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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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4 **1 Cost-effectiveness analysis of pembrolizumab plus chemotherapy for previously**
5 **2 untreated metastatic non-small-cell lung cancer in the United States**

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33 Abstract

34 **Objectives:** We evaluated the cost-effectiveness of pembrolizumab plus standard chemotherapy in the
35 first-line setting for patients with metastatic non-small cell lung cancer (NSCLC) from the US-payer
36 perspective. **Methods:** We constructed a Markov model to analyse the cost-effectiveness of
37 pembrolizumab plus chemotherapy in the first-line treatment of metastatic NSCLC. Health outcomes
38 were estimated in quality-adjusted life-years (QALYs). The cost information was from Medicare in 2018.
39 One-way and probabilistic sensitivity analyses examined the impact of uncertainty and assumptions on
40 the results. **Results:** The base-case analysis demonstrated that pembrolizumab plus chemotherapy
41 provided an additional 0.78 QALYs at incremental cost of \$151,409, resulting in an incremental
42 cost-effectiveness ratio (ICER) of \$194,372/QALY. The ICER for pembrolizumab plus chemotherapy
43 was > \$149,680/QALY in all of our univariable and probabilistic sensitivity analyses. **Conclusions:**
44 Pembrolizumab in addition to chemotherapy provides modest incremental benefit at high incremental cost
45 per QALY for the treatment of previously untreated metastatic NSCLC.

46
47 **Keywords:** Lung cancer, cost-effectiveness analysis, pembrolizumab, immunotherapy, quality-adjusted
48 life years, sensitivity analysis.

50 Article Summary

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

58 1 Introduction

59 Globally, lung cancer had an incidence rate of 27.4 per 100,000 and a mortality rate of 23.1 per
60 100,000 in 2018 [1], and non-small cell lung cancer (NSCLC) accounted for the vast majority of these
61 cases [2]. Multiple drug regimens are available for the treatment of advanced NSCLC, including platinum
62 based combination chemotherapy, anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI),
63 epidermal growth factor receptor (EGFR)TKI and immune checkpoint inhibitors[2]. Immune checkpoint
64 inhibitors showed higher efficacy and less toxicity compared to other [3].

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5 65 A new era of treating advanced NSCLC is upon us after the emergence of immunosuppressive
6 66 agents [4]. Immune checkpoint inhibitors improve antitumor immunity by inhibiting programmed death
7 67 1(PD-1) receptor or programmed cell death ligand 1 (PD-L1) [2 5-7]. Pembrolizumab, a PD-1 inhibitor,
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9 68 was ratified by the US Food and Drug Administration (FDA) for treatment of advanced NSCLC in 2015
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11
12 69 [8 9].The Keynote-189 clinical trial showed pembrolizumab in combination with pemetrexed plus
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14 70 carboplatin or cisplatin could extended progression-free survival (PFS) by 3.9 months for patients with
15
16 71 metastatic NSCLC without sensitizing ALK or EGFR mutations [10].
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18 72 Although pembrolizumab plus chemotherapy improved survival significantly, the additional cost
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20 73 was notably high. Therefore, it is worth discussing whether pembrolizumab plus chemotherapy is a
21
22 74 cost-effective regimen. The goal of this study was to analyse the cost-effectiveness of pembrolizumab
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24 75 plus chemotherapy for previously untreated metastatic NSCLC without ALK or EGFR mutations from
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26 76 the US-payer perspective.
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27 77 **2 Material and methods**

28 78 **2.1 Decision model**

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34 79 A Markov model was built to simulate the flow process of patient morbidity, treatment, and
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36 80 survival for previously untreated metastatic NSCLC, using three states, namely PFS state, disease
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38 81 progression survival state, and death (Fig.1).All patients entranced the model in the PFS state, with
39
40 82 the treatment of pemetrexed combined platinum plus pembrolizumab or placebo. Patients who
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42 83 experienced progression could receive carboplatin plus pemetrexed, docetaxel plus ramucirumab,
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44 84 docetaxel monotherapy, nivolumab or pembrolizumab, because these regimens were used most in
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46 85 the Keynote-189 trial [10]. All patients were assumed to receive end-of-life care before death.
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48 86 Each health state was assigned a health utility from published studies. Only direct costs were
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50 87 considered and adapted for 2018 US dollars using the Medical Care Consumer Price Index. All costs and
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52 88 health outcomes were discounted at an annual discount rate of 3% [11]. The model simulated a 20-year
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54 89 period and each model cycle represented 21 days because in the clinical trial patients received
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56 90 pembrolizumab plus chemotherapy every 3 weeks [10]. The primary outputs of the Markov model
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58 91 included cost and quality-adjusted life years (QALYs), which were applied to estimate the incremental
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5 92 cost-effectiveness ratio (ICER). All analyses were performed in TreeAge pro 2018 software
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7 93 (<https://www.treeage.com>).

94 2.2 Model probabilities

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

104 2.3 Costs

105 Only direct costs, including the costs of the drug, premedication, administration and management of
106 serious adverse events (AEs) (Table 1 near here), were considered in our evaluation. In the PFS state, the
107 cost of the intravenous drug for 3-week cycle was based on the following doses: pembrolizumab
108 200mg/cycle, pemetrexed 500mg/m², cisplatin 75 mg/m² and carboplatin 400 mg/m².

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

113 Based on the Keynote-189 trial [10], 30.5% of the patients in the pembrolizumab plus chemotherapy
114 group and 46.6% in the placebo plus chemotherapy group received subsequent therapy after disease
115 progression. Among patients in the pembrolizumab plus chemotherapy group, 3% received carboplatin
116 plus pemetrexed, 2.3% received docetaxel plus ramucirumab, 17.8% received docetaxel, 4% received
117 nivolumab and 3.4% received continuation maintenance treatment of pembrolizumab; among patients in
118 the placebo plus chemotherapy group, 1.7% received docetaxel, 7.8% received nivolumab and 38%

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5 119 received crossover treatment with pembrolizumab. Patients who died accrued the cost of terminal care,
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7 120 including hospitalization, palliative chemotherapy, doctor consultation, laboratory, and diagnostic tests,
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9 121 according to the published literature [14].

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11 122 The mean value of a body-surface area and body weight are 1.84m² and 82kg, respectively [13 15].
12
13 123 The drug costs were taken from the Centers for Medicare and Medicaid Services[16]. Administration
14
15 124 costs were calculated according to the Medicare physician fee schedule for 2018[17]. The costs of AEs
16
17 125 and end-of-life care were derived from the published literature [13].

18 19 126 **2.4 Outcome measures**

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21
22 127 The outcome indicator of the study was QALYs, which is defined by the patient's life years and
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24 128 health utility. In accordance with the approach of Anna Oh et al [18], we also considered the disutility of
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26 129 AE. Baseline utility and disutility values were referenced in the published literature (Table 1 near here)
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28 130 [19 20].

29 30 131 **2.5 Analysis**

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33 132 The uncertainty of the parameters was evaluated by one-way sensitivity analysis and probabilistic
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35 133 sensitivity analysis, through the use of tornado diagrams and Monte Carlo simulation respectively. The
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37 134 beta distribution was applied for the utilities, and the lognormal distribution was applied for the cost.
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39 135 Utilities were varied over their 95% CIs. In general, the upper and lower limits of the parameters were
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41 136 taken from the literature, and if otherwise, upper and lower limits of 25% were set. All baseline values
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43 137 and ranges for variables are shown in Table 1.

44 45 138 **3 Results**

46 47 48 139 **3.1 Base case analysis**

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51 140 In the base case analysis, the lifetime cost of using pembrolizumab plus chemotherapy was \$288,532
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53 141 compared with \$137,123 for placebo plus chemotherapy. When considering effectiveness, the
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55 142 pembrolizumab plus chemotherapy strategy yielded 1.61 QALYs, compared with 0.83 QALYs for the
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57 143 placebo plus chemotherapy strategy. The ICER of pembrolizumab plus chemotherapy was calculated as
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59 144 \$194,372/QALY compared with the placebo plus chemotherapy.

145 **3.2 Sensitivity analysis**

146 The tornado diagrams present the results of one-way sensitivity analyses. Obviously, the cost of
147 pembrolizumab, the cost of subsequent treatment in the placebo-combination group and baseline utility
148 values of OS were the most relatively sensitive parameters, and the ICER range was from
149 \$149,680/QALY to \$239,065/QALY (Fig.2). The discount rate, the cost of subsequent treatment in the
150 pembrolizumab-combination group, the cost of pemetrexed, the baseline utility value of PFS and the cost
151 of AE management had little impact on the model.

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

158 **4 Discussion**

159 We performed a cost-effectiveness analysis of pembrolizumab in addition to chemotherapy in
160 previously untreated metastatic NSCLC. Based on our model, the ICER for pembrolizumab plus
161 chemotherapy was estimated as \$194,372/QALY compared with the placebo plus chemotherapy. The
162 results of probabilistic sensitivity analysis suggested that the cost-effectiveness probability of
163 pembrolizumab plus chemotherapy was 0% under the condition of a WTP threshold of \$130,000/QALY.

164 There were many published study estimated the cost-effectiveness of pembrolizumab monotherapy
165 as first-line setting for advanced NSCLC across multiple countries, with ICERs ranging from
166 \$52,000/QALY to \$110,000/QALY [14 21-24], and if pembrolizumab monotherapy was used as a
167 second-line treatment, the ICER was \$168,619/QALY compared with docetaxel [13]. As a second-line
168 treatment compared with docetaxel, the value of another immunosuppressive agent (nivolumab) was also
169 evaluated to have the ICERs of A\$220,029/QALY, CHF177,478/QALY and \$15,229/QALY, from the
170 perspective of Australia, Swiss and Canada, respectively [25-27]. Obviously the ICER we gained is
171 comparable with the previous published studies of immunosuppressive agents used for second-line
172 treatment [13 25-27]. These data provide reference value for evaluating the total cost of therapy and the

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5 173 value of regimens for advanced NSCLC.

6 174 Our one-way sensitivity analysis revealed that the cost of pembrolizumab had a great influence on
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8 175 the results of the study. High drug prices are the result of the monopoly of pharmaceutical companies and
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10 176 restrictions on the negotiating power of the payer [28]. This can be addressed by providing more
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12 177 meaningful price negotiation opportunities for payers and providing more evidence of a cost-effectiveness
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14 178 comparison of treatment regimens [28]. We can also reduce the cost of administration by using
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16 179 personalized dosing. Recent study has shown that personalized dosing (2mg/kg) and fixed dosing (200mg)
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18 180 of pembrolizumab have equivalent efficacy [29]. Avoiding drug waste is extremely important in an era of
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20 181 value-based cancer therapy [29]. When our study used 2 mg/kg of pembrolizumab based on the average
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22 182 weight of 82 kg [15], the ICER was reduced to \$171,751. We believe that manufacturers are responsible
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24 183 for providing multiple sizes of vials to minimize the chance of wastage.

25
26 184 However, there are few limitations to our study that deserve consideration. First, we used cost
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28 185 parameters provided by Medicare, which may be lower than private insurers [30]. Second, the health
29
30 186 utility values were taken from other data sources instead of patients who participated in the Keynote 189
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32 187 trial, which limits the accuracy of our results. Unfortunately, the clinical trial did not report the quality of
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34 188 life. Third, our analysis did not estimate the costs for all AEs in the PFS state, which may lead to
35
36 189 underestimation of AEs costs. However, considering the low incidence, we expect the inclusion of all
37
38 190 AEs would not change the conclusions of the present analysis. In addition, our model applied sensitivity
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40 191 analysis to a wide variation of these parameters, and it does not affect the results. Fourth, our analysis was
41
42 192 based on the Keynote 189 trial, which excluded patients with sensitizing EGFR or ALK translocation,
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44 193 because they usually used targeted agents as first-line treatment. However in the real-world setting, these
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46 194 patients with unknown EGFR or ALK translocation were also likely to be received PD-L1 testing and
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48 195 treated with pembrolizumab.

49 196 Overall, the combination of pembrolizumab and chemotherapy for patients with metastatic NSCLC
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51 197 that we studied has high incremental cost and modest incremental benefit. New treatment technology for
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53 198 tumour is continuously undergoing development, but the price of tumour drugs is also rising dramatically.
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55 199 Based on our analysis, pembrolizumab offers lower value at current cost. The provision of cost-effective
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57 200 care requires new pricing and payment systems to support. The process for approving new drugs and the
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201 process of incorporating them into the guidelines must balance costs and benefits, and our research can
202 offer decision-making information for this purpose.

203

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321 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

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

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5 324 **Fig.1** State transition diagram. The three circles show three main health states. Patients can transition
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7 325 from “progression-free survival” to “disease progression survival” or “death”
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10 327 **Fig.2** Tornado diagrams. The graphic shows the impact of varying individual model inputs on the
11
12 328 cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental
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14 329 cost-effectiveness ratio. NSCLC: non-small cell lung cancer
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18 331 **Fig.3** Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity
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20 332 analysis (for details, see Methods) comparing the cost-effectiveness of
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22 333 pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE:
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24 334 cost-effectiveness. NSCLC: non-small cell lung cancer
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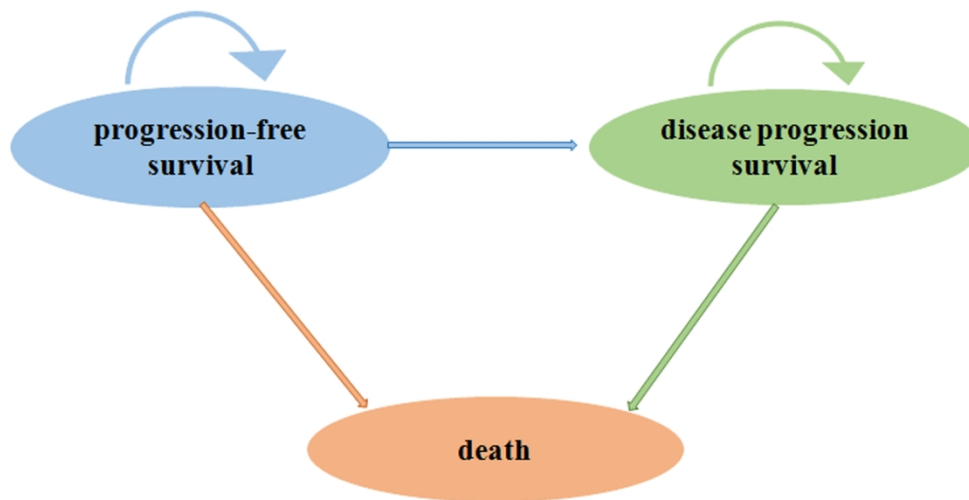


Fig.1 State transition diagram. The three circles show three main health states. Patients can transition from "progression-free survival" to "disease progression survival" or "death"

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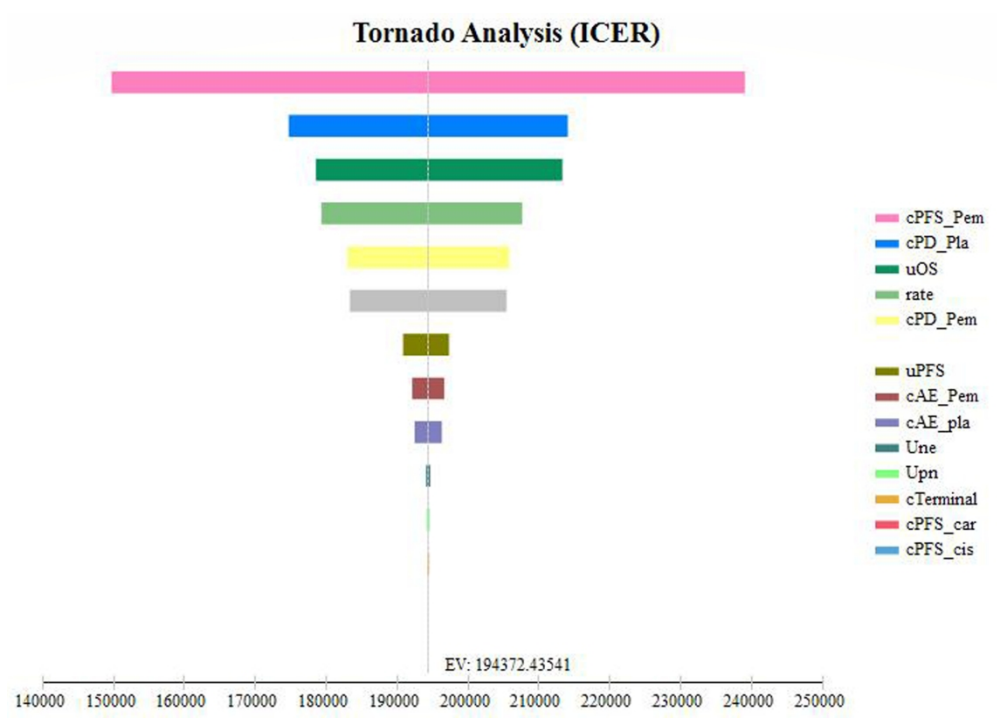


Fig.2 Tornado diagrams. The graphic shows the impact of varying individual model inputs on the cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental cost-effectiveness ratio. NSCLC: non-small cell lung cancer

1574x1111mm (96 x 96 DPI)

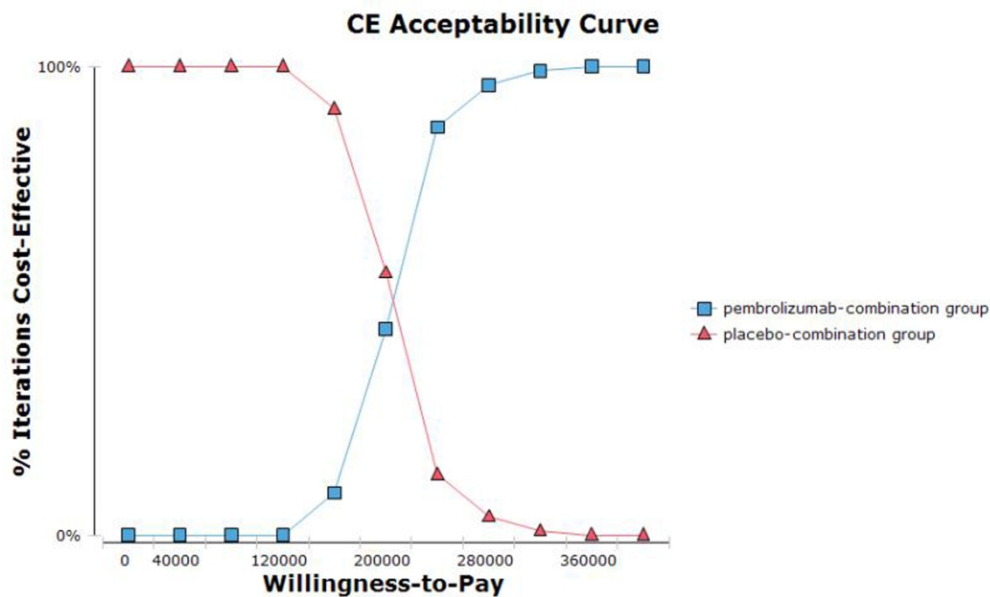


Fig.3 Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity analysis (for details, see Methods) comparing the cost-effectiveness of pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE: cost-effectiveness. NSCLC: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

169x104mm (600 x 600 DPI)

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 1

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	<i>Single study-based estimates</i> : Describe fully the design features of the single effectiveness study and why the single	

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 2

		study was a sufficient source of clinical effectiveness data.	
	11b	<i>Synthesis-based estimates</i> : 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	<i>Single study-based economic evaluation</i> : 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	<i>Model-based economic evaluation</i> : 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

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 3

		applicable, report incremental cost-effectiveness ratios.	
Characterizing uncertainty	20a	<i>Single study-based economic evaluation</i> : 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	<i>Model-based economic evaluation</i> : 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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 Husereau D, Drummond M, Petrou S, et al. 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. *Value Health* 2013;16:231-50.

BMJ Open

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

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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Oncology
Keywords:	Immunology < BASIC SCIENCES, CHEMOTHERAPY, HEALTH ECONOMICS

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Manuscripts

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4 **1 Cost-effectiveness analysis of pembrolizumab plus chemotherapy for previously**
5 **2 untreated metastatic non-small-cell lung cancer in the United States**

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9 3 *Xiaohui Zeng^{c,§}, Xiaomin Wan^{a,§}, Liubao Peng^a, Ye Peng^a, Fang Ma^b, Qiao Liu^a, Chongqing Tan^{a,*}*

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4 33 **Abstract**

5
6 34 **Objectives:** Evaluating the cost-effectiveness of pembrolizumab plus standard chemotherapy in the
7 first-line setting for patients with metastatic non-small cell lung cancer (NSCLC) from the US-payer
8 perspective.
9 36

10 37 **Design** A Markov model was constructed to analyse the cost-effectiveness of pembrolizumab plus
11 chemotherapy in the first-line treatment of metastatic NSCLC. Health outcomes were estimated in
12 quality-adjusted life-years (QALYs). The cost information was from Medicare in 2018. One-way and
13 probabilistic sensitivity analyses examined the impact of uncertainty and assumptions on the results.
14 40

15 41 **Setting** The US-payer perspective.

16 42 **Participants** A hypothetical US cohort of patients with previously untreated metastatic nonsquamous
17 NSCLC without EGFR or ALK mutations.
18 43

19 44 **Intervention** Pembrolizumab plus chemotherapy versus chemotherapy.

20 45 **Primary outcome measures** Costs, QALYs, incremental cost-effectiveness ratio (ICER) of
21 pembrolizumab plus chemotherapy expressed as cost per QALY gained compared with chemotherapy
22 46

23 47 **Results** The base-case analysis demonstrated that pembrolizumab plus chemotherapy provided an
24 additional 0.78 QALYs at incremental cost of \$151,409, resulting in an ICER of \$194,372/QALY. The
25 ICER for pembrolizumab plus chemotherapy was > \$149,680/QALY in all of our univariable and
26 probabilistic sensitivity analyses.
27 50

28 51 **Conclusions:** Pembrolizumab in addition to chemotherapy provides modest incremental benefit at high
29 incremental cost per QALY for the treatment of previously untreated metastatic NSCLC.
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33 54 **Article Summary**

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35 55 1. The study strengths of this model-based economic assessment include that it is based on rigorous
36 randomized controlled trials.
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38 57 2. From a US payer perspective, the cost and outcome data included in the model are collected for
39 analysis.
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41 59 3. The limitation of this study is that because of the limited time scale of the model and the lack of
42 long-term data, not all potential outcomes are included.
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67 **1 Introduction**

68 Globally, lung cancer had an incidence rate of 27.4 per 100,000 and a mortality rate of 23.1 per
69 100,000 in 2018 ¹, and non-small cell lung cancer (NSCLC) accounted for the vast majority of these cases
70 ². Multiple drug regimens are available for the treatment of advanced NSCLC, including platinum based
71 combination chemotherapy, anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI),
72 epidermal growth factor receptor (EGFR)TKI and immune checkpoint inhibitors². Immune checkpoint
73 inhibitors showed higher efficacy and less toxicity compared to other therapies ³.

74 A new era of treating advanced NSCLC is upon us after the emergence of immunosuppressive
75 agents ⁴. Immune checkpoint inhibitors improve antitumor immunity by inhibiting programmed death
76 1(PD-1) receptor or programmed cell death ligand 1 (PD-L1) ^{2 5-7}. Pembrolizumab, a PD-1 inhibitor, was
77 approved by the US Food and Drug Administration (FDA) for treatment of advanced NSCLC in 2015 ⁸
78 ⁹.The Keynote-189 clinical trial showed pembrolizumab in combination with pemetrexed plus carboplatin
79 or cisplatin could extended progression-free survival (PFS) by 3.9 months for patients with metastatic
80 NSCLC without sensitizing ALK or EGFR mutations ¹⁰.

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

86 **2 Material and methods**

87 **2.1 Decision model**

88 A Markov model was built to simulate the flow process of patient morbidity, treatment, and
89 survival for previously untreated metastatic NSCLC, using three states, namely PFS state, disease
90 progression survival state, and death (Fig.1).All patients entranced the model in the PFS state, with
91 the treatment of pemetrexed combined platinum plus pembrolizumab or placebo. Patients who
92 experienced progression could receive carboplatin plus pemetrexed, docetaxel plus ramucirumab,
93 docetaxel monotherapy, nivolumab or pembrolizumab, because these regimens were used most in

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5 94 the Keynote-189 trial ¹⁰. All patients were assumed to receive end-of-life care before death.

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7 95 Each health state was assigned a health utility from published studies. Only direct costs were
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9 96 considered and adapted for 2018 US dollars using the Medical Care Consumer Price Index. All costs and
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11 97 health outcomes were discounted at an annual discount rate of 3% ¹¹. The model simulated a 20-year
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13 98 period and each model cycle represented 21 days because in the clinical trial patients received
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15 99 pembrolizumab plus chemotherapy every 3 weeks ¹⁰. The primary outputs of the Markov model included
16
17 100 cost and quality-adjusted life years (QALYs), which were applied to estimate the incremental
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19 101 cost-effectiveness ratio (ICER). All analyses were performed in TreeAge pro 2018 software
20
21 102 (<https://www.treeage.com>).

23 103 **2.2 Model probabilities**

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25 104 The probability of transition of disease progression and from any state to death were from the
26
27 105 survival curve of pembrolizumab or placebo combined with chemotherapy in the keynote-189 trial ¹⁰. We
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29 106 used the GetData Graph Digitizer software (version 2.25) to extract the data points of the Kaplan-Meier
30
31 107 curves. According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC),
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33 108 the PFS data points were fitted by a Weibull distribution, and overall survival (OS) data points were fitted
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35 109 with an exponential distribution ¹². The distribution parameters were calculated using the method of
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37 110 Hoyle et al ¹². Finally, the PFS and OS rates of each cycle were estimated by $\exp(-\lambda t^\gamma)$ and $\exp(-\lambda t)$,
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39 111 respectively, where λ is the scale parameter, γ is the shape parameter, and t is survival time (Table 1 near
40
41 112 here).

43 113 **2.3 Costs**

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45
46 114 Only direct costs, including the costs of the drug, premedication, administration and management of
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48 115 serious adverse events (AEs) (Table 1 near here), were considered in our evaluation. In the PFS state, the
49
50 116 cost of the intravenous drug for 3-week cycle was based on the following doses: pembrolizumab
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52 117 200mg/cycle, pemetrexed 500mg/m², cisplatin 75 mg/m² and carboplatin 400 mg/m².

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54 118 The model considered the hospitalization cost of patients with AE \geq grade 3, and the incidence
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56 119 rate exceeded 5% because these AEs were of great concern to clinicians¹³. And then the incidence rates of
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58 120 neutropenia and pneumonia from the Keynote-189 trial, were used to calculate the cost of AEs treatments
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5 121 ¹⁰.

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7 122 Based on the Keynote-189 trial ¹⁰, 30.5% of the patients in the pembrolizumab plus chemotherapy
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9 123 group and 46.6% in the placebo plus chemotherapy group received subsequent therapy after disease
10
11 124 progression. Among patients in the pembrolizumab plus chemotherapy group, 3% received carboplatin
12
13 125 plus pemetrexed, 2.3% received docetaxel plus ramucirumab, 17.8% received docetaxel, 4% received
14
15 126 nivolumab and 3.4% received continuation maintenance treatment of pembrolizumab; among patients in
16
17 127 the placebo plus chemotherapy group, 1.7% received docetaxel, 7.8% received nivolumab and 38%
18
19 128 received crossover treatment with pembrolizumab. Patients who died accrued the cost of terminal care,
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21 129 including hospitalization, palliative chemotherapy, doctor consultation, laboratory, and diagnostic tests,
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23 130 according to the published literature ¹⁴.

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25 131 The mean value of a body-surface area and body weight are 1.84m² and 82kg, respectively ^{13 15}. The
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27 132 drug costs were taken from the Centers for Medicare and Medicaid Services¹⁶. Administration costs were
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29 133 calculated according to the Medicare physician fee schedule for 2018¹⁷. The costs of AEs and end-of-life
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31 134 care were derived from the published literature ¹³.

32 33 135 **2.4 Outcome measures**

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36 136 The outcome indicator of the study was QALYs, which is defined by the patient's life years and
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38 137 health utility. In accordance with the approach of Anna Oh et al ¹⁸, we also considered the disutility of AE.
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40 138 Baseline utility and disutility values were referenced in the published literature (Table 1 near here) ^{19 20}.

41 42 139 **2.5 Analysis**

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45 140 The uncertainty of the parameters was evaluated by one-way sensitivity analysis and probabilistic
46
47 141 sensitivity analysis, through the use of tornado diagrams and Monte Carlo simulation respectively. The
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49 142 beta distribution was applied for the utilities, and the lognormal distribution was applied for the cost.
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51 143 Utilities were varied over their 95% CIs. In general, the upper and lower limits of the parameters were
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53 144 taken from the literature, and if otherwise, upper and lower limits of 25% were set. All baseline values
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55 145 and ranges for variables are shown in Table 1.

56 57 146 **2.6 Patient and public involvement**

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5 147 No patients or public were involved in the study.
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7 148 **3 Results**

9 149 **3.1 Base case analysis**

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13 150 Weibull and exponential models used to fit the survival curves from the clinical trial (supplementary
14
15 151 appendix 1), which show that the decision analysis model established in this study can reflect the clinical
16
17 152 effects very well. In the base case analysis, the lifetime cost of using pembrolizumab plus chemotherapy
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19 153 was \$288,532 compared with \$137,123 for placebo plus chemotherapy. When considering effectiveness,
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21 154 the pembrolizumab plus chemotherapy strategy yielded 1.61 QALYs, compared with 0.83 QALYs for the
22
23 155 placebo plus chemotherapy strategy. The ICER of pembrolizumab plus chemotherapy was calculated as
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25 156 \$194,372/QALY compared with the placebo plus chemotherapy. When pembrolizumab cost \$12.05 and
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27 157 \$31.38/mg, the ICERs approximated the WTP thresholds of \$100,000 and \$150,000/QALY, respectively
28
29 158 (Table2).

30 31 159 **3.2 Sensitivity analysis**

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33
34 160 The tornado diagrams present the results of one-way sensitivity analyses. Obviously, the cost of
35
36 161 pembrolizumab, the cost of subsequent treatment in the placebo-combination group and baseline utility
37
38 162 values of OS were the most relatively sensitive parameters, and the ICER range was from
39
40 163 \$149,680/QALY to \$239,065/QALY (Fig.2). The discount rate, the cost of subsequent treatment in the
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42 164 pembrolizumab-combination group, the cost of pemetrexed, the baseline utility value of PFS and the cost
43
44 165 of AE management had little impact on the model.

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46 166 The cost-effectiveness acceptability curve shows the probabilistic sensitivity analysis results of
47
48 167 different willingness-to-pay (WTP) thresholds (Fig.3). The probability that pembrolizumab combined
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50 168 with chemotherapy is cost-effective increased as WTP increased. The results showed that the probability
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52 169 of pembrolizumab plus chemotherapy being cost-effective was 0% at a WTP threshold of
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54 170 \$130,000/QALY. If WTP threshold is \$192,000/QALY, the pembrolizumab plus chemotherapy strategy
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56 171 show a 50% chance cost-effectiveness (Fig.3).

57 172 **4 Discussion**

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5 173 We performed a cost-effectiveness analysis of pembrolizumab in addition to chemotherapy in
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7 174 previously untreated metastatic NSCLC. Based on our model, the ICER for pembrolizumab plus
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9 175 chemotherapy was estimated as \$194,372/QALY compared with the placebo plus chemotherapy. The
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11 176 results showed that the probability of pembrolizumab plus chemotherapy being cost-effective was 0% at a
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13 177 WTP threshold of \$130,000/QALY.

14
15 178 There are many other studies that have analyzed the cost-effectiveness of pembrolizumab for
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17 179 advanced NSCLC in different setting^{13 14 21-24}. In the KEYNOTE-024 trial, pembrolizumab demonstrated
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19 180 the incremental survival benefits and better safety profile versus chemotherapy for first-line treatment of
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21 181 PD-L1 -positive ($\geq 50\%$) metastatic NSCLC patients²⁵. Based on the KEYNOTE-024 trial, a US-based
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23 182 study found that pembrolizumab was cost effective, with an ICER of \$97,621/QALY¹⁴, a study by
24
25 183 Georgieva et al. demonstrated that pembrolizumab monotherapy was cost-effective in the US but not the
26
27 184 UK²⁴, a study by Hu X et al. conducted in the UK demonstrated that pembrolizumab plus chemotherapy
28
29 185 was not cost-effective, with an ICER of £86,913/QALY²³, and a French study found that pembrolizumab
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31 186 appears cost-effective²². Our results differ from the above results may be due to different health systems
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33 187 and costs in different countries, which leads to different cost-effectiveness conclusions. Based on the
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35 188 KEYNOTE-010 trial, a study analysed the cost-effectiveness of pembrolizumab and docetaxel as
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37 189 second-line treatment for PD-L1 positive advanced NSCLC from the US third-party payer perspective.
38
39 190 The results showed that the ICER was \$168,619/QALY, which was cost-effective at a threshold of three
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41 191 times GDP per capita (\$171,660)¹³. These data provide reference value for evaluating the total cost of
42
43 192 therapy and the value of regimens for advanced NSCLC.

44
45 193 Our one-way sensitivity analysis revealed that the cost of pembrolizumab had a great influence on
46
47 194 the results of the study. High drug prices are the result of the monopoly of pharmaceutical companies and
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49 195 restrictions on the negotiating power of the payer²⁶. This can be addressed by providing more meaningful
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51 196 price negotiation opportunities for payers and providing more evidence of a cost-effectiveness
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53 197 comparison of treatment regimens²⁶. We can also reduce the cost of administration by using personalized
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55 198 dosing. Recent study has shown that personalized dosing (2mg/kg) and fixed dosing (200mg) of
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57 199 pembrolizumab have equivalent efficacy²⁷. Avoiding drug waste is extremely important in an era of
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59 200 value-based cancer therapy²⁷. When our study used 2 mg/kg of pembrolizumab based on the average
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5 201 weight of 82 kg¹⁵, the ICER was reduced to \$171,751. We believe that manufacturers are responsible for
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7 202 providing multiple sizes of vials to minimize the chance of wastage.

8
9 203 However, there are few limitations to our study that deserve consideration. First, we used cost
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11 204 parameters provided by Medicare, which may be lower than private insurers²⁸. Second, the health utility
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13 205 values were taken from other data sources instead of patients who participated in the Keynote 189 trial,
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15 206 which limits the accuracy of our results. Unfortunately, the clinical trial did not report the quality of life.
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17 207 Third, our analysis did not estimate the costs for all AEs in the PFS state, which may lead to
18
19 208 underestimation of AEs costs. However, considering the low incidence, we expect the inclusion of all
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21 209 AEs would not change the conclusions of the present analysis. In addition, our model applied sensitivity
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23 210 analysis to a wide variation of these parameters, and it does not affect the results. Fourth, our analysis was
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25 211 based on the Keynote 189 trial, which excluded patients with sensitizing EGFR or ALK translocation,
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27 212 because they usually used targeted agents as first-line treatment. However in the real-world setting, these
28
29 213 patients with unknown EGFR or ALK translocation were also likely to be received PD-L1 testing and
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31 214 treated with pembrolizumab. Finally, our study directly compared pembrolizumab plus chemotherapy
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33 215 with chemotherapy according to the KEYNOTE-189 trial. Although there are other potential first-line
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35 216 treatments for advanced non-small cell lung cancer, our study did not indirectly compare them because of
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37 217 the lack of convincing trial data and robust head-to-head trial data.

38 218 Overall, the combination of pembrolizumab and chemotherapy for patients with metastatic NSCLC
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40 219 that we studied has high incremental cost and modest incremental benefit. New treatment technology for
41
42 220 tumour is continuously undergoing development, but the price of tumour drugs is also rising dramatically.
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44 221 Based on our analysis, pembrolizumab offers lower value at current cost. The provision of cost-effective
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46 222 care requires new pricing and payment systems to support. The process for approving new drugs and the
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48 223 process of incorporating them into the guidelines must balance costs and benefits, and our research can
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50 224 offer decision-making information for this purpose.

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12
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335 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

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

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338 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

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

340 * Only the cost of pembrolizumab was varied.

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5 360 **Fig.1** State transition diagram. The three circles show three main health states. Patients can transition
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7 361 from “progression-free survival” to “disease progression survival” or “death”

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10 363 **Fig.2** Tornado diagrams. The graphic shows the impact of varying individual model inputs on the
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12 364 cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental
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14 365 cost-effectiveness ratio. NSCLC: non-small cell lung cancer

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18 367 **Fig.3** Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity
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20 368 analysis (for details, see Methods) comparing the cost-effectiveness of
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22 369 pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE:
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24 370 cost-effectiveness. NSCLC: non-small cell lung cancer

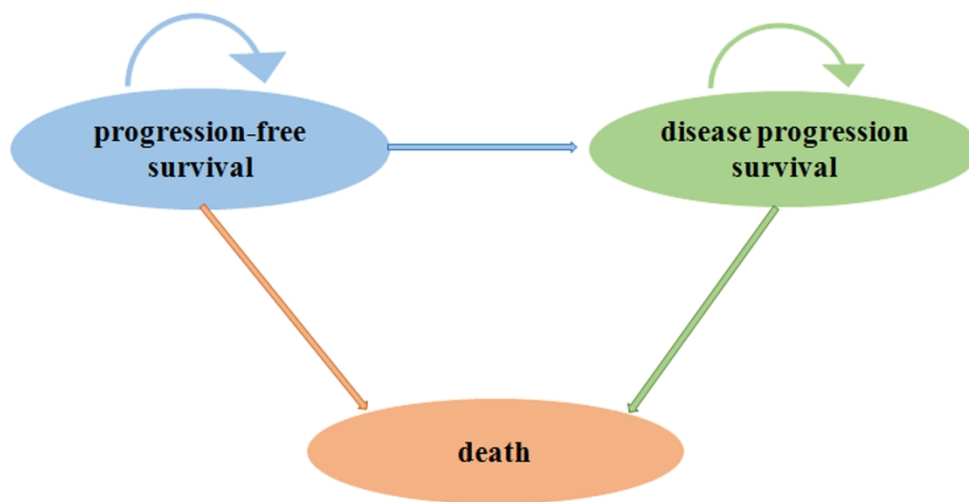


Fig.1 State transition diagram. The three circles show three main health states. Patients can transition from "progression-free survival" to "disease progression survival" or "death"

82x45mm (600 x 600 DPI)

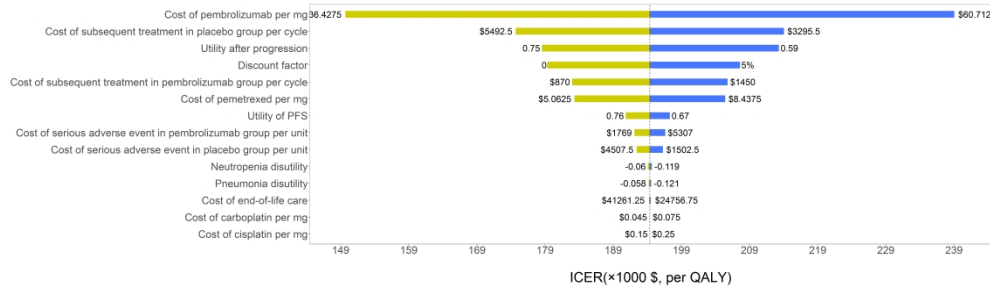


Fig.2 Tornado diagrams. The graphic shows the impact of varying individual model inputs on the cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental cost-effectiveness ratio. NSCLC: non-small cell lung cancer

889x254mm (300 x 300 DPI)

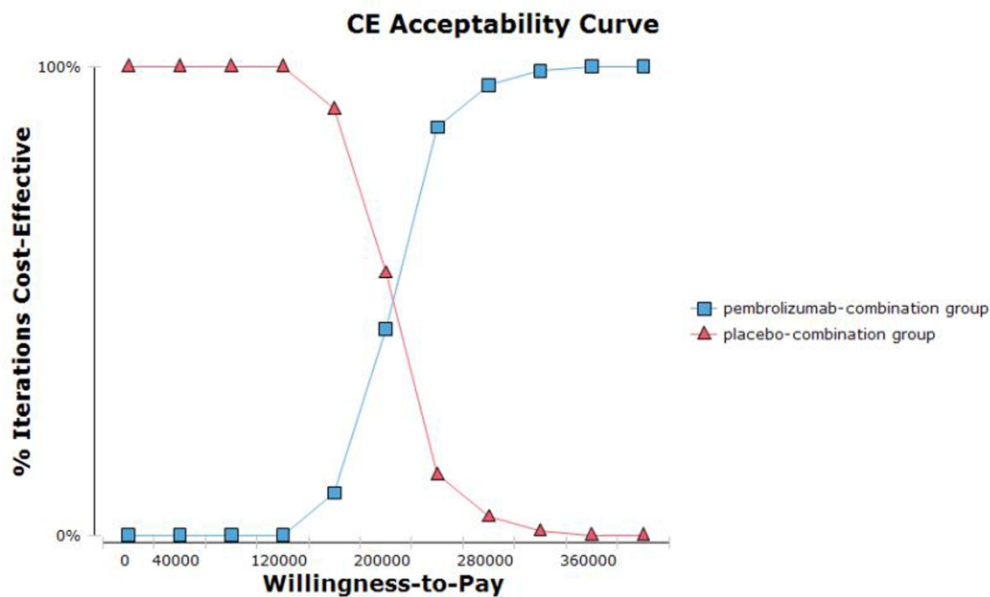
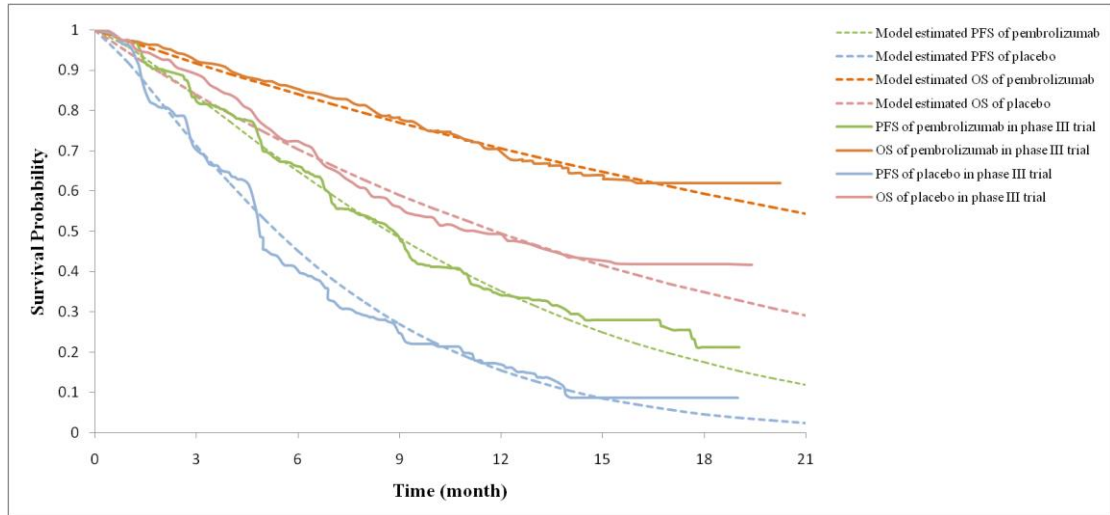


Fig.3 Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity analysis (for details, see Methods) comparing the cost-effectiveness of pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE: cost-effectiveness. NSCLC: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

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 1

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	<i>Single study-based estimates</i> : Describe fully the design features of the single effectiveness study and why the single	

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 2

		study was a sufficient source of clinical effectiveness data.	
	11b	<i>Synthesis-based estimates</i> : 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	<i>Single study-based economic evaluation</i> : 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	<i>Model-based economic evaluation</i> : 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

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 3

		applicable, report incremental cost-effectiveness ratios.	
Characterizing uncertainty	20a	<i>Single study-based economic evaluation</i> : 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	<i>Model-based economic evaluation</i> : 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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BMJ Open

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

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Date Submitted by the Author:	12-Nov-2019
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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Oncology
Keywords:	Immunology < BASIC SCIENCES, CHEMOTHERAPY, HEALTH ECONOMICS

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4 **1 Cost-effectiveness analysis of pembrolizumab plus chemotherapy for previously**
5 **2 untreated metastatic non-small-cell lung cancer in the United States**

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9 3 *Xiaohui Zeng^{c,§}, Xiaomin Wan^{a,§}, Liubao Peng^a, Ye Peng^a, Fang Ma^b, Qiao Liu^a, Chongqing Tan^{a,*}*

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35 9 **Word count:** 1821.
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33 Abstract

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

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

41 **Setting:** The US-payer perspective.

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

44 **Interventions:** Pembrolizumab plus chemotherapy versus chemotherapy.

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

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

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

54 Article Summary

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

67 **1 Introduction**

68 Globally, lung cancer had an incidence rate of 27.4 per 100,000 and a mortality rate of 23.1 per
69 100,000 in 2018 ¹, and non-small cell lung cancer (NSCLC) accounted for the vast majority of these cases
70 ². Multiple drug regimens are available for the treatment of advanced NSCLC, including platinum based
71 combination chemotherapy, anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI),
72 epidermal growth factor receptor (EGFR)TKI and immune checkpoint inhibitors². Immune checkpoint
73 inhibitors showed higher efficacy and less toxicity compared to other therapies ³.

74 A new era of treating advanced NSCLC is upon us after the emergence of immunosuppressive
75 agents ⁴. Immune checkpoint inhibitors improve antitumor immunity by inhibiting programmed death
76 1(PD-1) receptor or programmed cell death ligand 1 (PD-L1) ^{2 5-7}. Pembrolizumab, a PD-1 inhibitor, was
77 approved by the US Food and Drug Administration (FDA) for treatment of advanced NSCLC in 2015 ⁸
78 ⁹.The Keynote-189 clinical trial showed pembrolizumab in combination with pemetrexed plus carboplatin
79 or cisplatin could extended progression-free survival (PFS) by 3.9 months for patients with metastatic
80 NSCLC without sensitizing ALK or EGFR mutations ¹⁰.

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

86 **2 Material and methods**

87 **2.1 Decision model**

88 A Markov model was built to simulate the flow process of patient morbidity, treatment, and
89 survival for previously untreated metastatic NSCLC, using three states, namely PFS state, disease
90 progression survival state, and death (Fig.1).All patients entranced the model in the PFS state, with
91 the treatment of pemetrexed combined platinum plus pembrolizumab or placebo. Patients who
92 experienced progression could receive carboplatin plus pemetrexed, docetaxel plus ramucirumab,
93 docetaxel monotherapy, nivolumab or pembrolizumab, because these regimens were used most in

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5 94 the Keynote-189 trial ¹⁰. All patients were assumed to receive end-of-life care before death.

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7 95 Each health state was assigned a health utility from published studies. Only direct costs were
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9 96 considered and adapted for 2018 US dollars using the Medical Care Consumer Price Index. All costs and
10
11 97 health outcomes were discounted at an annual discount rate of 3% ¹¹. The model simulated a 20-year
12
13 98 period and each model cycle represented 21 days because in the clinical trial patients received
14
15 99 pembrolizumab plus chemotherapy every 3 weeks ¹⁰. The primary outputs of the Markov model included
16
17 100 cost and quality-adjusted life years (QALYs), which were applied to estimate the incremental
18
19 101 cost-effectiveness ratio (ICER). All analyses were performed in TreeAge pro 2018 software
20
21 102 (<https://www.treeage.com>).

23 103 **2.2 Model probabilities**

24
25 104 The probability of transition of disease progression and from any state to death were from the
26
27 105 survival curve of pembrolizumab or placebo combined with chemotherapy in the keynote-189 trial ¹⁰. We
28
29 106 used the GetData Graph Digitizer software (version 2.25) to extract the data points of the Kaplan-Meier
30
31 107 curves. According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC),
32
33 108 the PFS data points were fitted by a Weibull distribution, and overall survival (OS) data points were fitted
34
35 109 with an exponential distribution ¹². The distribution parameters were calculated using the method of
36
37 110 Hoyle et al ¹². Finally, the PFS and OS rates of each cycle were estimated by $\exp(-\lambda t^\gamma)$ and $\exp(-\lambda t)$,
38
39 111 respectively, where λ is the scale parameter, γ is the shape parameter, and t is survival time (Table 1 near
40
41 112 here).

43 113 **2.3 Costs**

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45
46 114 Only direct costs, including the costs of the drug, premedication, administration and management of
47
48 115 serious adverse events (AEs) (Table 1 near here), were considered in our evaluation. In the PFS state, the
49
50 116 cost of the intravenous drug for 3-week cycle was based on the following doses: pembrolizumab
51
52 117 200mg/cycle, pemetrexed 500mg/m², cisplatin 75 mg/m² and carboplatin 400 mg/m².

53
54 118 The model considered the hospitalization cost of patients with AE \geq grade 3, and the incidence
55
56 119 rate exceeded 5% because these AEs were of great concern to clinicians¹³. And then the incidence rates of
57
58 120 neutropenia and pneumonia from the Keynote-189 trial, were used to calculate the cost of AEs treatments
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5 121 ¹⁰.

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7 122 Based on the Keynote-189 trial ¹⁰, 30.5% of the patients in the pembrolizumab plus chemotherapy
8
9 123 group and 46.6% in the placebo plus chemotherapy group received subsequent therapy after disease
10
11 124 progression. Among patients in the pembrolizumab plus chemotherapy group, 3% received carboplatin
12
13 125 plus pemetrexed, 2.3% received docetaxel plus ramucirumab, 17.8% received docetaxel, 4% received
14
15 126 nivolumab and 3.4% received continuation maintenance treatment of pembrolizumab; among patients in
16
17 127 the placebo plus chemotherapy group, 1.7% received docetaxel, 7.8% received nivolumab and 38%
18
19 128 received crossover treatment with pembrolizumab. Patients who died accrued the cost of terminal care,
20
21 129 including hospitalization, palliative chemotherapy, doctor consultation, laboratory, and diagnostic tests,
22
23 130 according to the published literature ¹⁴.

24
25 131 The mean value of a body-surface area and body weight are 1.84m² and 82kg, respectively ^{13 15}. The
26
27 132 drug costs were taken from the Centers for Medicare and Medicaid Services¹⁶. Administration costs were
28
29 133 calculated according to the Medicare physician fee schedule for 2018¹⁷. The costs of AEs and end-of-life
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31 134 care were derived from the published literature ¹³.

32 135 **2.4 Outcome measures**

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36 136 The outcome indicator of the study was QALYs, which is defined by the patient's life years and
37
38 137 health utility. In accordance with the approach of Anna Oh et al ¹⁸, we also considered the disutility of AE.
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40 138 Baseline utility and disutility values were referenced in the published literature (Table 1 near here) ^{19 20}.

41 42 139 **2.5 Analysis**

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45 140 The uncertainty of the parameters was evaluated by one-way sensitivity analysis and probabilistic
46
47 141 sensitivity analysis, through the use of tornado diagrams and Monte Carlo simulation respectively. The
48
49 142 beta distribution was applied for the utilities, and the lognormal distribution was applied for the cost.
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51 143 Utilities were varied over their 95% CIs. In general, the upper and lower limits of the parameters were
52
53 144 taken from the literature, and if otherwise, upper and lower limits of 25% were set. All baseline values
54
55 145 and ranges for variables are shown in Table 1.

56 57 146 **2.6 Patient and public involvement**

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5 147 No patients or public were involved in the study.
6

7 148 **3 Results**
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10 149 **3.1 Base case analysis**
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12
13 150 Weibull and exponential models used to fit the survival curves from the clinical trial (supplementary
14
15 151 appendix 1), which show that the decision analysis model established in this study can reflect the clinical
16
17 152 effects very well. In the base case analysis, the lifetime cost of using pembrolizumab plus chemotherapy
18
19 153 was \$288,532 compared with \$137,123 for placebo plus chemotherapy. When considering effectiveness,
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21 154 the pembrolizumab plus chemotherapy strategy yielded 1.61 QALYs, compared with 0.83 QALYs for the
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23 155 placebo plus chemotherapy strategy. The ICER of pembrolizumab plus chemotherapy was calculated as
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25 156 \$194,372/QALY compared with the placebo plus chemotherapy. When pembrolizumab cost \$12.05 and
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27 157 \$31.38/mg, the ICERs approximated the WTP thresholds of \$100,000 and \$150,000/QALY, respectively
28
29 158 (Table2).
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31 159 **3.2 Sensitivity analysis**
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34 160 The tornado diagrams present the results of one-way sensitivity analyses. Obviously, the cost of
35
36 161 pembrolizumab, the cost of subsequent treatment in the placebo-combination group and baseline utility
37
38 162 values of OS were the most relatively sensitive parameters, and the ICER range was from
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40 163 \$149,680/QALY to \$239,065/QALY (Fig.2). The discount rate, the cost of subsequent treatment in the
41
42 164 pembrolizumab-combination group, the cost of pemetrexed, the baseline utility value of PFS and the cost
43
44 165 of AE management had little impact on the model.
45

46 166 The cost-effectiveness acceptability curve shows the probabilistic sensitivity analysis results of
47
48 167 different willingness-to-pay (WTP) thresholds (Fig.3). The probability that pembrolizumab combined
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50 168 with chemotherapy is cost-effective increased as WTP increased. The results showed that the probability
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52 169 of pembrolizumab plus chemotherapy being cost-effective was 0% at a WTP threshold of
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54 170 \$130,000/QALY. If WTP threshold is \$192,000/QALY, the pembrolizumab plus chemotherapy strategy
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56 171 show a 50% chance cost-effectiveness (Fig.3).
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58 172 The results of the subgroup analysis showed that pembrolizumab combined with chemotherapy was
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60 173 the most cost-effective (36%) for patients who had never smoked at a WTP threshold of \$100,000. When

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4 174 the WTP threshold was \$150,000, the probability of pembrolizumab combined with chemotherapy being
5 175 cost-effective in the subgroup of never-smoking and female patients was 100% (Supplementary Appendix
6 176 2).

9 177 **4 Discussion**

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11
12 178 We performed a cost-effectiveness analysis of pembrolizumab in addition to chemotherapy in
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14 179 previously untreated metastatic NSCLC. Based on our model, the ICER for pembrolizumab plus
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16 180 chemotherapy was estimated as \$194,372/QALY compared with the placebo plus chemotherapy. The
17
18 181 results showed that the probability of pembrolizumab plus chemotherapy being cost-effective was 0% at a
19
20 182 WTP threshold of \$130,000/QALY.

21
22 183 There are many other studies that have analyzed the cost-effectiveness of pembrolizumab for
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24 184 advanced NSCLC in different setting^{13 14 21-24}. In the KEYNOTE-024 trial, pembrolizumab demonstrated
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26 185 the incremental survival benefits and better safety profile versus chemotherapy for first-line treatment of
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28 186 PD-L1 -positive ($\geq 50\%$) metastatic NSCLC patients²⁵, Based on the KEYNOTE-024 trial, a US-based
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30 187 study found that pembrolizumab was cost effective, with an ICER of \$97,621/QALY¹⁴, a study by
31
32 188 Georgieva et al. demonstrated that pembrolizumab monotherapy was cost-effective in the US but not the
33
34 189 UK²⁴, a study by Hu X et al. conducted in the UK demonstrated that pembrolizumab plus chemotherapy
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36 190 was not cost-effective, with an ICER of £86,913/QALY²³, and a French study found that pembrolizumab
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38 191 appears cost-effective²². Our results differ from the above results may be due to different health systems
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40 192 and costs in different countries, which leads to different cost-effectiveness conclusions. Based on the
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42 193 KEYNOTE-010 trial, a study analysed the cost-effectiveness of pembrolizumab and docetaxel as
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44 194 second-line treatment for PD-L1 positive advanced NSCLC from the US third-party payer perspective.
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46 195 The results showed that the ICER was \$168,619/QALY, which was cost-effective at a threshold of three
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48 196 times GDP per capita (\$171,660)¹³. These data provide reference value for evaluating the total cost of
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50 197 therapy and the value of regimens for advanced NSCLC.

51 198 Our one-way sensitivity analysis revealed that the cost of pembrolizumab had a great influence on
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53 199 the results of the study. High drug prices are the result of the monopoly of pharmaceutical companies and
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55 200 restrictions on the negotiating power of the payer²⁶. This can be addressed by providing more meaningful
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57 201 price negotiation opportunities for payers and providing more evidence of a cost-effectiveness
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59 202 comparison of treatment regimens²⁶. We can also reduce the cost of administration by using personalized
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5 203 dosing. Recent study has shown that personalized dosing (2mg/kg) and fixed dosing (200mg) of
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7 204 pembrolizumab have equivalent efficacy ²⁷. Avoiding drug waste is extremely important in an era of
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9 205 value-based cancer therapy ²⁷. When our study used 2 mg/kg of pembrolizumab based on the average
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11 206 weight of 82 kg ¹⁵, the ICER was reduced to \$171,751. We believe that manufacturers are responsible for
12
13 207 providing multiple sizes of vials to minimize the chance of wastage.

14
15 208 However, there are few limitations to our study that deserve consideration. First, we used cost
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17 209 parameters provided by Medicare, which may be lower than private insurers ²⁸. Second, the health utility
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19 210 values were taken from other data sources instead of patients who participated in the Keynote 189 trial,
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21 211 which limits the accuracy of our results. Unfortunately, the clinical trial did not report the quality of life.
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23 212 Third, our analysis did not estimate the costs for all AEs in the PFS state, which may lead to
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25 213 underestimation of AEs costs. However, considering the low incidence, we expect the inclusion of all
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27 214 AEs would not change the conclusions of the present analysis. In addition, our model applied sensitivity
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29 215 analysis to a wide variation of these parameters, and it does not affect the results. Fourth, our analysis was
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31 216 based on the Keynote 189 trial, which excluded patients with sensitizing EGFR or ALK translocation,
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33 217 because they usually used targeted agents as first-line treatment. However in the real-world setting, these
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35 218 patients with unknown EGFR or ALK translocation were also likely to be received PD-L1 testing and
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37 219 treated with pembrolizumab. Finally, our study directly compared pembrolizumab plus chemotherapy
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39 220 with chemotherapy according to the KEYNOTE-189 trial. Although there are other potential first-line
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41 221 treatments for advanced non-small cell lung cancer, our study did not indirectly compare them because of
42
43 222 the lack of convincing trial data and robust head-to-head trial data.

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45 223 Overall, the combination of pembrolizumab and chemotherapy for patients with metastatic NSCLC
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47 224 that we studied has high incremental cost and modest incremental benefit. New treatment technology for
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49 225 tumour is continuously undergoing development, but the price of tumour drugs is also rising dramatically.
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51 226 Based on our analysis, pembrolizumab offers lower value at current cost. The provision of cost-effective
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53 227 care requires new pricing and payment systems to support. The process for approving new drugs and the
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55 228 process of incorporating them into the guidelines must balance costs and benefits, and our research can
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57 229 offer decision-making information for this purpose.

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236 Analysis and interpretation of the data: Liubao Peng, Ye Peng, Qiao Liu; The drafting and revising of the
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243 **Ethics statement:** Ethical approval was not necessary, because our economic evaluation is based on a
244 mathematical model analysis, and does not contain any studies with human participants or animals
245 performed.

246 **Data sharing statement:** No additional data available.

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337 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

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

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340 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

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

342 * Only the cost of pembrolizumab was varied.

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5 362 **Fig.1** State transition diagram. The three circles show three main health states. Patients can transition
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7 363 from “progression-free survival” to “disease progression survival” or “death”

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11 365 **Fig.2** Tornado diagrams. The graphic shows the impact of varying individual model inputs on the
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13 366 cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental
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15 367 cost-effectiveness ratio. NSCLC: non-small cell lung cancer

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19 369 **Fig.3** Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity
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21 370 analysis (for details, see Methods) comparing the cost-effectiveness of
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23 371 pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE:
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25 372 cost-effectiveness. NSCLC: non-small cell lung cancer

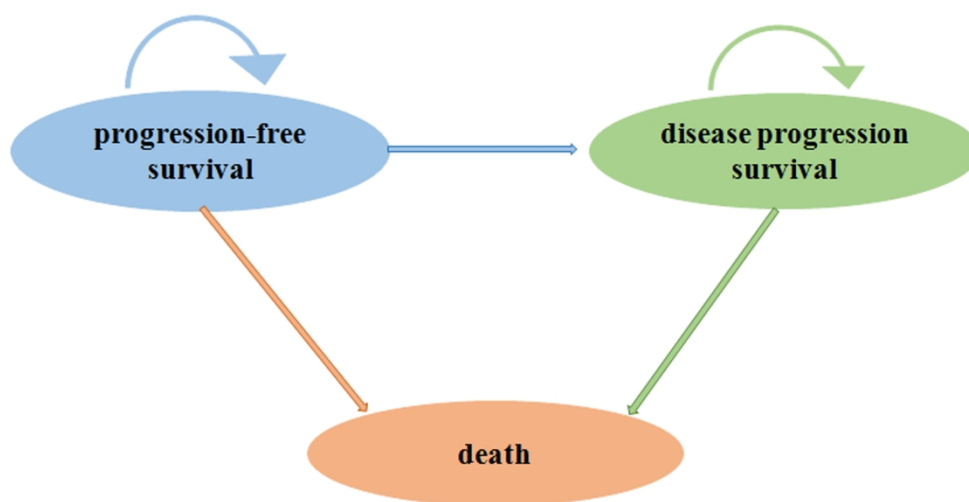


Fig.1 State transition diagram. The three circles show three main health states. Patients can transition from "progression-free survival" to "disease progression survival" or "death"

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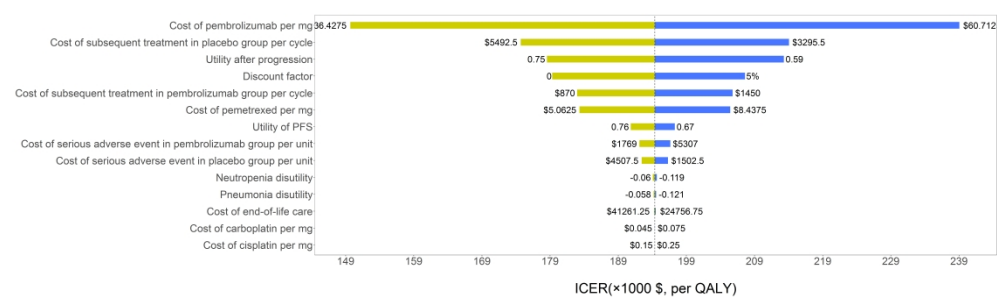


Fig.2 Tornado diagrams. The graphic shows the impact of varying individual model inputs on the cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental cost-effectiveness ratio. NSCLC: non-small cell lung cancer

889x254mm (300 x 300 DPI)

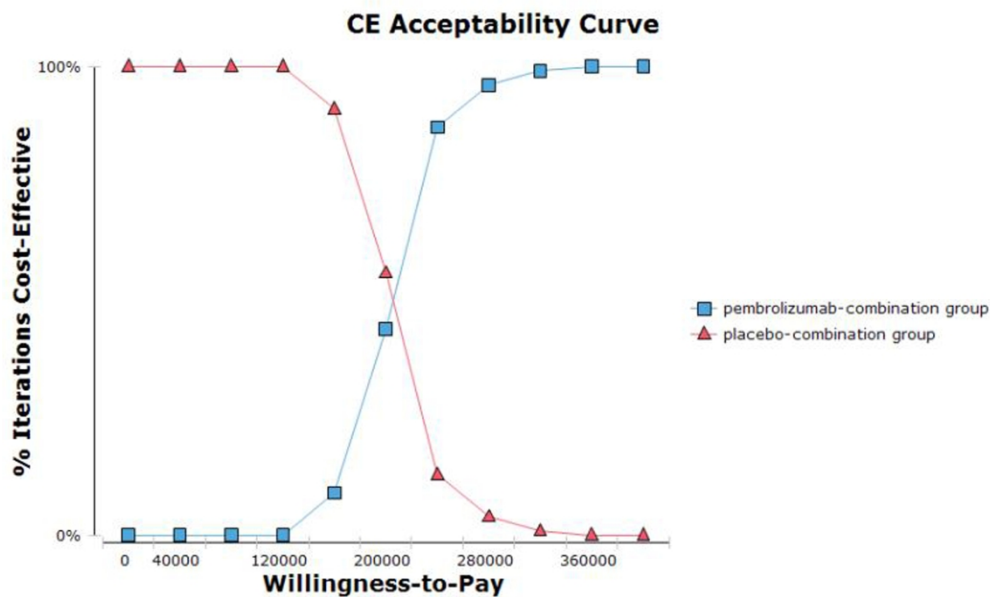
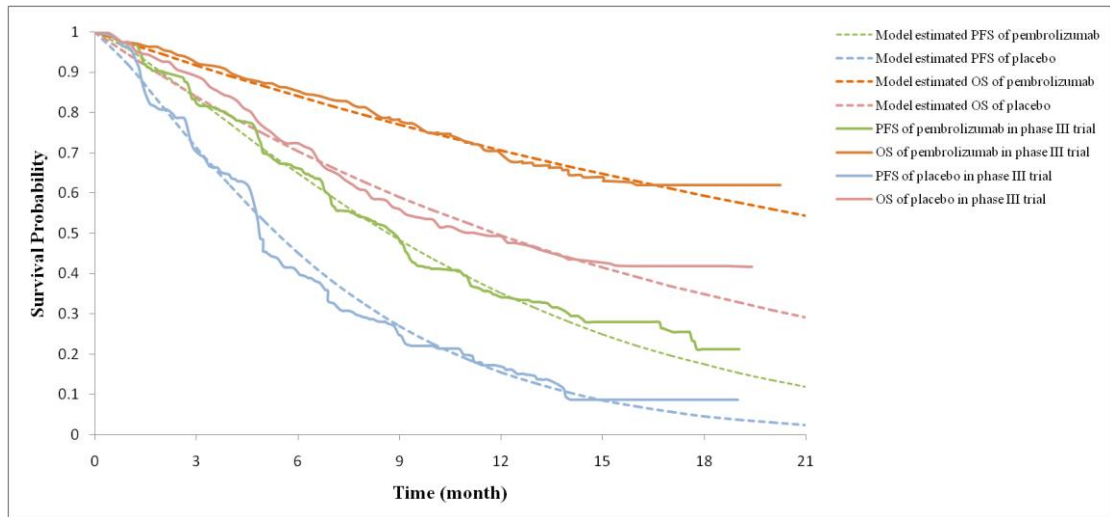


Fig.3 Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity analysis (for details, see Methods) comparing the cost-effectiveness of pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE: cost-effectiveness. NSCLC: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

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.

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.

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 1

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	<i>Single study-based estimates</i> : Describe fully the design features of the single effectiveness study and why the single	

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 2

		study was a sufficient source of clinical effectiveness data.	
	11b	<i>Synthesis-based estimates</i> : 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	<i>Single study-based economic evaluation</i> : 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	<i>Model-based economic evaluation</i> : 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

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 3

		applicable, report incremental cost-effectiveness ratios.	
Characterizing uncertainty	20a	<i>Single study-based economic evaluation</i> : 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	<i>Model-based economic evaluation</i> : 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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BMJ Open

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

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Secondary Subject Heading:	Oncology
Keywords:	Immunology < BASIC SCIENCES, CHEMOTHERAPY, HEALTH ECONOMICS

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Manuscripts

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4 **1 Cost-effectiveness analysis of pembrolizumab plus chemotherapy for previously**
5 **2 untreated metastatic non-small-cell lung cancer in the United States**

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9 3 *Xiaohui Zeng^{c,§}, Xiaomin Wan^{a,§}, Liubao Peng^a, Ye Peng^a, Fang Ma^b, Qiao Liu^a, Chongqing Tan^{a,*}*

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4 33 **Abstract**
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6 34 **Objectives:** Evaluating the cost-effectiveness of pembrolizumab plus standard chemotherapy in the
7 first-line setting for patients with metastatic non-small cell lung cancer (NSCLC) from the US-payer
8 perspective.
9 36

10 37 **Design:** A Markov model was constructed to analyse the cost-effectiveness of pembrolizumab plus
11 chemotherapy in the first-line treatment of metastatic NSCLC. Health outcomes were estimated in
12 quality-adjusted life-years (QALYs). The cost information was from Medicare in 2018. One-way and
13 probabilistic sensitivity analyses examined the impact of uncertainty and assumptions on the results.
14 40

15 41 **Setting:** The US-payer perspective.

16 42 **Participants:** A hypothetical US cohort of patients with previously untreated metastatic nonsquamous
17 NSCLC without EGFR or ALK mutations.
18 43

19 44 **Interventions:** Pembrolizumab plus chemotherapy versus chemotherapy.

20 45 **Primary outcome measures:** Costs, QALYs, incremental cost-effectiveness ratio (ICER) of
21 pembrolizumab plus chemotherapy expressed as cost per QALY gained compared with chemotherapy
22 46

23 47 **Results:** The base-case analysis demonstrated that pembrolizumab plus chemotherapy provided an
24 additional 0.78 QALYs at incremental cost of \$151,409, resulting in an ICER of \$194,372/QALY. The
25 ICER for pembrolizumab plus chemotherapy was > \$149,680/QALY in all of our univariable and
26 probabilistic sensitivity analyses.
27 50

28 51 **Conclusions:** Pembrolizumab in addition to chemotherapy provides modest incremental benefit at high
29 incremental cost per QALY for the treatment of previously untreated metastatic NSCLC.
30 52
31 53

32
33 54 **Article Summary**
34

- 35 55 1. The study strengths of this model-based economic assessment include that it is based on rigorous
36 randomized controlled trials.
37 56
38 57 2. From a US payer perspective, the cost and outcome data included in the model are collected for
39 analysis.
40 58
41 59 3. The limitation of this study is that because of the limited time scale of the model and the lack of
42 long-term data, not all potential outcomes are included.
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67 **1 Introduction**

68 Globally, lung cancer had an incidence rate of 27.4 per 100,000 and a mortality rate of 23.1 per
69 100,000 in 2018 ¹, and non-small cell lung cancer (NSCLC) accounted for the vast majority of these cases
70 ². Multiple drug regimens are available for the treatment of advanced NSCLC, including platinum based
71 combination chemotherapy, anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI),
72 epidermal growth factor receptor (EGFR)TKI and immune checkpoint inhibitors². Immune checkpoint
73 inhibitors showed higher efficacy and less toxicity compared to other therapies ³.

74 A new era of treating advanced NSCLC is upon us after the emergence of immunosuppressive
75 agents ⁴. Immune checkpoint inhibitors improve antitumor immunity by inhibiting programmed death
76 1(PD-1) receptor or programmed cell death ligand 1 (PD-L1) ^{2 5-7}. Pembrolizumab, a PD-1 inhibitor, was
77 approved by the US Food and Drug Administration (FDA) for treatment of advanced NSCLC in 2015 ⁸
78 ⁹.The Keynote-189 clinical trial showed pembrolizumab in combination with pemetrexed plus carboplatin
79 or cisplatin could extended progression-free survival (PFS) by 3.9 months for patients with metastatic
80 NSCLC without sensitizing ALK or EGFR mutations ¹⁰.

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

86 **2 Material and methods**

87 **2.1 Decision model**

88 A Markov model was built to simulate the flow process of patient morbidity, treatment, and
89 survival for previously untreated metastatic NSCLC, using three states, namely PFS state, disease
90 progression survival state, and death (Fig.1).All patients entranced the model in the PFS state, with
91 the treatment of pemetrexed combined platinum plus pembrolizumab or placebo. Patients who
92 experienced progression could receive carboplatin plus pemetrexed, docetaxel plus ramucirumab,
93 docetaxel monotherapy, nivolumab or pembrolizumab, because these regimens were used most in

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5 94 the Keynote-189 trial ¹⁰. All patients were assumed to receive end-of-life care before death.

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7 95 Each health state was assigned a health utility from published studies. Only direct costs were
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9 96 considered and adapted for 2018 US dollars using the Medical Care Consumer Price Index. All costs and
10
11 97 health outcomes were discounted at an annual discount rate of 3% ¹¹. The model simulated a 20-year
12
13 98 period and each model cycle represented 21 days because in the clinical trial patients received
14
15 99 pembrolizumab plus chemotherapy every 3 weeks ¹⁰. The primary outputs of the Markov model included
16
17 100 cost and quality-adjusted life years (QALYs), which were applied to estimate the incremental
18
19 101 cost-effectiveness ratio (ICER). All analyses were performed in TreeAge pro 2018 software
20
21 102 (<https://www.treeage.com>).

23 103 **2.2 Model probabilities**

24
25 104 The probability of transition of disease progression and from any state to death were from the
26
27 105 survival curve of pembrolizumab or placebo combined with chemotherapy in the keynote-189 trial ¹⁰. We
28
29 106 used the GetData Graph Digitizer software (version 2.25) to extract the data points of the Kaplan-Meier
30
31 107 curves. According to the Akaike information criterion (AIC) and Bayesian information criterion (BIC),
32
33 108 the PFS data points were fitted by a Weibull distribution, and overall survival (OS) data points were fitted
34
35 109 with an exponential distribution ¹². The distribution parameters were calculated using the method of
36
37 110 Hoyle et al ¹². Finally, the PFS and OS rates of each cycle were estimated by $\exp(-\lambda t^\gamma)$ and $\exp(-\lambda t)$,
38
39 111 respectively, where λ is the scale parameter, γ is the shape parameter, and t is survival time (Table 1 near
40
41 112 here).

43 113 **2.3 Costs**

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45
46 114 Only direct costs, including the costs of the drug, premedication, administration and management of
47
48 115 serious adverse events (AEs) (Table 1 near here), were considered in our evaluation. In the PFS state, the
49
50 116 cost of the intravenous drug for 3-week cycle was based on the following doses: pembrolizumab
51
52 117 200mg/cycle, pemetrexed 500mg/m², cisplatin 75 mg/m² and carboplatin 400 mg/m².

53
54 118 The model considered the hospitalization cost of patients with AE \geq grade 3, and the incidence
55
56 119 rate exceeded 5% because these AEs were of great concern to clinicians¹³. And then the incidence rates of
57
58 120 neutropenia and pneumonia from the Keynote-189 trial, were used to calculate the cost of AEs treatments
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5 121 ¹⁰.

6 122 Based on the Keynote-189 trial ¹⁰, 30.5% of the patients in the pembrolizumab plus chemotherapy
7 123 group and 46.6% in the placebo plus chemotherapy group received subsequent therapy after disease
8 124 progression. Among patients in the pembrolizumab plus chemotherapy group, 3% received carboplatin
9 125 plus pemetrexed, 2.3% received docetaxel plus ramucirumab, 17.8% received docetaxel, 4% received
10 126 nivolumab and 3.4% received continuation maintenance treatment of pembrolizumab; among patients in
11 127 the placebo plus chemotherapy group, 1.7% received docetaxel, 7.8% received nivolumab and 38%
12 128 received crossover treatment with pembrolizumab. Patients who died accrued the cost of terminal care,
13 129 including hospitalization, palliative chemotherapy, doctor consultation, laboratory, and diagnostic tests,
14 130 according to the published literature ¹⁴.

15 131 The mean value of a body-surface area and body weight are 1.84m² and 82kg, respectively ^{13 15}. The
16 132 drug costs were taken from the Centers for Medicare and Medicaid Services¹⁶. Administration costs were
17 133 calculated according to the Medicare physician fee schedule for 2018¹⁷. The costs of AEs and end-of-life
18 134 care were derived from the published literature ¹³.

19 135 **2.4 Outcome measures**

20 136 The outcome indicator of the study was QALYs, which is defined by the patient's life years and
21 137 health utility. In accordance with the approach of Anna Oh et al ¹⁸, we also considered the disutility of AE.
22 138 Baseline utility and disutility values were referenced in the published literature (Table 1 near here) ^{19 20}.

23 139 **2.5 Analysis**

24 140 The uncertainty of the parameters was evaluated by one-way sensitivity analysis and probabilistic
25 141 sensitivity analysis, through the use of tornado diagrams and Monte Carlo simulation respectively. The
26 142 beta distribution was applied for the utilities, and the lognormal distribution was applied for the cost.
27 143 Utilities were varied over their 95% CIs. In general, the upper and lower limits of the parameters were
28 144 taken from the literature, and if otherwise, upper and lower limits of 25% were set. All baseline values
29 145 and ranges for variables are shown in Table 1.

30 146 **2.6 Patient and public involvement**

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5 147 No patients or public were involved in the study.
6

7 148 **3 Results**

9 149 **3.1 Base case analysis**

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13 150 Weibull and exponential models used to fit the survival curves from the clinical trial (supplementary
14
15 151 appendix 1), which show that the decision analysis model established in this study can reflect the clinical
16
17 152 effects very well. In the base case analysis, the lifetime cost of using pembrolizumab plus chemotherapy
18
19 153 was \$288,532 compared with \$137,123 for placebo plus chemotherapy. When considering effectiveness,
20
21 154 the pembrolizumab plus chemotherapy strategy yielded 1.61 QALYs, compared with 0.83 QALYs for the
22
23 155 placebo plus chemotherapy strategy. The ICER of pembrolizumab plus chemotherapy was calculated as
24
25 156 \$194,372/QALY compared with the placebo plus chemotherapy. When pembrolizumab cost \$12.05 and
26
27 157 \$31.38/mg, the ICERs approximated the WTP thresholds of \$100,000 and \$150,000/QALY, respectively
28
29 158 (Table2).

30 31 159 **3.2 Sensitivity analysis**

32
33
34 160 The tornado diagrams present the results of one-way sensitivity analyses. Obviously, the cost of
35
36 161 pembrolizumab, the cost of subsequent treatment in the placebo-combination group and baseline utility
37
38 162 values of OS were the most relatively sensitive parameters, and the ICER range was from
39
40 163 \$149,680/QALY to \$239,065/QALY (Fig.2). The discount rate, the cost of subsequent treatment in the
41
42 164 pembrolizumab-combination group, the cost of pemetrexed, the baseline utility value of PFS and the cost
43
44 165 of AE management had little impact on the model.

45
46 166 The cost-effectiveness acceptability curve shows the probabilistic sensitivity analysis results of
47
48 167 different willingness-to-pay (WTP) thresholds (Fig.3). The probability that pembrolizumab combined
49
50 168 with chemotherapy is cost-effective increased as WTP increased. The results showed that the probability
51
52 169 of pembrolizumab plus chemotherapy being cost-effective was 0% at a WTP threshold of
53
54 170 \$130,000/QALY. If WTP threshold is \$192,000/QALY, the pembrolizumab plus chemotherapy strategy
55
56 171 show a 50% chance cost-effectiveness (Fig.3).

57 172 The results of the subgroup analysis showed that pembrolizumab combined with chemotherapy was
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59 173 the most cost-effective (36%) for patients who had never smoked at a WTP threshold of \$100,000. When
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4 174 the WTP threshold was \$150,000, the probability of pembrolizumab combined with chemotherapy being
5 175 cost-effective in the subgroup of never-smoking and female patients was 100% (Supplementary Appendix
6 176 2).

9 177 **4 Discussion**

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11
12 178 We performed a cost-effectiveness analysis of pembrolizumab in addition to chemotherapy in
13
14 179 previously untreated metastatic NSCLC. Based on our model, the ICER for pembrolizumab plus
15
16 180 chemotherapy was estimated as \$194,372/QALY compared with the placebo plus chemotherapy. The
17
18 181 results showed that the probability of pembrolizumab plus chemotherapy being cost-effective was 0% at a
19
20 182 WTP threshold of \$130,000/QALY.

21
22 183 There are many other studies that have analyzed the cost-effectiveness of pembrolizumab for
23
24 184 advanced NSCLC in different setting^{13 14 21-24}. In the KEYNOTE-024 trial, pembrolizumab demonstrated
25
26 185 the incremental survival benefits and better safety profile versus chemotherapy for first-line treatment of
27
28 186 PD-L1 -positive ($\geq 50\%$) metastatic NSCLC patients²⁵. Based on the KEYNOTE-024 trial, a US-based
29
30 187 study found that pembrolizumab was cost effective, with an ICER of \$97,621/QALY¹⁴, a study by
31
32 188 Georgieva et al. demonstrated that pembrolizumab monotherapy was cost-effective in the US but not the
33
34 189 UK²⁴, a study by Hu X et al. conducted in the UK demonstrated that pembrolizumab plus chemotherapy
35
36 190 was not cost-effective, with an ICER of £86,913/QALY²³, and a French study found that pembrolizumab
37
38 191 appears cost-effective²². Our results differ from the above results may be due to different health systems
39
40 192 and costs in different countries, which leads to different cost-effectiveness conclusions. Based on the
41
42 193 KEYNOTE-010 trial, a study analysed the cost-effectiveness of pembrolizumab and docetaxel as
43
44 194 second-line treatment for PD-L1 positive advanced NSCLC from the US third-party payer perspective.
45
46 195 The results showed that the ICER was \$168,619/QALY, which was cost-effective at a threshold of three
47
48 196 times GDP per capita (\$171,660)¹³. These data provide reference value for evaluating the total cost of
49
50 197 therapy and the value of regimens for advanced NSCLC.

51 198 Our one-way sensitivity analysis revealed that the cost of pembrolizumab had a great influence on
52
53 199 the results of the study. High drug prices are the result of the monopoly of pharmaceutical companies and
54
55 200 restrictions on the negotiating power of the payer²⁶. This can be addressed by providing more meaningful
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57 201 price negotiation opportunities for payers and providing more evidence of a cost-effectiveness
58
59 202 comparison of treatment regimens²⁶. We can also reduce the cost of administration by using personalized
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5 203 dosing. Recent study has shown that personalized dosing (2mg/kg) and fixed dosing (200mg) of
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7 204 pembrolizumab have equivalent efficacy ²⁷. Avoiding drug waste is extremely important in an era of
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9 205 value-based cancer therapy ²⁷. When our study used 2 mg/kg of pembrolizumab based on the average
10
11 206 weight of 82 kg ¹⁵, the ICER was reduced to \$171,751. We believe that manufacturers are responsible for
12
13 207 providing multiple sizes of vials to minimize the chance of wastage.

14
15 208 However, there are few limitations to our study that deserve consideration. First, we used cost
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17 209 parameters provided by Medicare, which may be lower than private insurers ²⁸. Second, the health utility
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19 210 values were taken from other data sources instead of patients who participated in the Keynote 189 trial,
20
21 211 which limits the accuracy of our results. Unfortunately, the clinical trial did not report the quality of life.
22
23 212 Third, our analysis did not estimate the costs for all AEs in the PFS state, which may lead to
24
25 213 underestimation of AEs costs. However, considering the low incidence, we expect the inclusion of all
26
27 214 AEs would not change the conclusions of the present analysis. In addition, our model applied sensitivity
28
29 215 analysis to a wide variation of these parameters, and it does not affect the results. Fourth, our analysis was
30
31 216 based on the Keynote 189 trial, which excluded patients with sensitizing EGFR or ALK translocation,
32
33 217 because they usually used targeted agents as first-line treatment. However in the real-world setting, these
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35 218 patients with unknown EGFR or ALK translocation were also likely to be received PD-L1 testing and
36
37 219 treated with pembrolizumab. Finally, our study directly compared pembrolizumab plus chemotherapy
38
39 220 with chemotherapy according to the KEYNOTE-189 trial. Although there are other potential first-line
40
41 221 treatments for advanced non-small cell lung cancer, our study did not indirectly compare them because of
42
43 222 the lack of convincing trial data and robust head-to-head trial data.

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45 223 Overall, the combination of pembrolizumab and chemotherapy for patients with metastatic NSCLC
46
47 224 that we studied has high incremental cost and modest incremental benefit. New treatment technology for
48
49 225 tumour is continuously undergoing development, but the price of tumour drugs is also rising dramatically.
50
51 226 Based on our analysis, pembrolizumab offers lower value at current cost. The provision of cost-effective
52
53 227 care requires new pricing and payment systems to support. The process for approving new drugs and the
54
55 228 process of incorporating them into the guidelines must balance costs and benefits, and our research can
56
57 229 offer decision-making information for this purpose.

58 230

231

232

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236 Analysis and interpretation of the data: Liubao Peng, Ye Peng, Qiao Liu; The drafting and revising of the
237 paper: Xiaohui Zeng and Xiaomin Wan; Final approved of manuscript: All authors; all authors agree to
238 be accountable for all aspects of the work.

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242 **Conflict of interest:** None declared.

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

246 **Data sharing statement:** The unit price we used in the article is freely available in Medicare & Medicaid
247 Services ([https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvg](https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html)
248 [SalesPrice/index.html](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
249 published literature on PubMed (Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus
250 Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* 2018; 378(22):2078-92. doi:
251 10.1056/NEJMoa1801005). The datasets generated during the current study are available from the
252 corresponding author on reasonable request.

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336 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

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

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339 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

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

341 * Only the cost of pembrolizumab was varied.

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5 361 **Fig.1** State transition diagram. The three circles show three main health states. Patients can transition
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7 362 from “progression-free survival” to “disease progression survival” or “death”
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10 364 **Fig.2** Tornado diagrams. The graphic shows the impact of varying individual model inputs on the
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12 365 cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental
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14 366 cost-effectiveness ratio. NSCLC: non-small cell lung cancer
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18 368 **Fig.3** Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity
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20 369 analysis (for details, see Methods) comparing the cost-effectiveness of
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22 370 pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE:
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24 371 cost-effectiveness. NSCLC: non-small cell lung cancer
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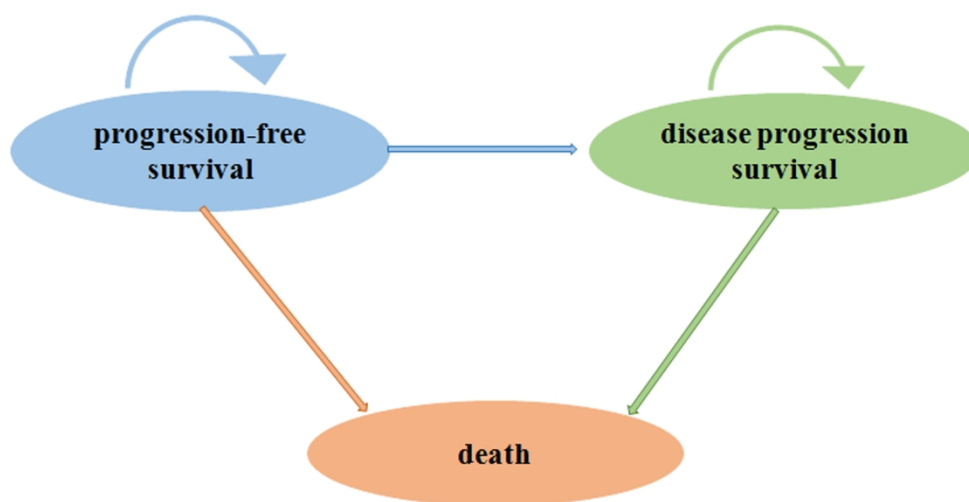


Fig.1 State transition diagram. The three circles show three main health states. Patients can transition from "progression-free survival" to "disease progression survival" or "death"

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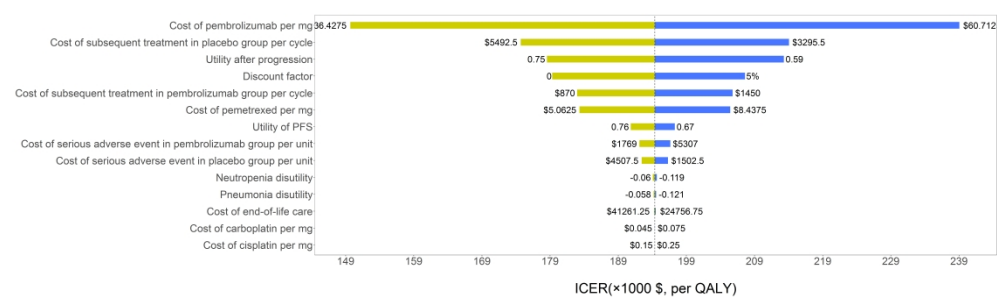


Fig.2 Tornado diagrams. The graphic shows the impact of varying individual model inputs on the cost-effectiveness of pembrolizumab plus chemotherapy for metastatic NSCLC. ICER: incremental cost-effectiveness ratio. NSCLC: non-small cell lung cancer

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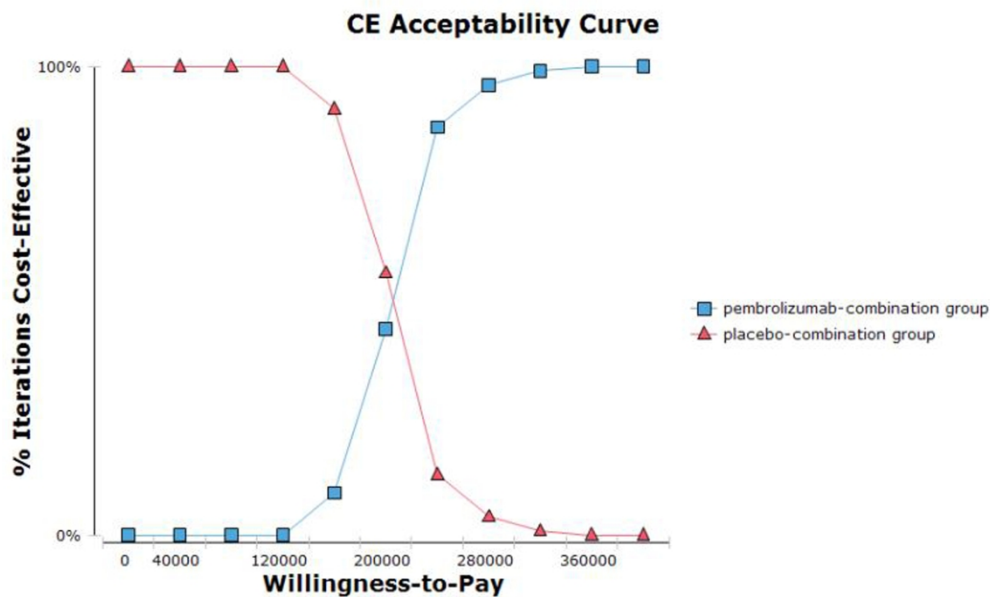
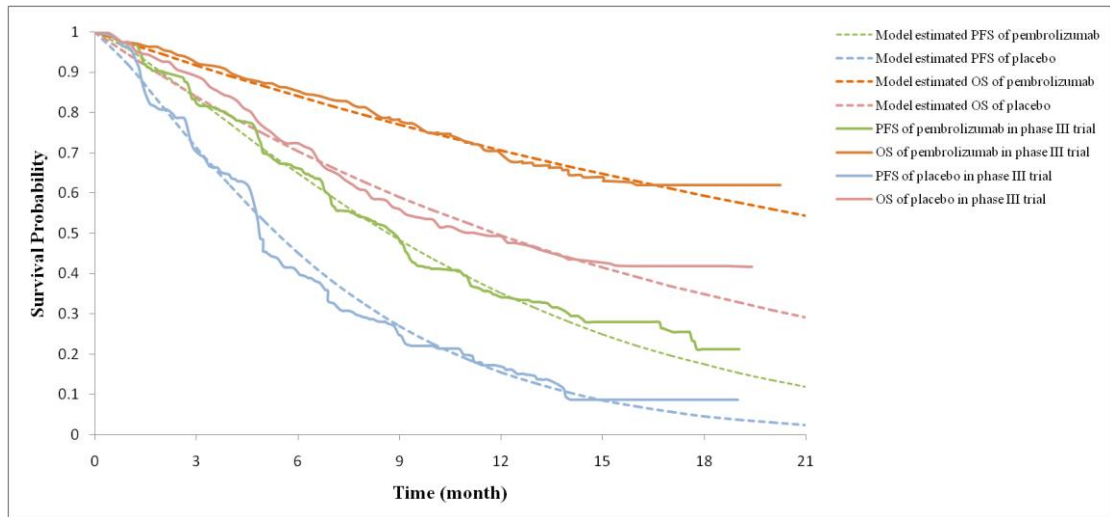


Fig.3 Cost-effectiveness acceptability curve. This plot represents the results of a probabilistic sensitivity analysis (for details, see Methods) comparing the cost-effectiveness of pembrolizumab-pemetrexed-platinum versus placebo-pemetrexed-platinum in metastatic NSCLC. CE: cost-effectiveness. NSCLC: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

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 1

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	<i>Single study-based estimates</i> : Describe fully the design features of the single effectiveness study and why the single	

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 2

		study was a sufficient source of clinical effectiveness data.	
	11b	<i>Synthesis-based estimates</i> : 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	<i>Single study-based economic evaluation</i> : 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	<i>Model-based economic evaluation</i> : 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

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 3

		applicable, report incremental cost-effectiveness ratios.	
Characterizing uncertainty	20a	<i>Single study-based economic evaluation</i> : 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	<i>Model-based economic evaluation</i> : 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>

The citation for the CHEERS Task Force Report is:
 Husereau D, Drummond M, Petrou S, et al. 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. *Value Health* 2013;16:231-50.