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Cost-Effectiveness of Pembrolizumab for Treatment of Platinum-Resistant Recurrent or Metastatic Head-and-Neck Squamous Cell Carcinoma in China

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4 **Cost-Effectiveness of Pembrolizumab for Treatment of Platinum-Resistant**
5 **Recurrent or Metastatic Head-and-Neck Squamous Cell Carcinoma in China**
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ABSTRACT

Objective: Pembrolizumab was recently demonstrated to have a survival benefit for patients with recurrent or metastatic head-and-neck squamous cell carcinoma (r/mHNSCC). However, the cost-effectiveness of pembrolizumab versus chemotherapy remained uncertain. This analysis aimed to describe the cost-effectiveness of pembrolizumab versus standard-of-care (SOC) therapy in r/mHNSCC in China.

Methods: A Markov model consisting of three health states (stable, progressive and dead) was developed to compare the costs and effectiveness of pembrolizumab with SOC in platinum-resistant r/mHNSCC. Model inputs for transition probabilities and toxicity were collected from the KEYNOTE-040 trial, while health utilities were estimated from a literature review. The cost data were acquired for the payer perspectives of China. Costs and outcomes were discounted at an annual rate of 3.0%. Incremental cost-effectiveness ratio (ICER) were calculated as cost per quality-adjusted life years (QALYs). Sensitivity analyses were conducted to test the uncertainties surrounding model parameters.

Results: The total mean cost of pembrolizumab versus standard-of-care was US\$37,787 and US\$32,491, respectively. As for effectiveness, pembrolizumab yielded 0.31 QALYs compared with 0.25 QALYs for SOC therapy. The ICER for pembrolizumab was US\$88,271/QALY versus SOC.

Conclusions: Pembrolizumab is not likely to be a cost-effective strategy compared with SOC therapy for platinum-resistant r/mHNSCC patients in China.

Keywords: Cost-effectiveness, Immunotherapy, Pembrolizumab, head-and-neck squamous cell carcinoma, Markov model

Strengths and limitations of this study

1. Pembrolizumab was recently approved to have a survival benefit for patients with recurrent or metastatic head-and-neck squamous cell carcinoma (r/mHNSCC). However, the cost-effectiveness of pembrolizumab in treating r/mHNSCC was still unknown.

2. To our knowledge, this is the first cost-effectiveness analysis comparing pembrolizumab with methotrexate, docetaxel, or cetuximab for treating patients with r/mHNSCC.

3. The main limitations of the study are that resource use in clinical trials may not represent resources for real clinical practice since clinical trials were conducted in a selected population meeting inclusion and exclusion criteria.

SUBHEADING: *Pembrolizumab cost-effectiveness for Head-and-Neck Squamous Cell Carcinoma*

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) represents a major global cause of cancer-associated morbidity and death with a worldwide incidence of 550,000 cases and 380,000 deaths per year.^{1 2} After definitive treatment, approximately 30-40% of patients with HNSCC will progress^{3 4} and about 50-60% will have recurrent disease.⁵ Platinum-based systemic chemotherapy regimens is commonly used in the first-line treatment for patients with recurrent or metastatic HNSCC (r/mHNSCC). For patients with failure of first-line platinum therapy, the commonly used drug is methotrexate.⁶ The second-line of paclitaxel or docetaxel has a certain salvage effect if the first-line therapy does not receive the taxane.^{7 8} Cetuximab is also suitable for patients who have not been exposed to this drug or have a poor PS score.⁹

Checkpoint inhibitors of the programmed cell death protein 1 (PD-1) have shown impressive effects on a number of cancers.¹⁰⁻¹³ In recent years, anti-PD-1 drugs have developed rapidly in advanced HNSCC. The Food and Drug Administration (FDA) of the US continuously approved the indications of pembrolizumab and nivolumab for the treatment of recurrent or metastatic HNSCC. The recently reported KEYNOTE-040¹⁴ study found a survival benefit for patients with platinum-resistant recurrent or metastatic disease who received pembrolizumab . In this clinical trial, patients were randomly assigned to receive pembrolizumab or standard-of-care (SOC) (docetaxel, methotrexate, or cetuximab). The study showed that median overall survival was 8.4

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4 months (95% CI: 6.4–9.4) in the pembrolizumab group and 6.9 months (95% CI: 5.9–
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6 8.0) in SOC group. Thus pembrolizumab extended the median overall survival by 1.5
7
8 months. Also, patients in pembrolizumab group had a favourable safety profile
9
10 compared with patients treated with conventional therapy. Although there is a
11
12 significant improvement in the treatment of patients with r/mHNSCC, the prognosis
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14 remains relatively poor and the economic value of pembrolizumab in this population
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16 remains unknown. The objective of our study was to assess the cost-effectiveness of
17
18 pembrolizumab compared with standard agents in the treatment of r/mHNSCC to find
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20 the more cost-effective therapy in China.

21 **METHODS**

22 **Patients and treatments**

23
24 The target patients in the model were in line with the eligibility criteria for the
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26 randomized, open-label, phase 3 clinical trial (KEYNOTE-040). This included HNSCC
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28 patients that progressed during or after platinum-containing therapy for recurrent and/or
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30 metastatic disease, or whose disease recurred or progressed within 3-6 months of
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32 platinum-containing therapy for locally advanced disease. Patients were randomly
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34 assigned to receive either pembrolizumab or investigator's choice of SOC therapy. The
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36 same treatment mix as in the SOC arm (26.2% methotrexate, 44.4% docetaxel, 29.4%
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38 cetuximab) was assumed in our model without adoptions, as it represents the standard
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40 of care. Patients assigned to pembrolizumab arm received 200 mg every 3 weeks
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42 intravenously. In the SOC arm, patients received 40 mg/m² body surface area of
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44 methotrexate per week intravenously (could be increased to 60 mg/m² in the absence
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46 of toxicity), 75 mg/m² of docetaxel every 3 weeks intravenously, or 250 mg/m² of
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48 cetuximab per week intravenously following a loading dose of 400 mg/m². Treatment
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50 continued until progression was confirmed on a scan obtained at least 4 weeks later or
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52 other criteria requiring discontinuation were met.

53 **Model Structure**

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55 We compared the cost-effectiveness of pembrolizumab with methotrexate, docetaxel,
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57 or cetuximab for patients with platinum-resistant r/mHNSCC. We conducted a Markov
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59 model by TreeAge pro Suite (TreeAge Software Inc, Williamstown, MA, USA) to
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4 simulate treatments, adverse events, costs, survival, and quality of life among simulated
5 patients (Fig. 1). Three mutually exclusive health states, progression-free (stable state),
6 progressive disease (cancer progression) and death, were included in the state transition
7 diagram (Fig. 1B). Patients started receiving pembrolizumab or standard chemotherapy
8 in the stable state, and could stay in or move to progressive disease or death at a cycle
9 length due to their assigned transition probabilities. The simulation was conducted in
10 three-week cycles for a period of 30 years during which all patients were expected to
11 die. Transition probabilities of every state were calculated based on the following
12 equation: $P(1 \text{ month}) = 1 - 0.5^{(1/\text{median time to event})}$. The equation was derived from $P = 1 -$
13 e^{-R} and $R = -\ln(0.5)/(\text{time to event}/\text{number of treatment cycles})$.¹⁵⁻¹⁷

23 Cost

24 Since the therapeutic drugs were administered weekly or every three weeks in the
25 KEYNOTE-040 test, the cycle length of our model was three weeks. Therefore, all the
26 costs we provided were for every three weeks. All aspects of direct medical costs for
27 treating the disease, including the cost for pembrolizumab or standard therapy, imaging
28 and laboratory tests, hospitalization, administration for stable state and the cost for
29 subsequent therapy in disease progressive, were taken into account. Since patients
30 randomized to the SOC arm received one of three chemotherapy regimens, the drug
31 acquisition cost was calculated as a weighted average cost based on the patients'
32 number of each regimen in KEYNOTE-040. In addition, time cost calculated according
33 to median monthly salary in China were also considered. The incidence of adverse
34 events comes from clinical trials KEYNOTE-040. Costs due to severe (grade 3-4)
35 treatment-related adverse events were either derived from the literature^{18 19} or
36 calculated from the perspective of Chinese society. Costs for grade 1-2 adverse events
37 were deemed to be negligible. All costs in the model were adjusted to US dollars based
38 on the 2018 average exchange rate (US\$ = CYN 6.6174) and discounted at a rate of 3%
39 annually (Table 1).

56 Utilities and outcome measures

57 Effectiveness was measured in quality-adjusted life-years (QALYs), which is defined
58 as a composite measure of the duration of time spent in each of the health states
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4 multiplied by the utility score for each state. In this study, health utility scores were
5 obtained from the previously published literature,²⁰ with an estimation of 0.65 in the
6 stable state per year, 0.52 in the progression state per year and 0 in the death state (Table
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10 1).

11 The cost-effectiveness of pembrolizumab versus methotrexate, docetaxel, or
12 cetuximab was assessed by incremental cost-effectiveness ratio (ICER), which
13 expressed as the incremental cost between the two treatment approaches per QALY
14 gained. Treatments were considered “cost-effective” if the ICER was less than a
15 willingness-to-pay threshold (WTP) of US\$28,130/QALY. The threshold of
16 US\$28,130/QALY was three times of China's per capita GDP according to the World
17 Health Organization recommendations for cost-effectiveness analysis.
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25 **Sensitivity analysis**

26 Univariate analysis was performed for model parameters subject to uncertainty. The
27 value of parameters was varied one at a time by $\pm 20\%$ except for discount rate ranging
28 from 0 to 8%. A tornado analysis was used to rank-order the following parameters in
29 order of potential impact on the outputs. The parameters included cost of
30 pembrolizumab, cost of standard care, cost for stable state, cost for progressive state,
31 probability from stable to progression, probability from stable to death, utility for stable
32 and progressive state.
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40 Probabilistic sensitivity analyses (PSA) were also performed using a second-order
41 Monte Carlo simulation to evaluate the robustness of the model to further address the
42 uncertainty in model input parameters. Every time the model was run, all parameters
43 were varied over their defined distribution (gamma distributions for costs, and beta
44 distributions for values with a range between 0 and 1) simultaneously. The simulation
45 included 1000 iterations.
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52 **RESULTS**

53 **Base Case**

54 All the patients were dead in both arms at the termination of model simulation. Patients
55 in the pembrolizumab group yielded 0.31 QALYs compared with 0.25 QALYs for
56 patients in the SOC group. Total costs incurred was US\$37.787 in the pembrolizumab
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4 group and US\$32,491 in the SOC group. These results led to an ICER of US\$88,271
5 per QALY higher than WTP, indicating that pembrolizumab is not cost-effective
6 compared with SOC therapy.
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9 **Sensitivity analyses**

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11 Results of univariate sensitivity analyses are depicted in the tornado diagram in Figure
12 2. The variables with the most impact on the ICER included utility values for
13 progressive state, cost of pembrolizumab as well as cost for cancer progression. Within
14 the +/- 20% range of each variable, ICER remained > US\$28,130 per QALY.
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18 Finally, probabilistic sensitivity analysis over 1,000 iterations was performed to
19 vary distributions of cost, survival and utility simultaneously. The cost-effectiveness
20 acceptability curve is displayed in Figure 3A. It was demonstrated that standard therapy
21 was more likely to be cost-effective compared with pembrolizumab at WTP value of
22 US\$28,130/QALY. The scatterplot of the results of each iteration is shown in Figure
23 3B. The majority of the points were above the WTP threshold line and falling in the
24 first quadrant, indicating that pembrolizumab was not cost-effective versus standard
25 care.
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28 **DISCUSSION**

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30 To our knowledge, this is the first cost-effectiveness analysis comparing
31 pembrolizumab with methotrexate, docetaxel, or cetuximab for treating patients with
32 r/mHNSCC. Clinical data were derived from the KEYNOTE-040 trial, which
33 demonstrated improved overall survival for pembrolizumab versus SOC therapy.
34 Model results suggested that if we considered the conventional WTP threshold of
35 US\$28,130/QALY as our cut-off, pembrolizumab was not cost-effective compared
36 with standard therapy in r/mHNSCC, providing an ICER of US\$88,271 per QALY. A
37 large incremental cost and a slight benefit in health outcome led to the high ICER
38 exceeding WTP threshold. Moreover, both univariate sensitivity analysis and
39 probabilistic sensitivity analysis demonstrated robust cost-effectiveness results to
40 uncertainty of model input parameters.
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58 Similar economic assessments of pembrolizumab for the treatment of non-small
59 cell lung cancer (NSCLC) in China consistently lead to the same conclusion. An
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4 evaluation of pembrolizumab compared with chemotherapy for the treatment of PD-L1
5 positive, NSCLC in China resulted in an ICER of US\$103,128 per QALY. However,
6 results may be diverse in different countries or cancer types. Georgieva et al.²¹
7 suggested that first-line pembrolizumab for advanced NSCLC may be cost-effective
8 compared to platinum-doublet chemotherapy in the US but not in the UK, despite very
9 similar ICER values in both countries. Sarfaty et al.²² found that second-line
10 pembrolizumab for advanced bladder cancer might be considered cost-effective in the
11 US but not in the UK and Australia. The difference in cost-effectiveness and WTP
12 thresholds between countries likely explained the difference in findings related to the
13 cost-effectiveness of pembrolizumab.
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23 This analysis also had several limitations. As with most cost-effectiveness analyses,
24 resource use in clinical trials may not represent resources for real clinical practice since
25 clinical trials were conducted in a selected population meeting inclusion and exclusion
26 criteria. Also, since clinical outcomes and utilities were based on previously published
27 studies instead of prospective data, the results in this analysis may be biased.
28 Additionally, pembrolizumab could be a cost-effective strategy for treating patients
29 with r/mHNSCC in developed countries with WTP thresholds greater than US\$80,000.
30 Finally, although PSA can directly reflect the influence of model uncertainty on the
31 results, it generally assumes that the parameters are independent of each other, which
32 may affect the credibility of the results of pharmacoeconomic evaluation. Considering
33 that the results are still stable when the random simulations are carried out for 10,000
34 times, we believe that are credible.
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46 Despite the above limitations, we still believe that our analysis is reasonable. The
47 analysis was based on China Guidelines for Pharmacoeconomic Evaluations and
48 Manual²³ and joint recommendations of Cost-Effectiveness in Health and Medicine.²⁴
49 Furthermore, extensive sensitivity analyses presented in this manuscript were
50 performed to evaluate uncertainty on the outcomes. In conclusion, although
51 pembrolizumab improves overall survival in patients with r/mHNSCC, this therapy is
52 not a cost-effective strategy compared with standard therapy in China.
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Contributors Study conception and design: WX, HD and PH; Acquisition of data: XZ, YT and GX; Analysis and interpretation of data: WX and HD; Drafting of manuscript: WX and QF; All authors revised the first draft and agreed with the final version.

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45 TABLES

46 **Table 1** Parameters for cost-effectiveness model

47 Variable	48 Value	49 Range		50 Distribution	51 Source
		52 Min	53 Max		
54 Transition probabilities					
55 Pembrolizumab					
56 Progression from stable state	0.281	0.225	0.337	Beta	[14]
57 Death from stable state	0.079	0.063	0.095	Beta	[14]
58 Mortality after progression	0.104	0.083	0.125	Beta	[14]
59 Standard chemotherapy					

Progression from stable state	0.260	0.208	0.312	Beta	[14]
Death from stable state	0.096	0.076	0.115	Beta	[14]
Mortality after progression	0.140	0.112	0.168	Beta	[14]
Utilities					
Stable state	0.650	0.500	1.000	Beta	[21]
Progressive state	0.520	0.200	0.700	Beta	[21]
Cost					
Pembrolizumab	5421	4337	6506	Gamma	Calculated
Standard first	1439	1151	1727	Gamma	Calculated
Standard	1253	1002	1503	Gamma	Calculated
Administration	13	10	15	Gamma	Calculated
Test	154	123	185	Gamma	Calculated
Time Cost	32	26	39	Gamma	Calculated
Severe Adverse Events					
Pembrolizumab	1227	981	1472	Gamma	Calculated
Standard	5855	4684	7027	Gamma	Calculated
Cancer progression	2555	1677	3620	Gamma	[18]

FIGURE LEGENDS

Figure 1 Model structure. (A) Abbreviated decision tree and Markov model; (B) Model states and transitions.

Figure 2 Tornado plot of the univariate sensitivity analyses for pembrolizumab vs. standard of care therapy.

Figure 3 Probabilistic sensitivity analyses for pembrolizumab vs. SOC therapy. (A) Cost-effectiveness acceptability curve; (B) cost-effectiveness plane. WTP: willingness to pay; SOC: standard of care.

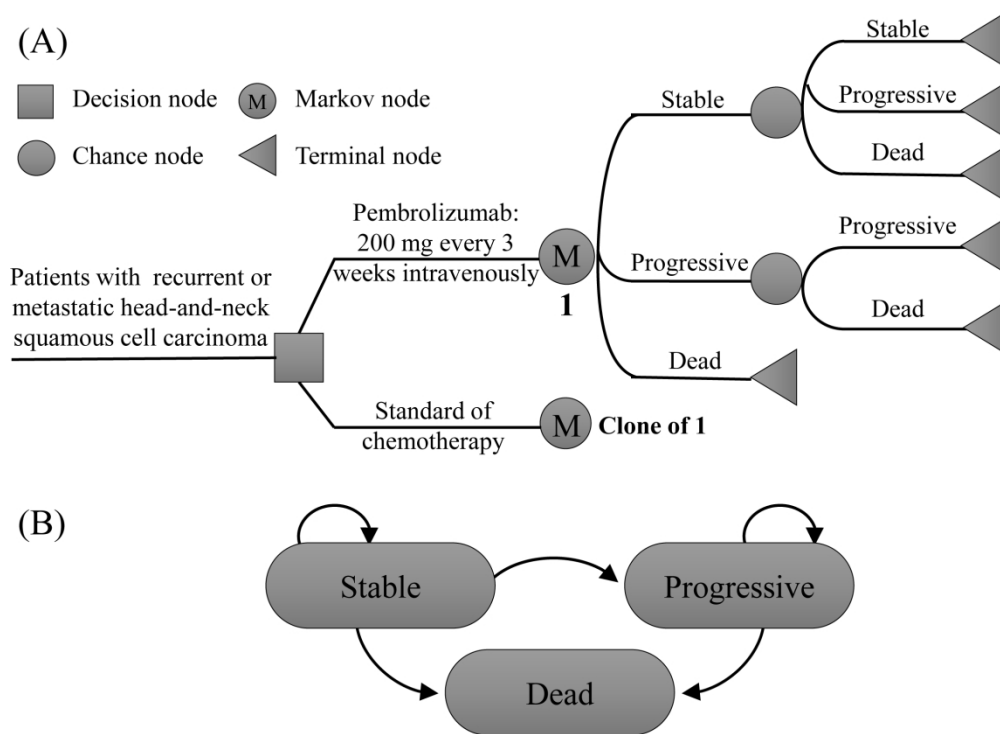


Figure 1 Model structure. (A) Abbreviated decision tree and Markov model; (B) Model states and transitions.

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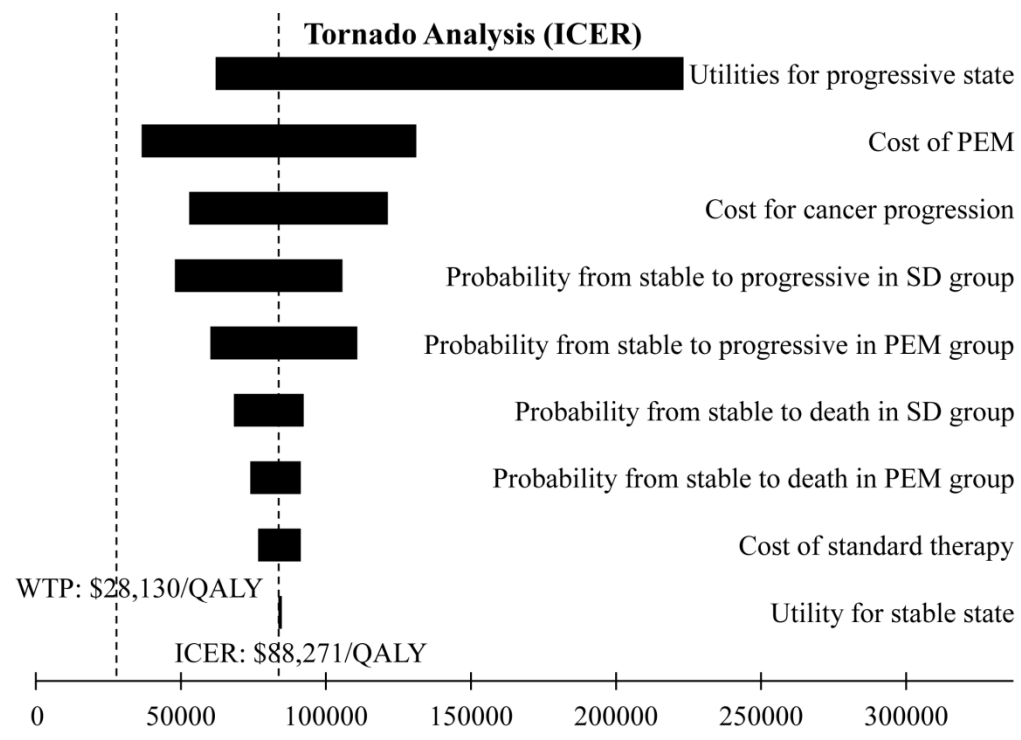


Figure 2 Tornado plot of the univariate sensitivity analyses for pembrolizumab vs. standard of care therapy.

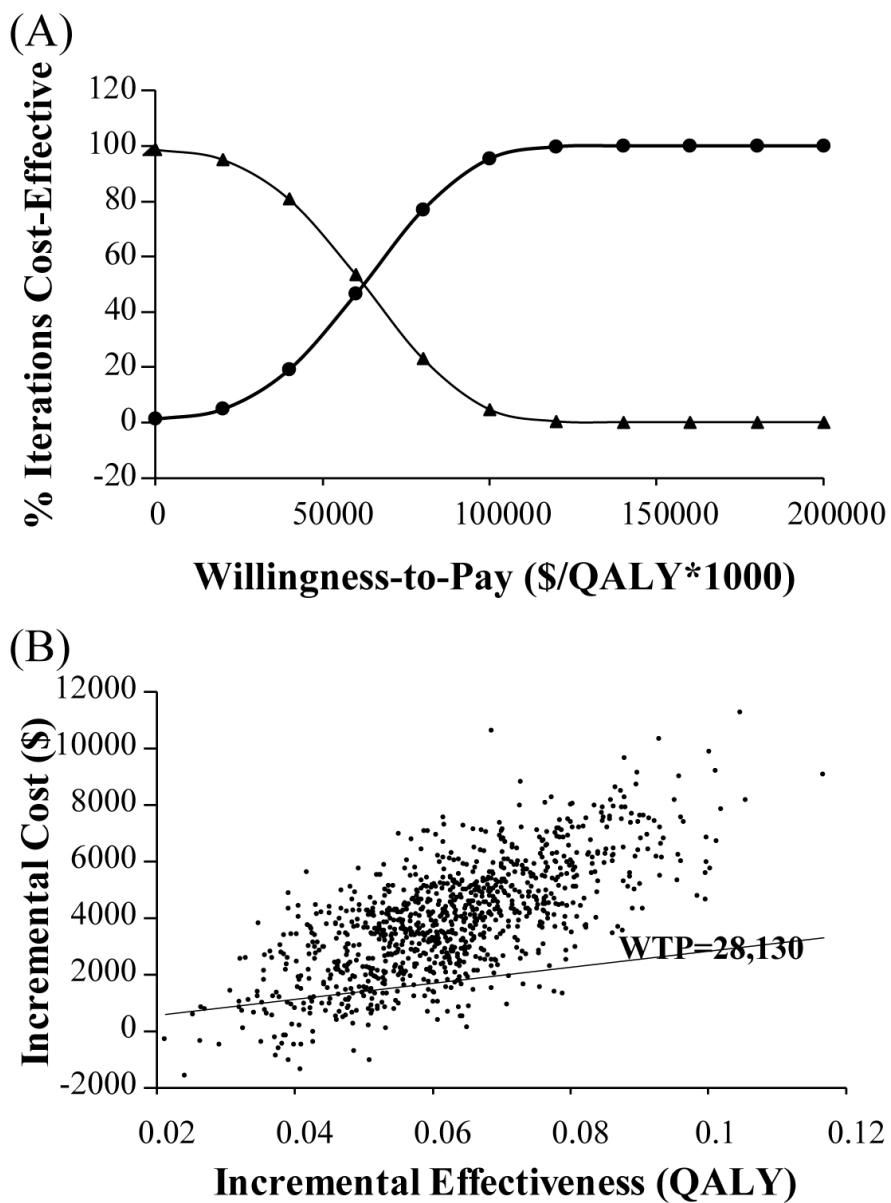


Figure 3 Probabilistic sensitivity analyses for pembrolizumab vs. SOC therapy. (A) Cost-effectiveness acceptability curve; (B) cost-effectiveness plane. WTP: willingness to pay; SOC: standard of care.

BMJ Open

Cost-Effectiveness of pembrolizumab for treatment of platinum-resistant recurrent or metastatic head-and-neck squamous cell carcinoma in China: an economic analysis based on a randomised, open label, phase III Trial

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4 1 **Cost-Effectiveness of pembrolizumab for treatment of platinum-resistant**
5 **recurrent or metastatic head-and-neck squamous cell carcinoma in China: an**
6 **economic analysis based on a randomised, open label, phase III Trial**
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1 ABSTRACT

2 **Background:** Pembrolizumab was recently demonstrated to have a survival benefit for
3 patients with recurrent or metastatic head-and-neck squamous cell carcinoma
4 (r/mHNSCC). However, the cost-effectiveness of pembrolizumab versus chemotherapy
5 in China remained uncertain.

6 **Objectives:** This analysis aimed to describe the cost-effectiveness of pembrolizumab
7 versus standard-of-care (SOC) therapy in r/mHNSCC in China.

8 **Design:** A Markov model consisting of three health states (stable, progressive and dead)
9 was developed to compare the costs and effectiveness of pembrolizumab with SOC in
10 platinum-resistant r/mHNSCC. Model inputs for transition probabilities and toxicity
11 were collected from the KEYNOTE-040 trial, while health utilities were estimated from
12 a literature review. The cost data were acquired for the payer's perspective of China.
13 Costs and outcomes were discounted at an annual rate of 3.0%. Sensitivity analyses
14 were conducted to test the uncertainties surrounding model parameters.

15 **Outcome measures:** The primary outcome was incremental cost-effectiveness ratios
16 (ICERs), which were calculated as cost per quality-adjusted life years (QALYs).

17 **Results:** The total mean cost of pembrolizumab versus standard-of-care was
18 US\$45,861 and US\$41,950, respectively. As for effectiveness, pembrolizumab yielded
19 0.31 QALYs compared with 0.25 QALYs for SOC therapy. The ICER for
20 pembrolizumab versus SOC was US\$65,186/QALY, which was higher than
21 willingness-to-pay threshold (WTP) of US\$28,130/QALY in China. The univariate
22 sensitivity analysis indicated that utility values for progressive state, probability from
23 stable to progressive in SD group as well as cost of pembrolizumab were the three most
24 influential variables on ICER. The probabilistic sensitivity analyses demonstrated that
25 standard therapy was more likely to be cost-effective compared with pembrolizumab at
26 WTP value of US\$28,130/QALY. Results were robust across both univariate analysis
27 and probabilistic sensitivity analyses.

28 **Conclusions:** Pembrolizumab is not likely to be a cost-effective strategy compared
29 with SOC therapy for platinum-resistant r/mHNSCC patients in China.

1

2 **Strengths and limitations of this study**

3 1. Pembrolizumab was recently approved to have a survival benefit for patients with
4 recurrent or metastatic head-and-neck squamous cell carcinoma (r/mHNSCC).
5 However, the cost-effectiveness of pembrolizumab in treating r/mHNSCC was still
6 unknown.

7 2. To our knowledge, this is the first cost-effectiveness analysis comparing
8 pembrolizumab with methotrexate, docetaxel, or cetuximab for treating patients with
9 r/mHNSCC.

10 3. The main limitations of the study are that resource use in clinical trials may not
11 represent resources for real clinical practice since clinical trials were conducted in a
12 selected population meeting inclusion and exclusion criteria.

13

14 ***SUBHEADING: Pembrolizumab cost-effectiveness for Head-and-Neck Squamous*** 15 ***Cell Carcinoma***

16

17 **INTRODUCTION**

18 Head and neck squamous cell carcinoma (HNSCC) represents a major global cause of
19 cancer-associated morbidity and death with a worldwide incidence of 550,000 cases
20 and 380,000 deaths per year.^{1 2} After definitive treatment, approximately 30-40% of
21 patients with HNSCC will progress^{3 4} and about 50-60% will have recurrent disease.⁵
22 Platinum-based systemic chemotherapy regimens are commonly used in the first-line
23 treatment for patients with recurrent or metastatic HNSCC (r/mHNSCC). For patients
24 with failure of first-line platinum therapy, the commonly used drug is methotrexate.⁶
25 The second-line of paclitaxel or docetaxel has a certain salvage effect if the first-line
26 therapy does not receive the taxane.^{7 8} Cetuximab is also suitable for patients who have
27 not been exposed to this drug or have a poor PS score.⁹

28 Checkpoint inhibitors of the programmed cell death protein 1 (PD-1) have shown
29 impressive effects on a number of cancers.¹⁰⁻¹³ In recent years, anti-PD-1 drugs have

1 developed rapidly in advanced HNSCC. The Food and Drug Administration (FDA) of
2 the US continuously approved the indications of pembrolizumab and nivolumab for the
3 treatment of recurrent or metastatic HNSCC. Indications of pembrolizumab approved
4 by China Food and Drug Administration (CFDA) include melanoma, non-small cell
5 lung cancer and esophageal cancer. Besides, because of the excellent tumor treatment
6 effect, pembrolizumab is also widely used in HNSCC, small cell lung cancer, classical
7 Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma,
8 gastric cancer, cervical cancer, colorectal cancer and many other cancer types according
9 to the recommendations of indications approved by FDA and several guidelines such
10 as NCCN (National Comprehensive Cancer Network) and CSCO (Chinese Society of
11 Clinical Oncology).

12 The recently reported KEYNOTE-040¹⁴ study found a survival benefit for patients
13 with platinum-resistant recurrent or metastatic disease who received pembrolizumab.
14 In this clinical trial, patients were randomly assigned to receive pembrolizumab or
15 standard-of-care (SOC) (docetaxel, methotrexate, or cetuximab). The study showed that
16 median overall survival was 8.4 months (95% CI: 6.4-9.4) in the pembrolizumab group
17 and 6.9 months (95% CI: 5.9-8.0) in SOC group. Thus, pembrolizumab extended the
18 median overall survival by 1.5 months. Also, patients in pembrolizumab group had a
19 favorable safety profile compared with patients in SOC group. Although there is a
20 significant improvement in the treatment of patients with r/mHNSCC, the prognosis
21 remains relatively poor and the economic value of pembrolizumab in this population
22 remains unknown. The objective of this study was to evaluate the cost-effectiveness of
23 pembrolizumab compared with standard treatment, in order to find the more cost-
24 effective therapy in the treatment of r/mHNSCC in China.

25 **METHODS**

26 **Trial Background**

27 The target patients in the model were in line with the eligibility criteria for the
28 randomised, open-label, phase 3 clinical trial (KEYNOTE-040). This included HNSCC
29 patients that progressed during or after platinum-containing therapy for recurrent and/or

1 metastatic disease. Patients that recurred or progressed within 3-6 months of platinum-
2 containing therapy for locally advanced disease were also included. Patients were
3 randomly assigned to receive either pembrolizumab or investigator's choice of SOC
4 therapy. The same treatment mixes as in the SOC arm (26.2% methotrexate, 44.4%
5 docetaxel, 29.4% cetuximab) was assumed in our model without adoptions, as it
6 represents the standard of care. Patients assigned to pembrolizumab arm received 200
7 mg every 3 weeks intravenously. In the SOC arm, patients received 40 mg/m² body
8 surface area of methotrexate per week intravenously (could be increased to 60 mg/m²
9 in the absence of toxicity), 75 mg/m² of docetaxel every 3 weeks intravenously, or 250
10 mg/m² of cetuximab per week intravenously following a loading dose of 400 mg/m².
11 Treatment continued until progression was confirmed on a scan obtained at least 4
12 weeks later or other criteria requiring discontinuation were met.

13 **Patients and Public Involvement**

14 There was patient representation on the KEYNOTE-040 trial. However, no patients or
15 public was involvement in this cost-effectiveness analysis.

16 **Model Structure**

17 We compared the cost-effectiveness of pembrolizumab with methotrexate, docetaxel,
18 or cetuximab for patients with platinum-resistant r/mHNSCC. We conducted a Markov
19 model by TreeAge pro Suite (TreeAge Software Inc, Williamstown, MA, USA) to
20 simulate treatments, adverse events, costs, survival, and quality of life among simulated
21 patients (Figure 1). The abbreviated decision tree and Markov model were presented in
22 Figure 1A. Three mutually exclusive health states, progression-free (stable state),
23 progressive disease (cancer progression) and death, were included in the state transition
24 diagram (Figure 1B). Patients started receiving pembrolizumab or standard
25 chemotherapy in the stable state, and could stay in or move to progressive disease or
26 death at a cycle length due to their assigned transition probabilities. The simulation was
27 conducted in three-week cycles for a period of 30 years during which all patients were
28 expected to die. Transition probabilities of every state were calculated based on the
29 following equation: $P(1\text{ month}) = 1 - 0.5^{(1/\text{median time to event})}$. The equation was derived

1 from $P = 1 - e^{-R}$ and $R = -\ln(0.5)/(\text{time to event}/\text{number of treatment cycles})$.¹⁵⁻¹⁷ The
2 modeled overall survival curve was presented in Supplementary Figure 1A. The
3 survival curve extracted using Engauge Digitizer software (version 4.1;
4 <http://digitizer.sourceforge.net>) from clinical trials was shown in Supplementary Figure
5 1B.

6 **Cost**

7 Since the therapeutic drugs were administered weekly or every three weeks in the
8 KEYNOTE-040 trial, the cycle length of our model was three weeks. Therefore, all the
9 costs we provided were for every three weeks. All aspects of direct medical costs for
10 treating the disease, including the cost for pembrolizumab or standard therapy, imaging
11 and laboratory tests, hospitalization, administration for stable state and the cost for
12 subsequent therapy in disease progressive, were taken into account. Since patients
13 randomised to the SOC arm received one of three chemotherapy regimens, the drug
14 acquisition cost was calculated as a weighted average cost based on the patients'
15 number of each regimen in KEYNOTE-040. In addition, time cost was estimated at
16 US\$35.73 per day on the basis of the average monthly salary in China in 2018¹⁸.
17 Supportive care cost and terminal cancer cost were also included and extracted from
18 published articles^{19 20}. The incidence of adverse events comes from clinical trials
19 KEYNOTE-040. Costs due to severe (grade 3-4) treatment-related adverse events were
20 either derived from the literature^{21 22} or calculated from the payer's perspective of China.
21 Costs for grade 1-2 adverse events were deemed to be negligible. All costs in the model
22 were adjusted to US dollars based on the 2018 average exchange rate (US\$ 1 = CNY
23 6.6174)²³ and discounted at a rate of 3% annually (Table 1).

24 **Utilities and outcome measures**

25 Effectiveness was measured in quality-adjusted life-years (QALYs), which equals the
26 survival time of the patient in a certain health state multiplied by the health utility value
27 (quality of life weight) during that period. In this study, health utility scores were
28 obtained from the previously published literature,²⁴ with an estimation of 0.65 in the
29 stable state per year, 0.52 in the progression state per year and 0 in the death state (Table

1 1).

2 The cost-effectiveness of pembrolizumab versus methotrexate, docetaxel, or
3 cetuximab was assessed by incremental cost-effectiveness ratio (ICER), which
4 expressed as the incremental cost between the two treatment approaches per QALY
5 gained. Treatments were considered “cost-effective” if the ICER was less than a
6 willingness-to-pay threshold (WTP) of US\$28,130/QALY. The threshold of
7 US\$28,130/QALY was three times of China's per capita GDP according to the World
8 Health Organization recommendations for cost-effectiveness analysis.

9 **Sensitivity analysis**

10 Univariate analysis was performed for model parameters subject to uncertainty. The
11 value of parameters was varied one at a time by $\pm 20\%$ except for discount rate ranging
12 from 0 to 8%. A tornado analysis was used to rank-order the following parameters in
13 order of potential impact on the outputs. The parameters included cost of
14 pembrolizumab, cost of standard care, cost for stable state, cost for progressive state,
15 probability from stable to progression, probability from stable to death, utility for stable
16 and progressive state.

17 In order to evaluate the robustness of the model to further address the uncertainty
18 in model input parameters, probabilistic sensitivity analyses (PSA) were performed
19 using a second-order Monte Carlo simulation. Every time the model was run, all
20 parameters were varied over their defined distribution (gamma distributions for costs,
21 and beta distributions for values with a range between 0 and 1) simultaneously. The
22 simulation included 1,000 iterations.

23 **RESULTS**

24 **Base Case**

25 All the patients were dead in both arms at the termination of model simulation. Patients
26 in the pembrolizumab group yielded 0.31 QALYs compared with 0.25 QALYs for
27 patients in the SOC group. Total costs incurred was US\$45,861 in the pembrolizumab
28 group and US\$41,950 in the SOC group. These results led to an ICER of US\$65,186
29 per QALY higher than WTP, indicating that pembrolizumab is not cost-effective

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4 compared with SOC therapy.

5 2 **Sensitivity analyses**

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7 Results of univariate sensitivity analyses are depicted in the tornado diagram in Figure
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9 2. The variables with the most impact on the ICER included utility values for
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11 progressive state, probability from stable to progressive in SD group as well as cost of
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13 pembrolizumab. Within the +/- 20% range of each variable, ICER remained >
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15 US\$28,130 per QALY.
16

17
18 Finally, probabilistic sensitivity analysis over 1,000 iterations was performed to
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20 vary distributions of cost, survival and utility simultaneously. The cost-effectiveness
21
22 acceptability curve is displayed in Figure 3A. It was demonstrated that standard therapy
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24 was more likely to be cost-effective compared with pembrolizumab at WTP value of
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26 US\$28,130/QALY. The scatterplot of the results of each iteration is shown in Figure
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28 3B. The majority of the points were above the WTP threshold line and falling in the
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30 first quadrant, indicating that pembrolizumab was not cost-effective versus standard
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32 care.
33

34 16 **DISCUSSION**

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36 To our knowledge, this is the first cost-effectiveness analysis comparing
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38 pembrolizumab with methotrexate, docetaxel, or cetuximab for treating patients with
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40 r/mHNSCC. Clinical data were derived from the KEYNOTE-040 trial, which
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42 demonstrated improved overall survival for pembrolizumab versus SOC therapy.
43
44 Model results suggested that if we considered the conventional WTP threshold of
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46 US\$28,130/QALY as our cut-off, pembrolizumab was not cost-effective compared
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48 with standard therapy in r/mHNSCC, providing an ICER of US\$65,186 per QALY. A
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50 large incremental cost and a slight benefit in health outcome led to the high ICER
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52 exceeding WTP threshold. Moreover, both univariate sensitivity analysis and
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54 probabilistic sensitivity analysis demonstrated robust cost-effectiveness results to
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56 uncertainty of model input parameters.
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59 Similar economic assessments of pembrolizumab for the treatment of non-small
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cell lung cancer (NSCLC) in China consistently lead to the same conclusion²⁵. An

1 evaluation of pembrolizumab compared with chemotherapy for the treatment of PD-L1
2 positive, NSCLC in China resulted in an ICER of US\$103,128 per QALY. However,
3 results may be diverse in different countries or cancer types. Georgieva et al.²⁶
4 suggested that first-line pembrolizumab for advanced NSCLC may be cost-effective
5 compared to platinum-doublet chemotherapy in the US but not in the UK, despite very
6 similar ICER values in both countries. Sarfaty et al.²⁷ found that second-line
7 pembrolizumab for advanced bladder cancer might be considered cost-effective in the
8 US but not in the UK and Australia. The difference in cost-effectiveness and WTP
9 thresholds between countries likely explained the difference in findings related to the
10 cost-effectiveness of pembrolizumab.

11 This analysis also had several limitations. Like most cost-effectiveness analyses,
12 resources used in clinical trials might not represent resources for actual clinical practice
13 since clinical trials were conducted in a selected population that meeting inclusion and
14 exclusion criteria. Also, since clinical outcomes and utilities were based on previously
15 published studies instead of prospective data, the results in this analysis may be biased.
16 Additionally, pembrolizumab could be a cost-effective strategy for treating patients
17 with r/mHNSCC in developed countries with WTP thresholds greater than US\$80,000.
18 Finally, although PSA can directly reflect the influence of model uncertainty on the
19 results, it generally assumes that the parameters are independent of each other, which
20 may affect the credibility of the results of pharmacoeconomic evaluation. Considering
21 that the results are still stable when the random simulations are carried out for 1,000
22 times, we believe that are credible.

23 Despite the above limitations, we still believe that our analysis is reasonable. The
24 analysis was based on China Guidelines for Pharmacoeconomic Evaluations and
25 Manual²⁸ and joint recommendations of Cost-Effectiveness in Health and Medicine.²⁹
26 Furthermore, extensive sensitivity analyses presented in this manuscript were
27 performed to evaluate uncertainty on the outcomes. In conclusion, although
28 pembrolizumab improves overall survival in patients with r/mHNSCC, this therapy is
29 not a cost-effective strategy compared with standard therapy in China.

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13 10 **Contributors** Study conception and design: WX, HD and GY; Acquisition of data: QF,
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19 16 **Competing interests** None declared.

20 17 **Patient consent** Not required

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22 19 **Data sharing statement** No additional data available.

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1 TABLES

2 **Table 1** Parameters for cost-effectiveness model

Variable	Value	Range		Distribution	Source
		Min	Max		
Transition probabilities					
Pembrolizumab					
Progression from stable state	0.281	0.225	0.337	Beta	[14]
Death from stable state	0.079	0.063	0.095	Beta	[14]
Mortality after progression	0.104	0.083	0.125	Beta	[14]
Standard chemotherapy					
Progression from stable state	0.260	0.208	0.312	Beta	[14]
Death from stable state	0.096	0.076	0.115	Beta	[14]
Mortality after progression	0.140	0.112	0.168	Beta	[14]
Utilities					
Stable state	0.650	0.500	1.000	Beta	[26]
Progressive state	0.520	0.200	0.700	Beta	[26]
Cost					
Pembrolizumab	5421	4337	6506	Gamma	Calculated
Standard first	1439	1151	1727	Gamma	Calculated
Standard	1253	1002	1503	Gamma	Calculated
Administration	13	10	15	Gamma	Calculated
Test	154	123	185	Gamma	Calculated
Time Cost	750	600	900	Gamma	Calculated
Severe Adverse Events					
Pembrolizumab	1227	981	1472	Gamma	Calculated
Standard	5855	4684	7027	Gamma	Calculated
Cancer progression	2555	1677	3620	Gamma	[21]
Best supportive care	157.6	126.1	191.5	Gamma	[20]
Terminal cancer care	2039.4	1631.5	2447.3	Gamma	[19]

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4 FIGURE LEGENDS

5 **Figure 1** Model structure. (A) Abbreviated decision tree and Markov model; (B) Model
6 states and transitions.

7 **Figure 2** Tornado plot of the univariate sensitivity analyses for pembrolizumab vs.
8 standard of care therapy.

9 **Figure 3** Probabilistic sensitivity analyses for pembrolizumab vs. SOC therapy. (A)
10 Cost-effectiveness acceptability curve; (B) cost-effectiveness plane. WTP: willingness
11 to pay; SOC: standard of care.

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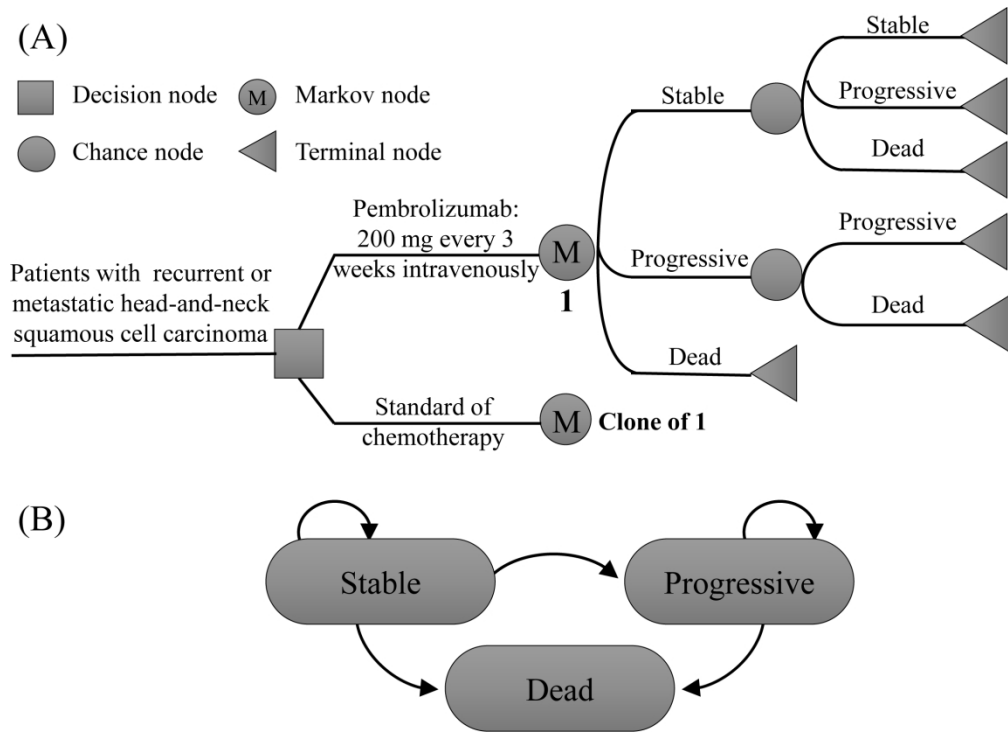
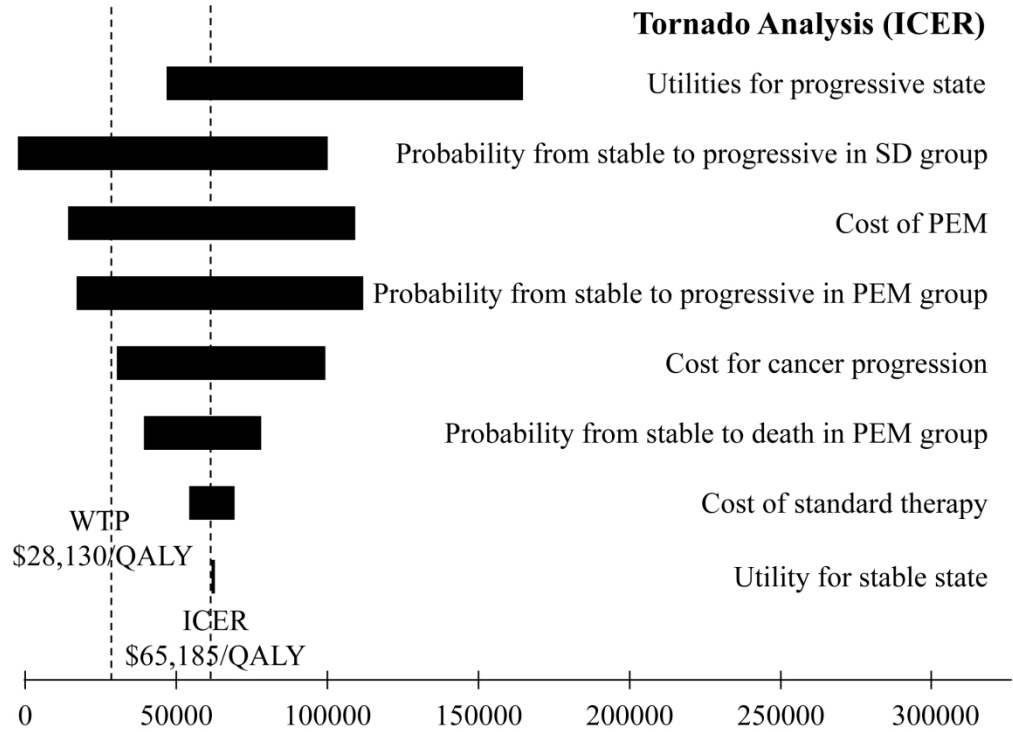
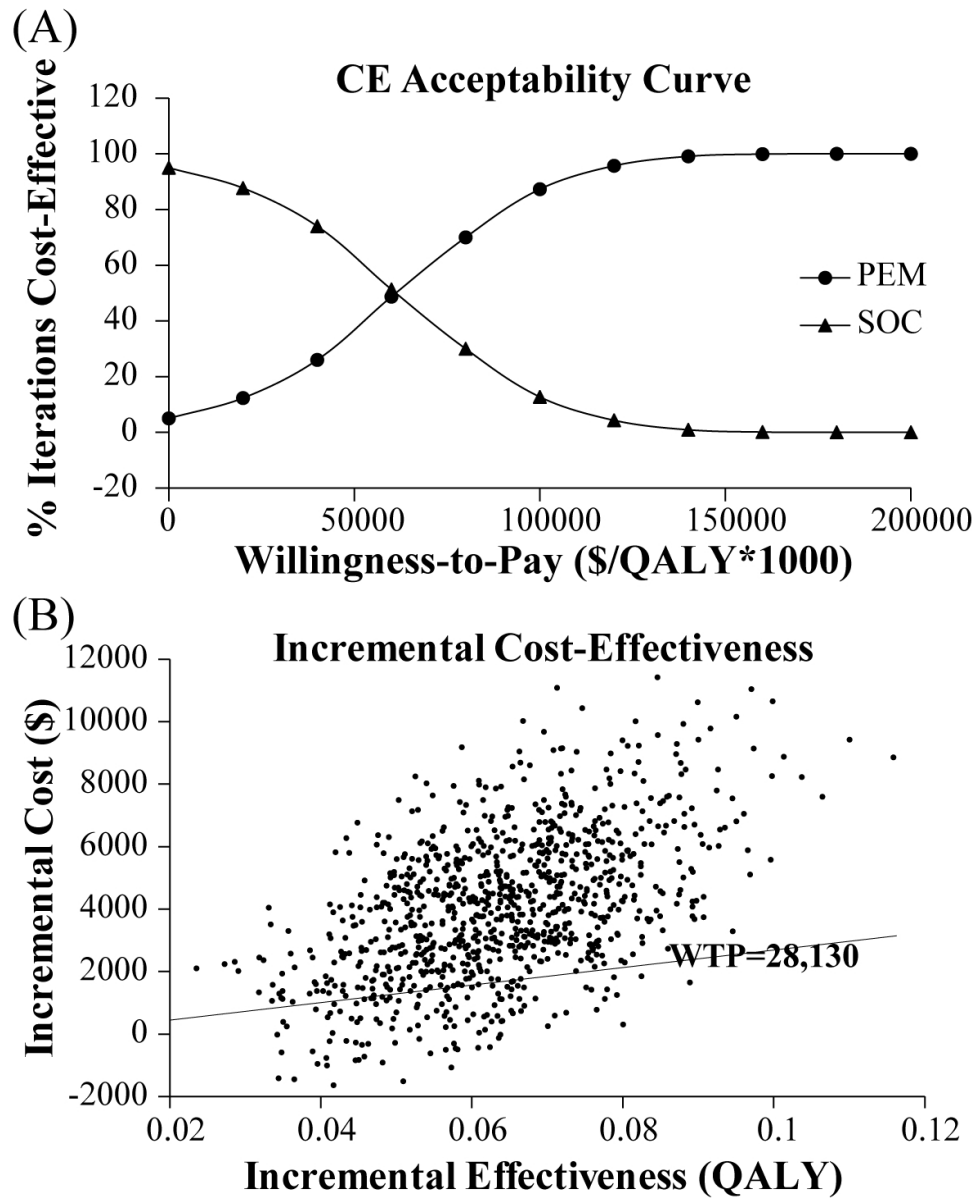


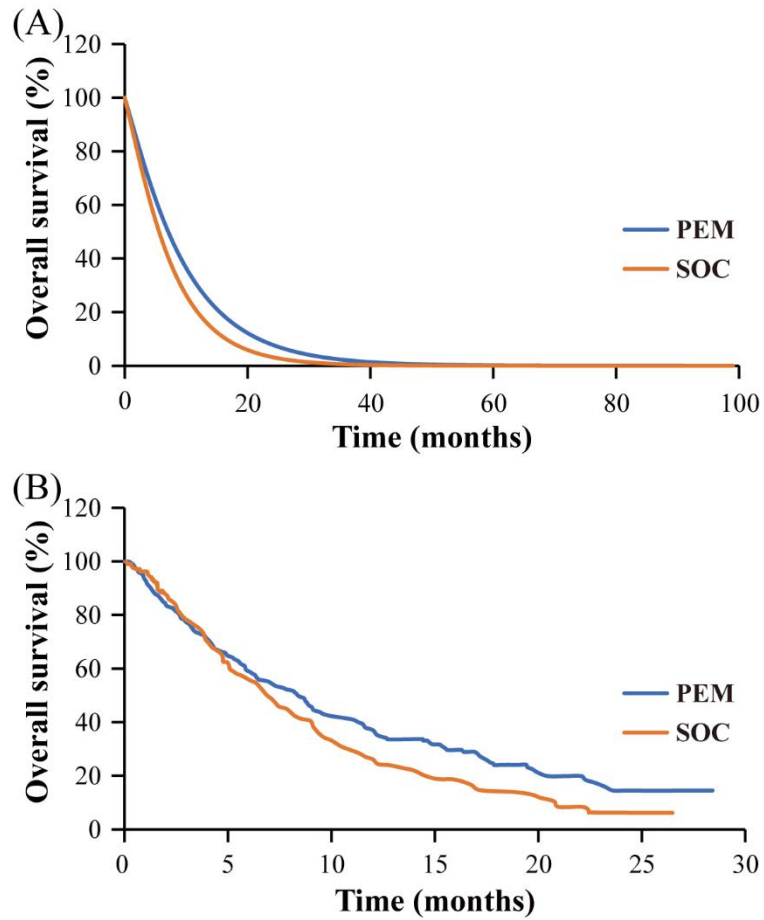
Figure 1 Model structure. (A) Abbreviated decision tree and Markov model; (B) Model states and transitions.



Tornado plot of the univariate sensitivity analyses for pembrolizumab vs. standard of care therapy.



Probabilistic sensitivity analyses for pembrolizumab vs. SOC therapy. (A) Cost-effectiveness acceptability curve; (B) cost-effectiveness plane. WTP: willingness to pay; SOC: standard of care.



Supplementary Figure 1 Overall survival curve. (A) Survival curve from Markov model; (B) Survival curve from KEYNOTE-040 trial.