BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038867
Article Type:	Original research
Date Submitted by the Author:	27-Mar-2020
Complete List of Authors:	Xin, Wenxiu; Zhejiang Cancer Hospital, Department of Pharmacy Ding, Haiying; Zhejiang Cancer Hospital, Department of Pharmacy Zheng, Xiaowei; Zhejiang Cancer Hospital, Department of pharmacy Tong, Yinghui; Zhejiang Cancer Hospital, Department of Pharmacy Xu, Gaoqi; Zhejiang Cancer Hospital, Department of Pharmacy Yang, Guonong; Zhejiang Cancer Hospital, Department of Pharmacy
Keywords:	CLINICAL PHARMACOLOGY, HEALTH ECONOMICS, Head & neck tumours < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Wenxiu Xin,[1,2,#] Haiying Ding,[1,#] Xiaowei Zheng,[1] Yinghui Tong,[1] Gaoqi Xu,[1] Guonong Yang[*]

[1] Department of Pharmacy, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China

[2] Key Laboratory of Head and Neck Translational Research of Zhejiang Province, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China

[#]These authors contributed equally to this work

[*]Corresponding author:

Wenxiu Xin, Department of Pharmacy/Key Laboratory of Head and Neck Translational Research of Zhejiang Province, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, No.1 Banshan Road, Hangzhou 310022, China. Email: xinwx@zjcc.org.cn

Guonong Yang, Department of Pharmacy/ Key Laboratory of Head and Neck Translational Research of Zhejiang Province, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, No.1 Banshan Road, Hangzhou 310022, China. Email: yanggn@zjcc.org.cn

Word count: 1871

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-040[14] 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

months (95% CI: 6·4–9·4) in the pembrolizumab group and 6.9 months (95% CI: 5·9–8·0) in SOC group. Thus pembrolizumab extended the median overall survival by 1.5 months. Also, patients in pembrolizumab group had a favourable safety profile compared with patients treated with conventional therapy. Although there is a significant improvement in the treatment of patients with r/mHNSCC, the prognosis remains relatively poor and the economic value of pembrolizumab in this population remains unknown. The objective of our study was to assess the cost-effectiveness of pembrolizumab compared with standard agents in the treatment of r/mHNSCC to find the more cost-effective therapy in China.

METHODS

Patients and treatments

The target patients in the model were in line with the eligibility criteria for the randomized, open-label, phase 3 clinical trial (KEYNOTE-040). This included HNSCC patients that progressed during or after platinum-containing therapy for recurrent and/or metastatic disease, or whose disease recurred or progressed within 3-6 months of platinum-containing therapy for locally advanced disease. Patients were randomly assigned to receive either pembrolizumab or investigator's choice of SOC therapy. The same treatment mix as in the SOC arm (26.2% methotrexate, 44.4% docetaxel, 29.4% cetuximab) was assumed in our model without adoptions, as it represents the standard of care. Patients assigned to pembrolizumab arm received 200 mg every 3 weeks intravenously. In the SOC arm, patients received 40 mg/m^2 body surface area of methotrexate per week intravenously (could be increased to 60 mg/m^2 in the absence of toxicity), 75 mg/m^2 of docetaxel every 3 weeks intravenously, or 250 mg/m^2 of cetuximab per week intravenously following a loading dose of 400 mg/m^2. Treatment continued until progression was confirmed on a scan obtained at least 4 weeks later or other criteria requiring discontinuation were met.

Model Structure

We compared the cost-effectiveness of pembrolizumab with methotrexate, docetaxel, or cetuximab for patients with platinum-resistant r/mHNSCC. We conducted a Markov model by TreeAge pro Suite (TreeAge Software Inc, Williamstown, MA, USA) to

simulate treatments, adverse events, costs, survival, and quality of life among simulated patients (Fig. 1). Three mutually exclusive health states, progression-free (stable state), progressive disease (cancer progression) and death, were included in the state transition diagram (Fig. 1B). Patients started receiving pembrolizumab or standard chemotherapy in the stable state, and could stay in or move to progressive disease or death at a cycle length due to their assigned transition probabilities. The simulation was conducted in three-week cycles for a period of 30 years during which all patients were expected to die. Transition probabilities of every state were calculated based on the following equation: P (1 month) = $1-0.5^{(1/\text{median time to event})}$. The equation was derived from $P = 1-e^{-R}$ and R = -ln(0.5)/(time to event/number of treatment cycles).[15-17]

Cost

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

Utilities and outcome measures

Effectiveness was measured in quality-adjusted life-years (QALYs), which is defined as a composite measure of the duration of time spent in each of the health states

multiplied by the utility score for each state. In this study, health utility scores were obtained from the previously published literature,[20] with an estimation of 0.65 in the stable state per year, 0.52 in the progression state per year and 0 in the death state (Table 1).

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

Sensitivity analysis

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

Probabilistic sensitivity analyses (PSA) were also performed using a second-order Monte Carlo simulation to evaluate the robustness of the model to further address the uncertainty in model input parameters. Every time the model was run, all parameters were varied over their defined distribution (gamma distributions for costs, and beta distributions for values with a range between 0 and 1) simultaneously. The simulation included 1000 iterations.

RESULTS

Base Case

All the patients were dead in both arms at the termination of model simulation. Patients in the pembrolizumab group yielded 0.31 QALYs compared with 0.25 QALYs for patients in the SOC group. Total costs incurred was US$37.787 in the pembrolizumab

group and US$32,491 in the SOC group. These results led to an ICER of US$88,271 per QALY higher than WTP, indicating that pembrolizumab is not cost-effective compared with SOC therapy.

Sensitivity analyses

Results of univariate sensitivity analyses are depicted in the tornado diagram in Figure 2. The variables with the most impact on the ICER included utility values for progressive state, cost of pembrolizumab as well as cost for cancer progression. Within the +/- 20% range of each variable, ICER remained > US$28,130 per QALY.

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

DISCUSSION

To our knowledge, this is the first cost-effectiveness analysis comparing pembrolizumab with methotrexate, docetaxel, or cetuximab for treating patients with r/mHNSCC. Clinical data were derived from the KEYNOTE-040 trial, which demonstrated improved overall survival for pembrolizumab versus SOC therapy. Model results suggested that if we considered the conventional WTP threshold of US$28,130/QALY as our cut-off, pembrolizumab was not cost-effective compared with standard therapy in r/mHNSCC, providing an ICER of US$88,271 per QALY. A large incremental cost and a slight benefit in health outcome led to the high ICER exceeding WTP threshold. Moreover, both univariate sensitivity analysis and probabilistic sensitivity analysis demonstrated robust cost-effectiveness results to uncertainty of model input parameters.

Similar economic assessments of pembrolizumab for the treatment of non-small cell lung cancer (NSCLC) in China consistently lead to the same conclusion. An

evaluation of pembrolizumab compared with chemotherapy for the treatment of PD-L1 positive, NSCLC in China resulted in an ICER of US$103,128 per QALY. However, results may be diverse in different countries or cancer types. Georgieva et al.[21] suggested that first-line pembrolizumab for advanced NSCLC may be cost-effective compared to platinum-doublet chemotherapy in the US but not in the UK, despite very similar ICER values in both countries. Sarfaty et al.[22] found that second-line pembrolizumab for advanced bladder cancer might be considered cost-effective in the US but not in the UK and Australia. The difference in cost-effectiveness and WTP thresholds between countries likely explained the difference in findings related to the cost-effectiveness of pembrolizumab.

This analysis also had several limitations. As with most cost-effectiveness analyses, 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. Also, since clinical outcomes and utilities were based on previously published studies instead of prospective data, the results in this analysis may be biased. Additionally, pembrolizumab could be a cost-effective strategy for treating patients with r/mHNSCC in developed countries with WTP thresholds greater than US$80,000. Finally, although PSA can directly reflect the influence of model uncertainty on the results, it generally assumes that the parameters are independent of each other, which may affect the credibility of the results of pharmacoeconomic evaluation. Considering that the results are still stable when the random simulations are carried out for 10,000 times, we believe that are credible.

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

Author affiliations

[1] Department of Pharmacy, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China

[2] Key Laboratory of Head and Neck Translational Research of Zhejiang Province, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China

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.

Funding This research was supported by Natural Science Foundation of Zhejiang Province (LQ18H160018) and Natural Science Foundation of China (81903898).

Competing interests None declared.

Patient consent Not required

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-86. doi: 10.1002/ijc.29210 [published Online First: 2014/09/16]

2. Fitzmaurice C, Allen C, Barber RM, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2017;3:524-48. doi: 10.1001/jamaoncol.2016.5688 [published Online First: 2016/12/06]

3. Beitler JJ, Zhang Q, Fu KK, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys* 2014;89:13-20. doi: 10.1016/j.ijrobp.2013.12.027 [published Online First: 2014/03/13]

4. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol* 2014;32:2940-50. doi: 10.1200/jco.2013.53.5633 [published Online First: 2014/08/27]

5. Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. *Ann Oncol* 2010;21 Suppl 7:vii252-61. doi: 10.1093/annonc/mdq453 [published Online First: 2010/10/15]

6. Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol* 2009;27:1864-71. doi: 10.1200/jco.2008.17.0530 [published Online First: 2009/03/18]

7. Argiris A, Ghebremichael M, Gilbert J, et al. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: an eastern cooperative oncology group trial. *J Clin Oncol* 2013;31:1405-14. doi: 10.1200/jco.2012.45.4272 [published Online First: 2013/03/06]

8. Soulieres D, Faivre S, Mesia R, et al. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Oncol*

2017;18:323-35. doi: 10.1016/s1470-2045(17)30064-5 [published Online First: 2017/01/31]

9. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol* 2007;25:2171-7. doi: 10.1200/jco.2006.06.7447 [published Online First: 2007/06/01]

10. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2018;378:1277-90. doi: 10.1056/NEJMoa1712126 [published Online First: 2018/03/22]

11. Vaughn DJ, Bellmunt J, Fradet Y, et al. Health-Related Quality-of-Life Analysis From KEYNOTE-045: A Phase III Study of Pembrolizumab Versus Chemotherapy for Previously Treated Advanced Urothelial Cancer. *J Clin Oncol* 2018;36:1579-87. doi: 10.1200/jco.2017.76.9562 [published Online First: 2018/03/29]

12. Carlino MS, Long GV, Schadendorf D, et al. Outcomes by line of therapy and programmed death ligand 1 expression in patients with advanced melanoma treated with pembrolizumab or ipilimumab in KEYNOTE-006: A randomised clinical trial. *Eur J Cancer* 2018;101:236-43. doi: 10.1016/j.ejca.2018.06.034 [published Online First: 2018/08/11]

13. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*

2019;393:1819-30. doi: 10.1016/s0140-6736(18)32409-7 [published Online First: 2019/04/09]

14. Cohen EEW, Soulieres D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet* 2019;393:156-67. doi: 10.1016/s0140-6736(18)31999-8 [published Online First: 2018/12/05]

15. A L-C, D F, JA D, et al. Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. *J Clin Oncol* 2015;33:3781-7.

16. JR B. Markov models in medical decision making: a practical guide. *Med decis making* 1993;13:322-38.

17. TJ H, L H, BJ M, et al. Bevacizumab in treatment of high-risk ovarian cancer--a cost-effectiveness analysis. *The oncologist* 2014;19:523-7.

18. Wu B, Dong B, Xu Y, et al. Economic evaluation of first-line treatments for metastatic renal cell carcinoma: a cost-effectiveness analysis in a health resource-limited setting. *PLoS One* 2012;7:e32530. doi: 10.1371/journal.pone.0032530 [published Online First: 2012/03/14]

19. Wu B, Ye M, Chen H, et al. Costs of trastuzumab in combination with chemotherapy for HER2-positive advanced gastric or gastroesophageal junction cancer: an economic evaluation in the Chinese context. *Clin Ther* 2012;34:468-79. doi: 10.1016/j.clinthera.2012.01.012 [published Online First: 2012/02/14]

20. Hannouf MB, Sehgal C, Cao JQ, et al. Cost-effectiveness of adding cetuximab to platinum-based chemotherapy for first-line treatment of recurrent or metastatic head and neck cancer. *PLoS One* 2012;7:e38557. doi: 10.1371/journal.pone.0038557 [published Online First: 2012/06/30]

21. Georgieva M, da Silveira Nogueira Lima JP, Aguiar P, Jr., et al. Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer. *Lung Cancer* 2018;124:248-54. doi: 10.1016/j.lungcan.2018.08.018 [published Online First: 2018/10/01]

22. Sarfaty M, Hall PS, Chan KKW, et al. Cost-effectiveness of Pembrolizumab in Second-line Advanced Bladder Cancer. *Eur Urol* 2018;74:57-62. doi: 10.1016/j.eururo.2018.03.006 [published Online First: 2018/03/27]

23. GE Liu SH, JH Wu, J Wu, L Yang, HC Li. China guidelines for pharmacoeconomic evaluations and manual. *Beijing: Science Press* 2015

24. S. Shepard D. Cost-effectiveness in Health and Medicine. By M.R. Gold, J.E Siegel, L.B. Russell, and M.C. Weinstein (eds). New York: Oxford University Press, 19961999.

TABLES

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	[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.

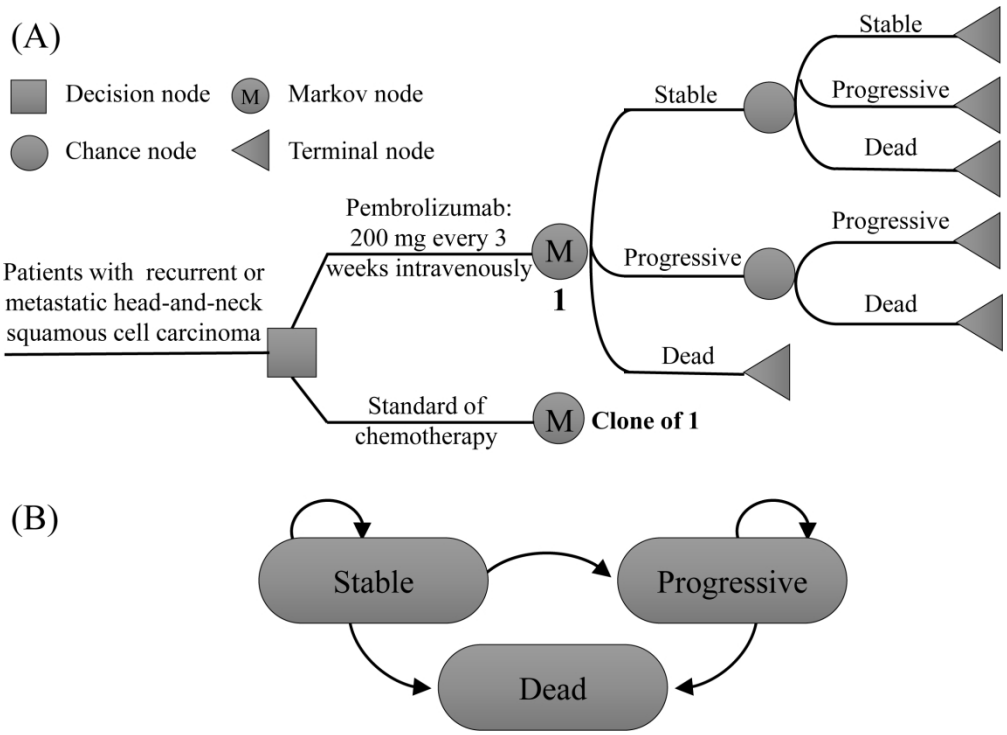


Figure 1 Model structure. (A) Abbreviated decision tree and Markov model; (B) Model states and transitions.

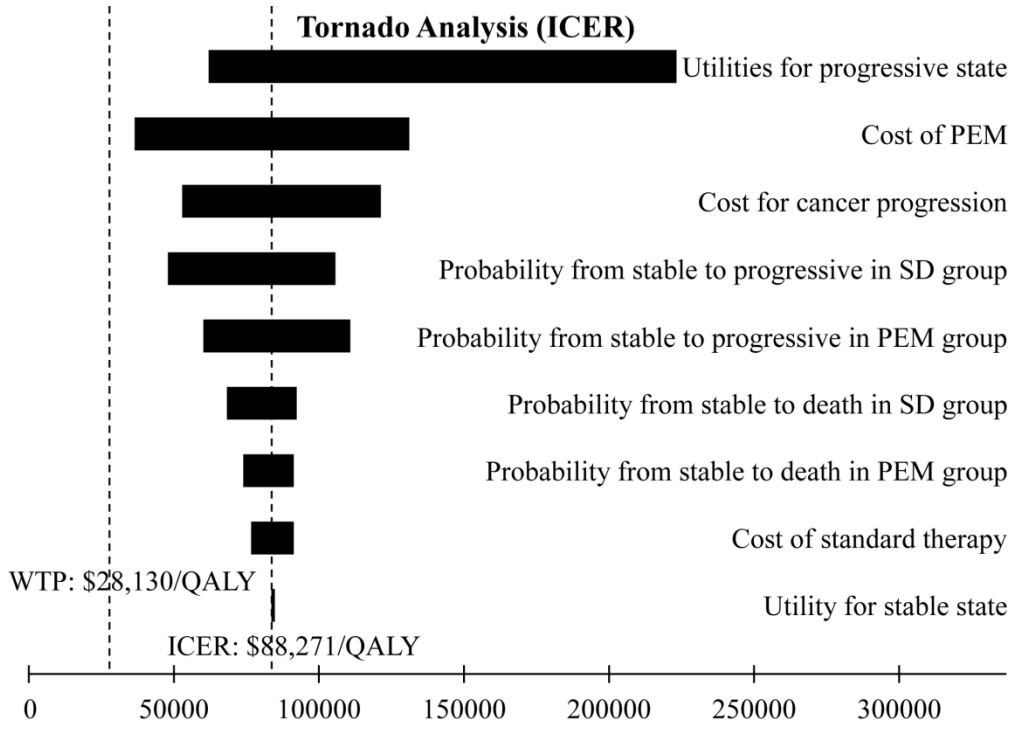


Figure 2 Tornado plot of the univariate sensitivity analyses for pembrolizumab vs. standard of care therapy.

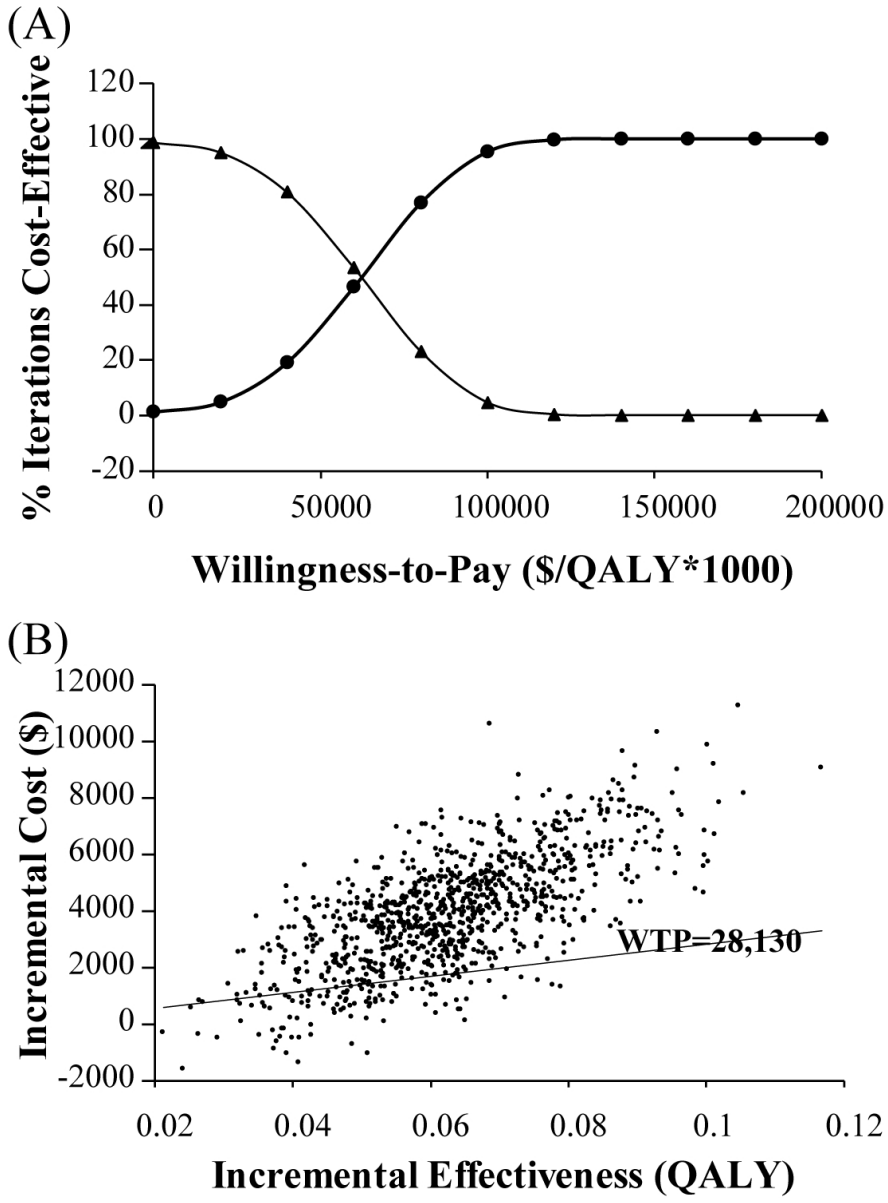


Figure 3 Probabilistic sensitivity analyses for pembrolizumab vs. SOC therapy. (A) Cost-effectiveness acceptability curve; (B) cost-effectiveness plane. WTP: willingness to pay; SOC: standard of care.

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038867.R1
Article Type:	Original research
Date Submitted by the Author:	03-Aug-2020
Complete List of Authors:	Xin, Wenxiu; Zhejiang Cancer Hospital, Department of Pharmacy Ding, Haiying; Zhejiang Cancer Hospital, Department of Pharmacy Fang, Qilu; Zhejiang Cancer Hospital, Department of Pharmacy Zheng, Xiaowei; Zhejiang Cancer Hospital, Department of pharmacy Tong, Yinghui; Zhejiang Cancer Hospital, Department of Pharmacy Xu, Gaoqi; Zhejiang Cancer Hospital, Department of Pharmacy Yang, Guonong; Zhejiang Cancer Hospital, Department of Pharmacy
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Oncology, Health economics
Keywords:	CLINICAL PHARMACOLOGY, HEALTH ECONOMICS, Head & neck tumours < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Wenxiu Xin,[1,2,3,#,*] Haiying Ding,[1,2,#] Qilu Fang, [1,2] Xiaowei Zheng,[1,2] Yinghui Tong,[1,2] Gaoqi Xu,[1,2] Guonong Yang[1,2,*]

[1] Department of Pharmacy, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China

[2] Institute of Cancer and Basic Medicine（IBMC）, Chinese Academy of Sciences, Hangzhou, China

[3] Key Laboratory of Head and Neck Translational Research of Zhejiang Province, Hangzhou, China

[#]These authors contributed equally to this work

[*]Corresponding author:
Wenxiu Xin
Department of Pharmacy, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), No.1 Banshan Road, Hangzhou 310022, China.
Tel: +86 8812 2438 Email: xinwx@zjcc.org.cn

Guonong Yang
Department of Pharmacy, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), No.1 Banshan Road, Hangzhou 310022, China.
Tel: +86 8812 2438 Email: yanggn@zjcc.org.cn

Word count: 2408

ABSTRACT

Background: 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 in China remained uncertain.

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

Design: 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's perspective of China. Costs and outcomes were discounted at an annual rate of 3.0%. Sensitivity analyses were conducted to test the uncertainties surrounding model parameters.

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

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

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

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 are 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. Indications of pembrolizumab approved by China Food and Drug Administration (CFDA) include melanoma, non-small cell lung cancer and esophageal cancer. Besides, because of the excellent tumor treatment effect, pembrolizumab is also widely used in HNSCC, small cell lung cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, gastric cancer, cervical cancer, colorectal cancer and many other cancer types according to the recommendations of indications approved by FDA and several guidelines such as NCCN (National Comprehensive Cancer Network) and CSCO (Chinese Society of Clinical Oncology).

The recently reported KEYNOTE-040[14] 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 months (95% CI: 6·4-9·4) in the pembrolizumab group and 6.9 months (95% CI: 5·9-8·0) in SOC group. Thus, pembrolizumab extended the median overall survival by 1.5 months. Also, patients in pembrolizumab group had a favorable safety profile compared with patients in SOC group. Although there is a significant improvement in the treatment of patients with r/mHNSCC, the prognosis remains relatively poor and the economic value of pembrolizumab in this population remains unknown. The objective of this study was to evaluate the cost-effectiveness of pembrolizumab compared with standard treatment, in order to find the more cost-effective therapy in the treatment of r/mHNSCC in China.

METHODS

Trial Background

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

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

Patients and Public Involvement

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

Model Structure

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

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

Cost

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

Utilities and outcome measures

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

1).

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

Sensitivity analysis

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

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

RESULTS

Base Case

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

compared with SOC therapy.

Sensitivity analyses

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

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

DISCUSSION

To our knowledge, this is the first cost-effectiveness analysis comparing pembrolizumab with methotrexate, docetaxel, or cetuximab for treating patients with r/mHNSCC. Clinical data were derived from the KEYNOTE-040 trial, which demonstrated improved overall survival for pembrolizumab versus SOC therapy. Model results suggested that if we considered the conventional WTP threshold of US$28,130/QALY as our cut-off, pembrolizumab was not cost-effective compared with standard therapy in r/mHNSCC, providing an ICER of US$65,186 per QALY. A large incremental cost and a slight benefit in health outcome led to the high ICER exceeding WTP threshold. Moreover, both univariate sensitivity analysis and probabilistic sensitivity analysis demonstrated robust cost-effectiveness results to uncertainty of model input parameters.

Similar economic assessments of pembrolizumab for the treatment of non-small cell lung cancer (NSCLC) in China consistently lead to the same conclusion[25]. An

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

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

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

Author affiliations

[1] Department of Pharmacy, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China

[2] Key Laboratory of Head and Neck Translational Research of Zhejiang Province, Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China

Contributors Study conception and design: WX, HD and GY; Acquisition of data: QF, XZ, YT and GX; Analysis and interpretation of data: WX and HD; Drafting of manuscript: WX and GY; All authors revised the first draft and agreed with the final version.

Funding This research was supported by Natural Science Foundation of Zhejiang Province (LQ18H160018) and Natural Science Foundation of China (81903898).

Competing interests None declared.

Patient consent Not required

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-86. doi: 10.1002/ijc.29210 [published Online First: 2014/09/16]
2. Fitzmaurice C, Allen C, Barber RM, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2017;3:524-48. doi: 10.1001/jamaoncol.2016.5688 [published Online First: 2016/12/06]
3. Beitler JJ, Zhang Q, Fu KK, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys* 2014;89:13-20. doi: 10.1016/j.ijrobp.2013.12.027 [published Online First: 2014/03/13]

4. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol* 2014;32:2940-50. doi: 10.1200/jco.2013.53.5633 [published Online First: 2014/08/27]

5. Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. *Ann Oncol* 2010;21 Suppl 7:vii252-61. doi: 10.1093/annonc/mdq453 [published Online First: 2010/10/15]

6. Stewart JS, Cohen EE, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol* 2009;27:1864-71. doi: 10.1200/jco.2008.17.0530 [published Online First: 2009/03/18]

7. Argiris A, Ghebremichael M, Gilbert J, et al. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: an eastern cooperative oncology group trial. *J Clin Oncol* 2013;31:1405-14. doi: 10.1200/jco.2012.45.4272 [published Online First: 2013/03/06]

8. Soulieres D, Faivre S, Mesia R, et al. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Oncol* 2017;18:323-35. doi: 10.1016/s1470-2045(17)30064-5 [published Online First: 2017/01/31]

9. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol* 2007;25:2171-7. doi: 10.1200/jco.2006.06.7447 [published Online First: 2007/06/01]

10. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2018;378:1277-90. doi: 10.1056/NEJMoa1712126 [published Online First: 2018/03/22]

11. Vaughn DJ, Bellmunt J, Fradet Y, et al. Health-Related Quality-of-Life Analysis From KEYNOTE-045: A Phase III Study of Pembrolizumab Versus Chemotherapy for Previously Treated Advanced Urothelial Cancer. *J Clin Oncol* 2018;36:1579-87. doi: 10.1200/jco.2017.76.9562 [published Online First: 2018/03/29]

12. Carlino MS, Long GV, Schadendorf D, et al. Outcomes by line of therapy and programmed death ligand 1 expression in patients with advanced melanoma treated with pembrolizumab or ipilimumab in KEYNOTE-006: A randomised clinical trial. *Eur J Cancer* 2018;101:236-43. doi: 10.1016/j.ejca.2018.06.034 [published Online First: 2018/08/11]

13. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019;393:1819-30. doi: 10.1016/s0140-6736(18)32409-7 [published Online First: 2019/04/09]

14. Cohen EEW, Soulieres D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet* 2019;393:156-67. doi: 10.1016/s0140-6736(18)31999-8 [published Online First: 2018/12/05]

15. A L-C, D F, JA D, et al. Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST

Study. *J Clin Oncol* 2015;33:3781-7.

16. JR B. Markov models in medical decision making: a practical guide. *Med decis making* 1993;13:322-38.
17. TJ H, L H, BJ M, et al. Bevacizumab in treatment of high-risk ovarian cancer--a cost-effectiveness analysis. *The oncologist* 2014;19:523-7.
18. Huang J, Liao W, Zhou J, et al. Cost-effectiveness analysis of adjuvant treatment for resected pancreatic cancer in China based on the ESPAC-4 trial. *Cancer Manag Res* 2018;10:4065-72. doi: 10.2147/cmar.s172704 [published Online First: 2018/10/17]
19. Wu B, Yao Y, Zhang K, et al. RAS testing and cetuximab treatment for metastatic colorectal cancer: a cost-effectiveness analysis in a setting with limited health resources. *Oncotarget* 2017;8:71164-72. doi: 10.18632/oncotarget.17029 [published Online First: 2017/10/21]
20. Wu B, Zhang Q, Sun J. Cost-effectiveness of nivolumab plus ipilimumab as first-line therapy in advanced renal-cell carcinoma. *J Immunother Cancer* 2018;6:124. doi: 10.1186/s40425-018-0440-9 [published Online First: 2018/11/22]
21. Wu B, Dong B, Xu Y, et al. Economic evaluation of first-line treatments for metastatic renal cell carcinoma: a cost-effectiveness analysis in a health resource-limited setting. *PLoS One* 2012;7:e32530. doi: 10.1371/journal.pone.0032530 [published Online First: 2012/03/14]
22. Wu B, Ye M, Chen H, et al. Costs of trastuzumab in combination with chemotherapy for HER2-positive advanced gastric or gastroesophageal junction cancer: an economic evaluation in the Chinese context. *Clin Ther* 2012;34:468-79. doi: 10.1016/j.clinthera.2012.01.012 [published Online First: 2012/02/14]
23. Zhang PF, Xie D, Wen F, et al. Lenalidomide plus rituximab Vs rituximab alone in relapsed or refractory indolent lymphoma: A cost-effectiveness analysis. *Cancer Med* 2020 doi: 10.1002/cam4.3121 [published Online First: 2020/06/04]
24. Hannouf MB, Sehgal C, Cao JQ, et al. Cost-effectiveness of adding cetuximab to platinum-based chemotherapy for first-line treatment of recurrent or metastatic head and neck cancer. *PLoS One* 2012;7:e38557. doi: 10.1371/journal.pone.0038557 [published Online First: 2012/06/30]
25. Wan N, Zhang TT, Hua SH, et al. Cost-effectiveness analysis of pembrolizumab plus chemotherapy with PD-L1 test for the first-line treatment of NSCLC. *Cancer Med* 2020;9:1683-93. doi: 10.1002/cam4.2793 [published Online First: 2020/01/17]
26. Georgieva M, da Silveira Nogueira Lima JP, Aguiar P, Jr., et al. Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer. *Lung Cancer* 2018;124:248-54. doi: 10.1016/j.lungcan.2018.08.018 [published Online First: 2018/10/01]
27. Sarfaty M, Hall PS, Chan KKW, et al. Cost-effectiveness of Pembrolizumab in Second-line Advanced Bladder Cancer. *Eur Urol* 2018;74:57-62. doi: 10.1016/j.eururo.2018.03.006 [published Online First: 2018/03/27]
28. GE Liu SH, JH Wu, J Wu, L Yang, HC Li. China guidelines for pharmacoeconomic evaluations and manual. *Beijing: Science Press* 2015
29. S. Shepard D. Cost-effectiveness in Health and Medicine. By M.R. Gold, J.E Siegel, L.B. Russell, and M.C. Weinstein (eds). New York: Oxford University Press, 19961999.

TABLES

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]

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.

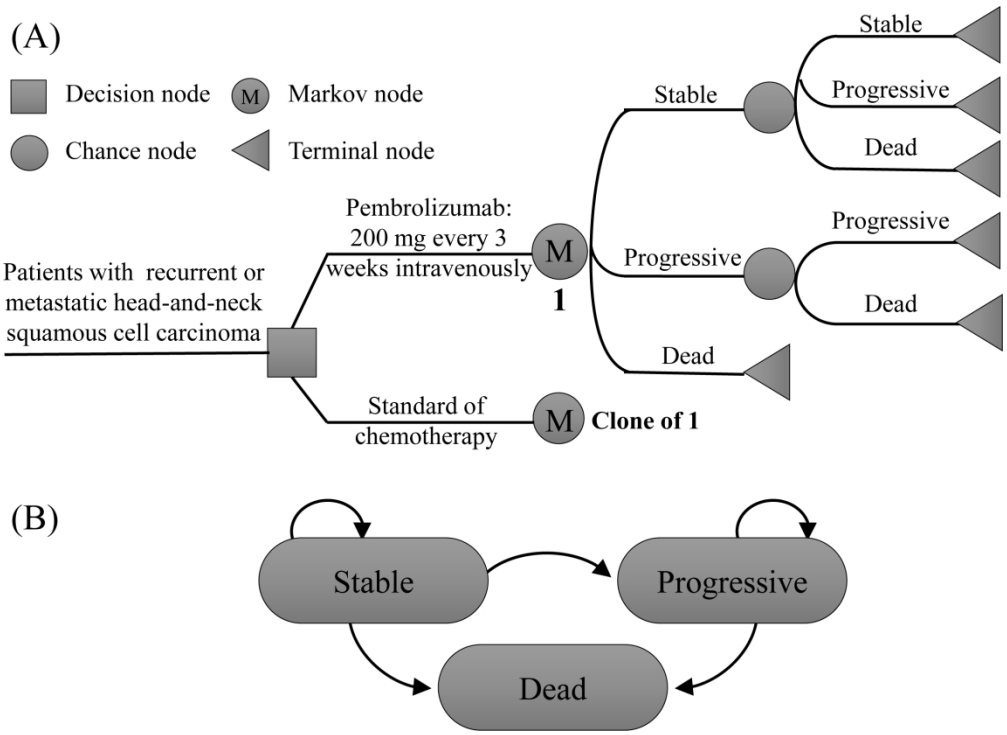
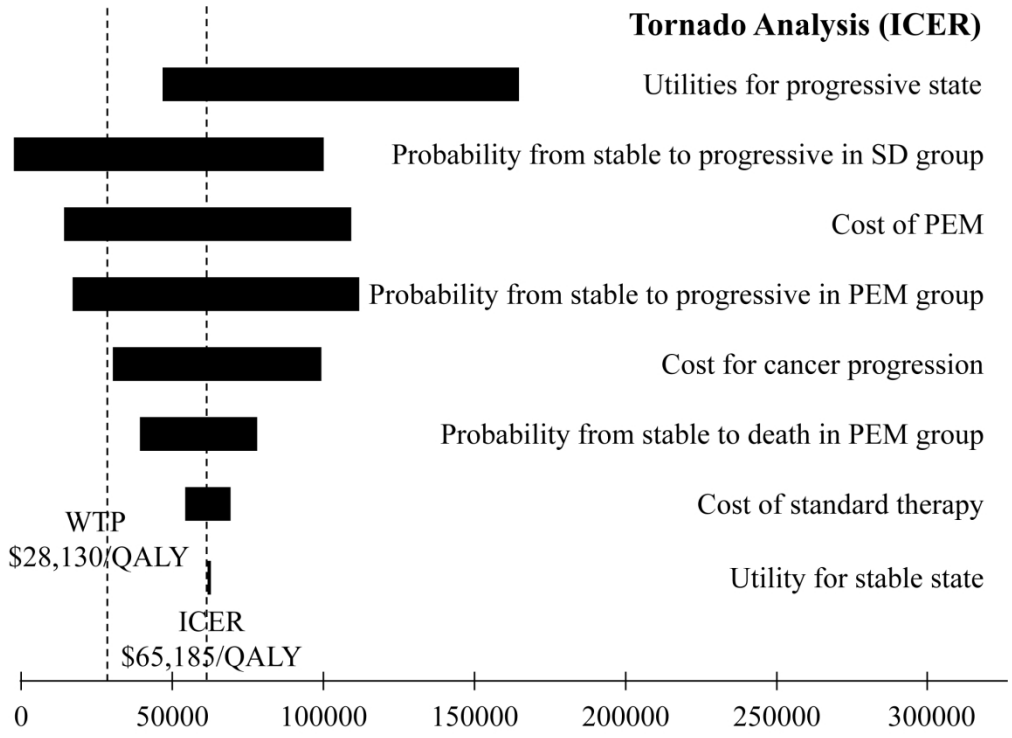
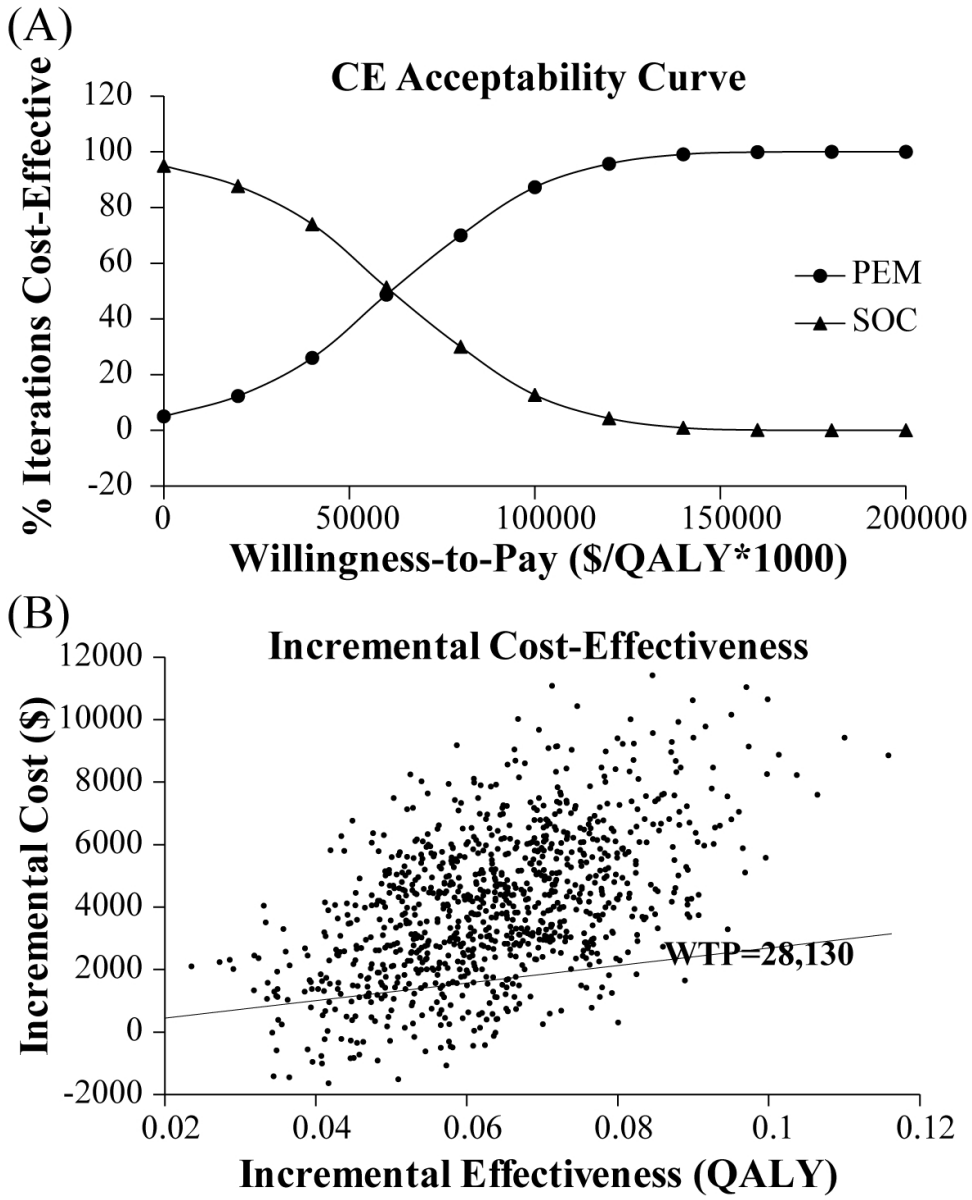


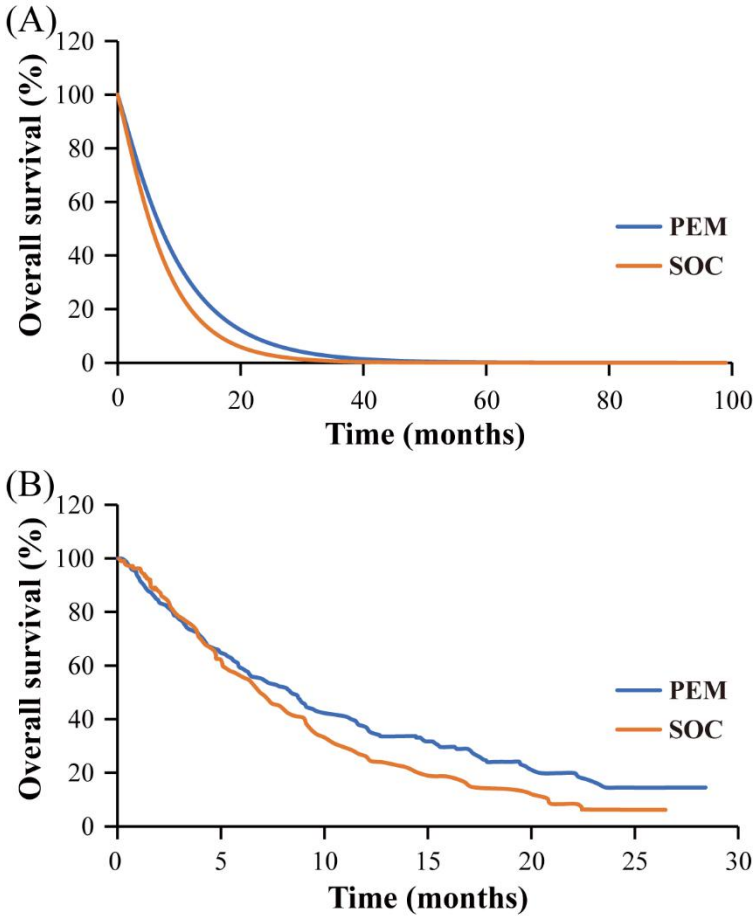
Figure 1 Model structure. (A) Abbreviated decision tree and Markov model; (B) Model states and transitions.



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.



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