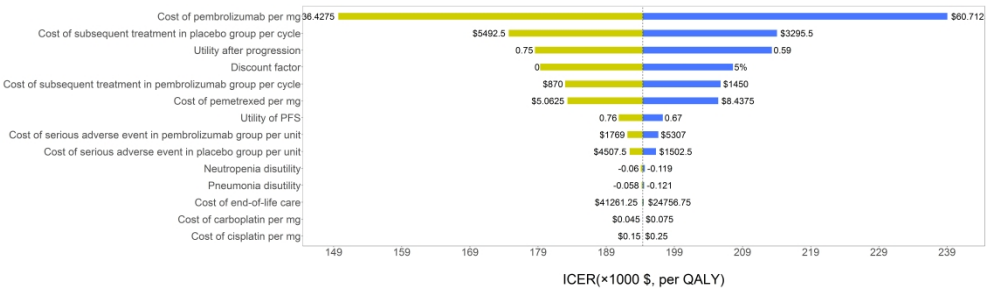


Fig.2 Tornado diagrams. The graphic shows the impact of varying individual model inputs on the cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental cost-effectiveness ratio. NSCLC: non-small cell lung cancer

889x254mm (300 x 300 DPI)

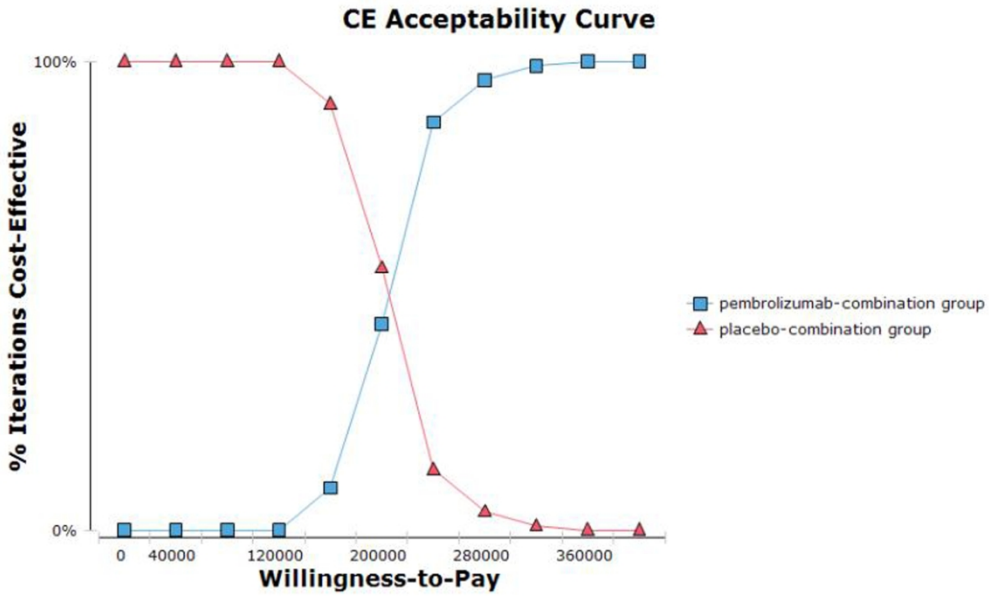
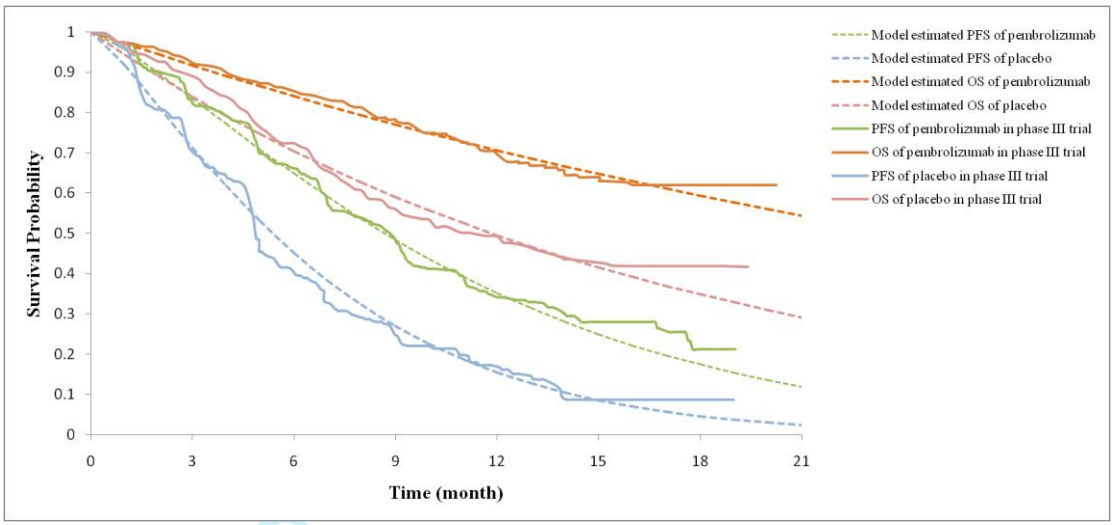


Fig.3 Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity analysis (for details, see Methods) comparing the cost-effectiveness of pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE: cost-effectiveness. NSCLC: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

169x104mm (600 x 600 DPI)



Supplementary appendix 1. Survival curves. PFS and OS were fitted with Weibull and exponential model, respectively, according to the original curves shown in clinical trials. PFS: progression-free survival; OS: overall survival.

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section	Item No	Recommendation	Reported on page No/line No
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	P1/ L1-2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	P2/L33-45
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	P2-3/L58-76
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	P3/L79-80
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	P3/L81-85
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	P3/L76
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	P3/L82
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	P3/L88-89
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	P3/L88
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	P3/L90-91
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single	

		study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	P5/L126-130
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P4-5/L104-125
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P3/L86-87
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	P3/L79
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	P3/L80-85
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P5/L131-137
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	P12/L321
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If	P5/L139-144

		applicable, report incremental cost-effectiveness ratios.	

Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	P6/L145-157
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P6-P8/L158-202
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	P8/L210-212
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	P8/L213

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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

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

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Word count: 1821.

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 anICER of $194,372/QALY. The 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.

Article Summary

1. The study strengths of this model-based economic assessment include that it is based on rigorous randomized controlled trials.
2. From a US payer perspective, the cost and outcome data included in the model are collected for analysis.
3. 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.

1 Introduction

Globally, lung cancer had an incidence rate of 27.4per 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 to 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 extended progression-free survival (PFS) by 3.9 months for patients with metastatic NSCLC without sensitizing 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.

2 Material and methods

2.1 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 (Fig.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).

2.2 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 (version 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).

2.3 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 200mg/cycle, pemetrexed 500mg/m^2, cisplatin 75 mg/m^2 and carboplatin 400 mg/m^2.

The model considered the hospitalization cost of patients with AE $\geqq$ 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 hospitalization, 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 1.84m^2 and 82kg, 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].

2.4 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].

2.5 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 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.

2.6 Patient and public involvement

No patients or public were involved in the study.

3 Results

3.1 Base case analysis

Weibull and exponential models used to fit the survival curves from the clinical trial (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 (Table2).

3.2 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 from $149,680/QALY to $239,065/QALY (Fig.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 (Fig.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 (Fig.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% (Supplementary Appendix 2).

4 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 analyzed 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 US but not the UK[24], a study by Hu X 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 personalized

dosing. Recent study has shown that personalized dosing (2mg/kg) and fixed dosing (200mg) 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 minimize 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 sensitizing 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.

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Conflict of interest: None declared.

Ethics statement: Ethical approval was not necessary, because our economic evaluation is based on a mathematical model analysis, and does not contain any studies with human participants or animals performed.

Data sharing statement: No additional data available.

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Table 1 Parameters for Cost Effectiveness Model

Parameter	Pembrolizumab		Placebo		Distribution
	Value	Ranges	Value	Ranges	
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]	33009	+/- 25%	33009	+/- 25%	Lognorm
AE hospitalization 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

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

Table 2 Pembrolizuman plus Chemotherapy Cost-Effectiveness at Additional Modeled Price Points

Parameter	Base-Case Model Analysis*	
WTP value, $/QALY	100000	15000
Nivolumab cost, $/mg	12.05	31.38
Total cost, $	176197	235651
QALYs	1.61	1.61
ICER, $/QALY	99915	149907

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; WTP: Willingness-to-pay.

* Only the cost of pembrolizumab was varied.

Fig.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"

Fig.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

Fig.3 Cost-effectiveness 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 metastatic NSCLC. CE: cost-effectiveness. NSCLC: non-small cell lung cancer

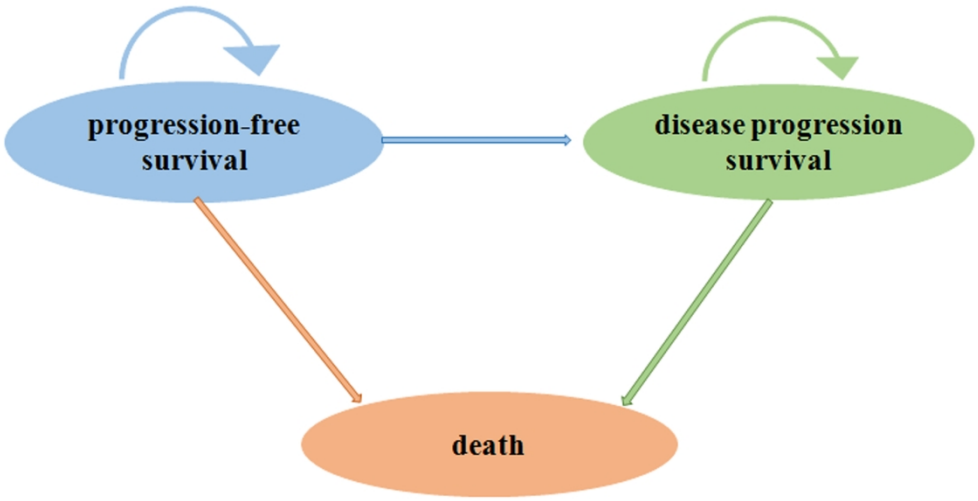

Fig.1 State transition diagram. The three circles show three main health states. Patients can transition from "progression-free survival" to "disease progression survival" or "death"

82x45mm (600 x 600 DPI)

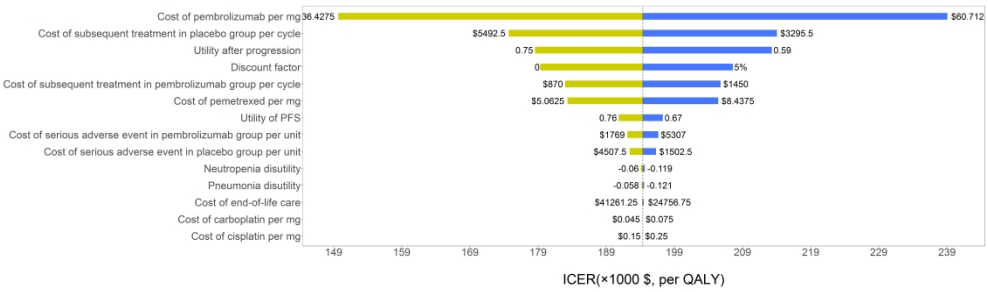

Fig.2 Tornado diagrams. The graphic shows the impact of varying individual model inputs on the cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental cost-effectiveness ratio. NSCLC: non-small cell lung cancer

889x254mm (300 x 300 DPI)

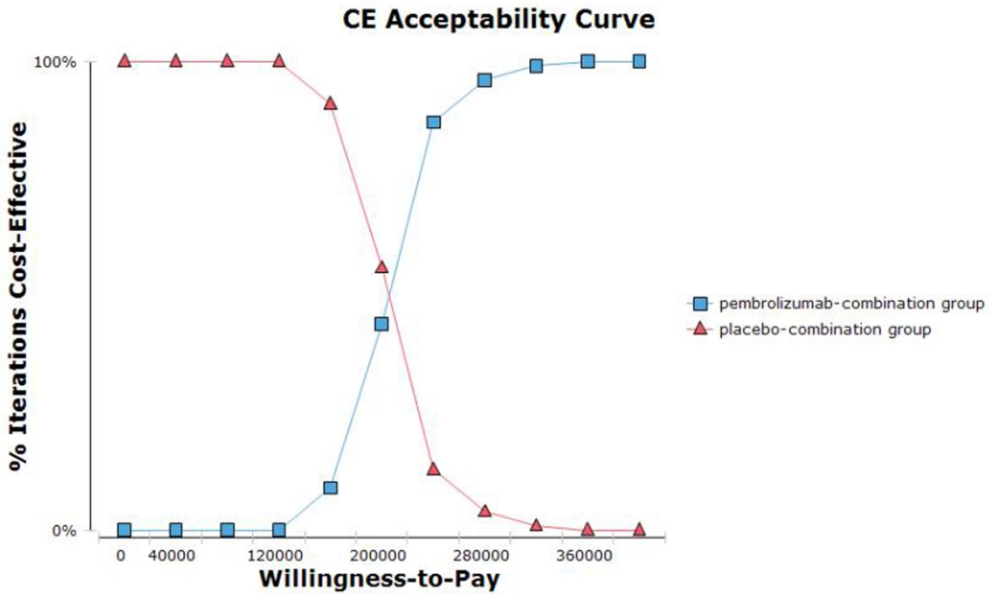

Fig.3 Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity analysis (for details, see Methods) comparing the cost-effectiveness of pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE: cost-effectiveness. NSCLC: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

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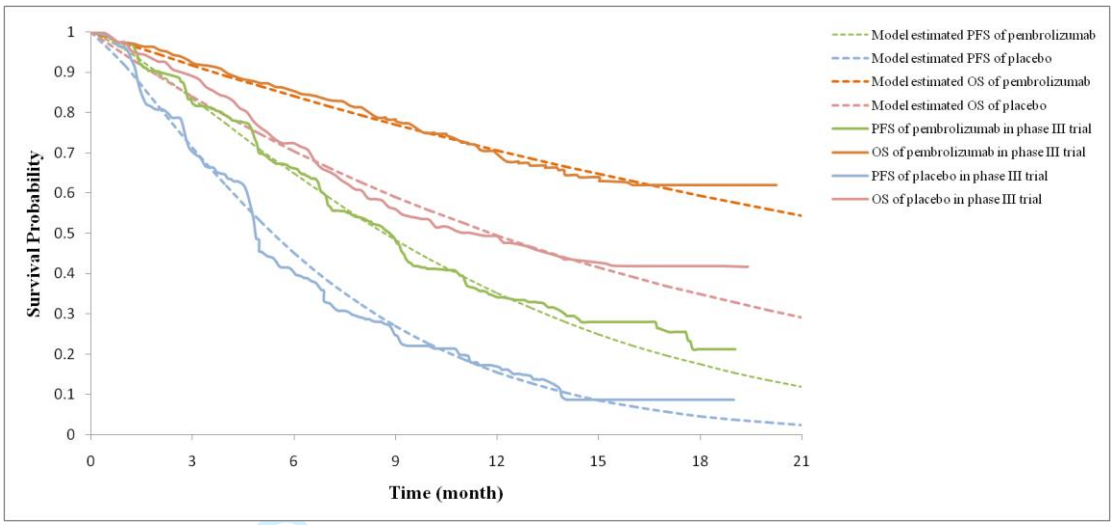

Supplementary appendix 1. Survival curves. PFS and OS were fitted with Weibull and exponential model, respectively, according to the original curves shown in clinical trials. PFS: progression-free survival; OS: overall survival.

Supplementary appendix 2 Results for subgroup analyses

Subgroup	OS HR (95% CI)	PFS HR (95% CI)	ICER	Cost-effectiveness probability at the threshold of $100000/QALY	Cost-effectiveness probability at the threshold of $150000/QALY
Sex					
Male	0.70 (0.50–0.99)	0.66 (0.50–0.87)	172432	0	15%
Female	0.29 (0.19–0.44)	0.40 (0.29–0.54)	115344	3%	100%
Smoking status					
Current or former	0.54 (0.41–0.71)	0.54 (0.43–0.66)	151882	0	40%
Never	0.23 (0.10–0.54)	0.43 (0.23–0.81)	99695	36%	100%
PD-L1 tumor proportion score					
<1%	0.59 (0.38–0.92)	0.75 (0.53–1.05)	132478	1%	86%
1-49%	0.55 (0.34–0.90)	0.55 (0.37–0.81)	152694	0	38%
≥50%	0.42 (0.26–0.68)	0.36 (0.25–0.52)	154361	0	30%

PFS: progression-free survival; OS: overall survival; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section	Item No	Recommendation	Reported on page No/line No
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	P1/ L1-2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	P2/L33-45
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	P2-3/L58-76
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	P3/L79-80
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	P3/L81-85
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	P3/L76
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	P3/L82
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	P3/L88-89
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	P3/L88
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	P3/L90-91
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single	

		study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	P5/L126-130
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P4-5/L104-125
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P3/L86-87
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	P3/L79
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	P3/L80-85
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P5/L131-137
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	P12/L321
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If	P5/L139-144

		applicable, report incremental cost-effectiveness ratios.	

Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	P6/L145-157
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P6-P8/L158-202
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	P8/L210-212
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	P8/L213

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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

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

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Word count: 1821.

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 anICER of $194,372/QALY. The 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.

Article Summary

1. The study strengths of this model-based economic assessment include that it is based on rigorous randomized controlled trials.
2. From a US payer perspective, the cost and outcome data included in the model are collected for analysis.
3. 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.

1 Introduction

Globally, lung cancer had an incidence rate of 27.4per 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 to 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 extended progression-free survival (PFS) by 3.9 months for patients with metastatic NSCLC without sensitizing 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.

2 Material and methods

2.1 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 (Fig.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).

2.2 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 (version 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).

2.3 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 200mg/cycle, pemetrexed 500mg/m^2, cisplatin 75 mg/m^2 and carboplatin 400 mg/m^2.

The model considered the hospitalization cost of patients with AE $\geqq$ 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 hospitalization, 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 1.84m^2 and 82kg, 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].

2.4 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].

2.5 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 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.

2.6 Patient and public involvement

No patients or public were involved in the study.

3 Results

3.1 Base case analysis

Weibull and exponential models used to fit the survival curves from the clinical trial (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 (Table2).

3.2 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 from $149,680/QALY to $239,065/QALY (Fig.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 (Fig.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 (Fig.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% (Supplementary Appendix 2).

4 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 analyzed 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 US but not the UK[24], a study by Hu X 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 personalized

dosing. Recent study has shown that personalized dosing (2mg/kg) and fixed dosing (200mg) 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 minimize 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 sensitizing 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.

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Author Contributions: Study concepts and design: Chongqing Tan; Clinical program: Fang Ma; Analysis and interpretation of the data: Liubao Peng, Ye Peng, Qiao Liu; The drafting and revising of the paper: Xiaohui Zeng and Xiaomin Wan; Final approved of manuscript: All authors; all authors agree to be accountable for all aspects of the work.

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Conflict of interest: None declared.

Ethics statement: Ethical approval was not necessary, because our economic evaluation is based on a mathematical model analysis, and does not contain any studies with human participants or animals performed.

Data sharing statement: The unit price we used in the article is freely available in Medicare & Medicaid Services (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html). And the clinical trial parameters we used in the manuscript are derived from published literature on PubMed (Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018; 378(22):2078-92. doi: 10.1056/NEJMoa1801005). The datasets generated during the current study are available from the corresponding author on reasonable request.

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Table 1 Parameters for Cost Effectiveness Model

Parameter	Pembrolizumab		Placebo		Distribution
	Value	Ranges	Value	Ranges	
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]	33009	+/- 25%	33009	+/- 25%	Lognorm
AE hospitalization 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

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

Table 2 Pembrolizuman plus Chemotherapy Cost-Effectiveness at Additional Modeled Price Points

Parameter	Base-Case Model Analysis*	
WTP value, $/QALY	100000	15000
Nivolumab cost, $/mg	12.05	31.38
Total cost, $	176197	235651
QALYs	1.61	1.61
ICER, $/QALY	99915	149907

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; WTP: Willingness-to-pay.

* Only the cost of pembrolizumab was varied.

Fig.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"

Fig.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

Fig.3 Cost-effectiveness 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 metastatic NSCLC. CE: cost-effectiveness. NSCLC: non-small cell lung cancer

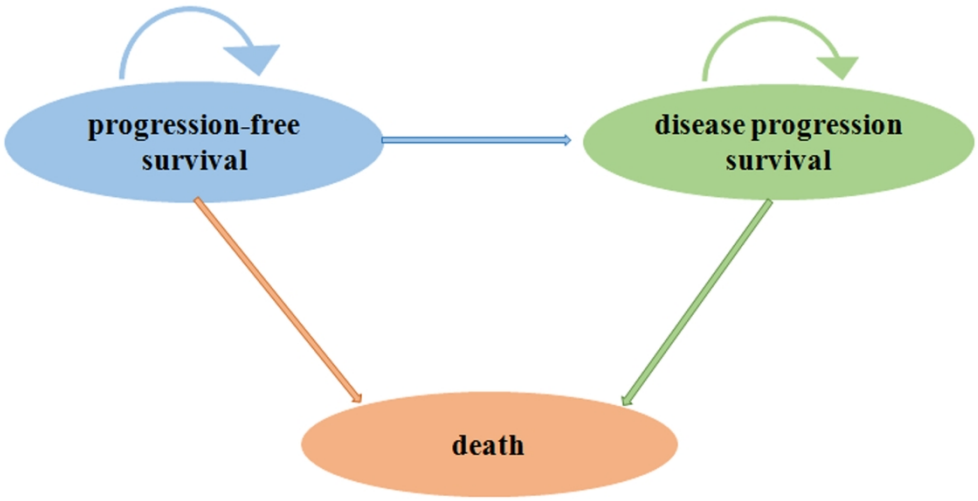

Fig.1 State transition diagram. The three circles show three main health states. Patients can transition from "progression-free survival" to "disease progression survival" or "death"

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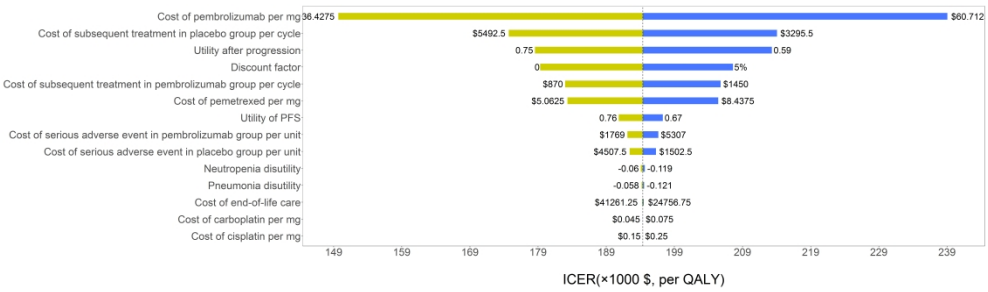

Fig.2 Tornado diagrams. The graphic shows the impact of varying individual model inputs on the cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental cost-effectiveness ratio. NSCLC: non-small cell lung cancer

889x254mm (300 x 300 DPI)

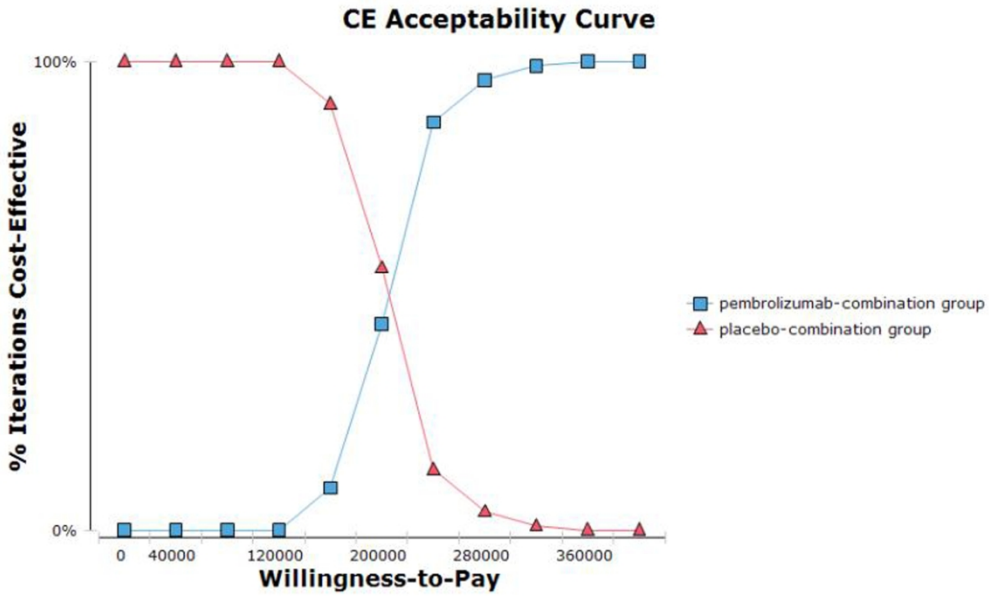

Fig.3 Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity analysis (for details, see Methods) comparing the cost-effectiveness of pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE: cost-effectiveness. NSCLC: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

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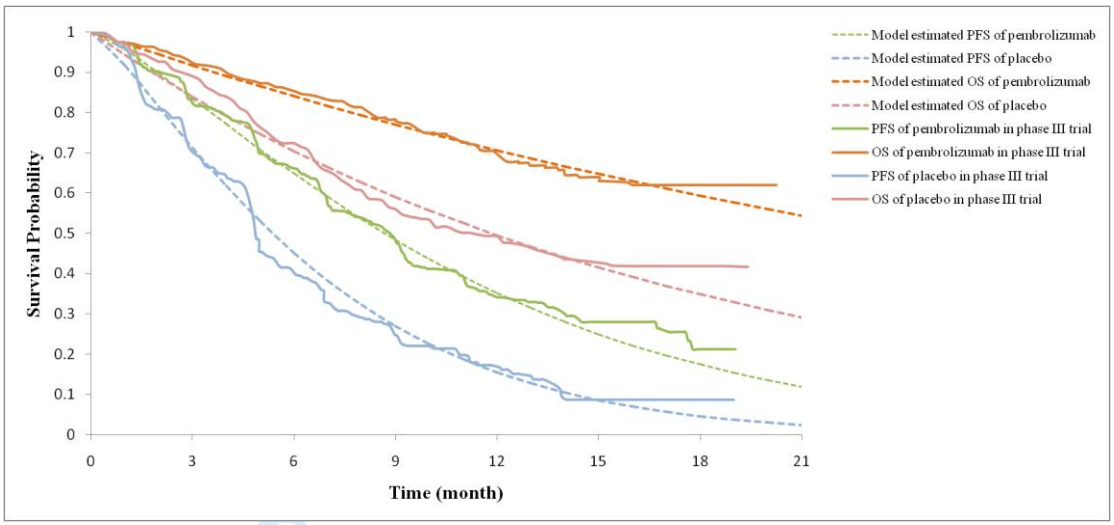

Supplementary appendix 1. Survival curves. PFS and OS were fitted with Weibull and exponential model, respectively, according to the original curves shown in clinical trials. PFS: progression-free survival; OS: overall survival.

Supplementary appendix 2 Results for subgroup analyses

Subgroup	OS HR (95% CI)	PFS HR (95% CI)	ICER	Cost-effectiveness probability at the threshold of $100000/QALY	Cost-effectiveness probability at the threshold of $150000/QALY
Sex					
Male	0.70 (0.50–0.99)	0.66 (0.50–0.87)	172432	0	15%
Female	0.29 (0.19–0.44)	0.40 (0.29–0.54)	115344	3%	100%
Smoking status					
Current or former	0.54 (0.41–0.71)	0.54 (0.43–0.66)	151882	0	40%
Never	0.23 (0.10–0.54)	0.43 (0.23–0.81)	99695	36%	100%
PD-L1 tumor proportion score					
<1%	0.59 (0.38–0.92)	0.75 (0.53–1.05)	132478	1%	86%
1-49%	0.55 (0.34–0.90)	0.55 (0.37–0.81)	152694	0	38%
≥50%	0.42 (0.26–0.68)	0.36 (0.25–0.52)	154361	0	30%

PFS: progression-free survival; OS: overall survival; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section	Item No	Recommendation	Reported on page No/line No
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	P1/ L1-2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	P2/L33-45
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	P2-3/L58-76
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	P3/L79-80
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	P3/L81-85
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	P3/L76
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	P3/L82
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	P3/L88-89
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	P3/L88
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	P3/L90-91
Measurement of effectiveness	11a	*Single study-based estimates*: Describe fully the design features of the single effectiveness study and why the single	

		study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	P5/L126-130
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation*: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation*: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P4-5/L104-125
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P3/L86-87
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	P3/L79
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	P3/L80-85
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P5/L131-137
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	P12/L321
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If	P5/L139-144

		applicable, report incremental cost-effectiveness ratios.	

Characterizing uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation*: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	P6/L145-157
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P6-P8/L158-202
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	P8/L210-212
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	P8/L213

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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