PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Xin, Wenxiu; Ding, Haiying; Fang, Qilu; Zheng, Xiaowei; Tong, Yinghui; Xu, Gaoqi; Yang, Guonong

VERSION 1 – REVIEW

REVIEWER	Jan Sieluk Merck & Co USA
REVIEW RETURNED	13-May-2020

GENERAL COMMENTS	It is a well-written manuscript. Many thanks for the opportunity to review. A couple of edits/suggestions: 1. Please describe the current treatment landscape in China. 2. Please specify the accepted cost-effectiveness thresholds in China. The results suggest that pembro is cost-effective in the United States. 3. Please describe the rationale for the choice of a Markov model as compared to other CEA modeling approaches. 4. Can you please explain how the Markov model based on short-term clinical trial data was extrapolated for 30-years? Extrapolation approaches may carry forward a period of relatively high mortality within the first year post-diagnosis or post-trial enrollment, and over-estimate mortality risks in later years when surviving patients are in remission or cured. Thanks. 5. How were costs of subsequent therapy following discontinuation of initial trial regimens accounted for? Did you account for supportive care costs? The possible states in your Markov model would likely yield different results for progression-free disease management costs and progressed disease management costs. 6. Do you plan on including the costs of Terminal Cancer Care? Thank you.

REVIEWER	Qiu Li West China Hospital Sichuan University, China
REVIEW RETURNED	27-Jun-2020

GENERAL COMMENTS	1. In this paper, there are serveral errors of academic term. eg, P7, "KEYNOTE-040 test" should be "KEYNOTE-040 trial"; P8 "US$37.787 " should be "US$37,787" ？etc.

	2. The words and sentences should be brief in the whole manuscript. 3. The time cost calculation is not well described. 4. The survival assumption in this study used equation, it is better to show the modeled survival curve compared with that in the trial. 5. In this paper, several citations are not rigorous. eg, “All costs in the model were adjusted to US dollars based on the 2018 average exchange rate (US$ = CYN 6.6174) ” ; "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" ;"Similar economic assessments of pembrolizumab for the treatment of non-small cell lung cancer (NSCLC) in China consistently lead to the same conclusion.",etc. Here are no references.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name
Jan Sieluk

Institution and Country
Merck & Co
USA

Please state any competing interests or state ‘None declared’:
Merck employee

Please leave your comments for the authors below
It is a well-written manuscript. Many thanks for the opportunity to review. A couple of edits/suggestions:

1. Please describe the current treatment landscape in China.
Response: Thank you for your positive comments. As suggested, we provided more detailed descriptions about the current treatment landscape of pembrolizumab in China. 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) et al. For more information, see the following: page 4, Line 3-11.

2. Please specify the accepted cost-effectiveness thresholds in China. The results suggest that pembro is cost-effective in the United States.
Response: In the incremental analysis, there is no unified standard on the value of QALYs in China at present. WHO has a recommendation for the economic evaluation with DALYs (Disability-Adjusted Life Years) as the output indicator: If ICER < per capita GDP, the increased cost is totally worth it; If per capita GDP < ICER < 3times per capita GDP, the increased cost is acceptable; If ICER > 3 times

per capita GDP, the increased cost is not worth it (WHO, 2010). The concepts of QALYs and DALYs are similar, both taking into account the survival time and survival status of patients in the disease state (health utility value is used in QALYs and disability index is used in DALYs). Since there is no recommendation for QALYs threshold in China and WHO, when the output index is QALYs, researchers can refer to the recommendation of WHO for DALYs according to 'China Guidelines for Pharmacoeconomic Evaluations 2019'.
China's per capita GDP in 2018 was US$9376.97. 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 (page 7, line 5-8).
We agree that the results of cost-effectiveness analysis will vary in developed and developing countries. Pembrolizumab may be cost-effective in some developed countries with higher WTP. In response to this question, we already took this into account when we began this study and you can refer to page 9, line 3-10 for detail.

3. Please describe the rationale for the choice of a Markov model as compared to other CEA modeling approaches.
Response: There are many types of models used in pharmacoeconomic evaluation, and they are still in the process of continuous development. Among them, the more commonly used models are Decision Tree model, Discrete Events Simulation Model, Markov model and Dynamic Transmission Models. The Decision Tree model is suitable for pharmacoeconomic evaluation of transient diseases with short research time, such as acute infection. Discrete Events Simulation Model is a model method which can be used to express the interaction between individual behavior, individual and individual, individual and group, as well as individual and environment. The Dynamic Transmission Model is mainly used to simulate the occurrence and development of diseases that can be transmitted among people, and can also simulate the direct and indirect effects that infectious disease control plans may have on the process. These three models are not suitable for the economic evaluation of malignant tumors.
Markov model is a special cyclic decision tree model, which is widely used to simulate chronic diseases in pharmacoeconomics (An Introduction to Markov Modelling for Economic Evaluation. Pharmacoeconomics. 1998 Apr;13(4):397-409.). Moreover, Markov model is also a commonly used model in the study of pharmacoeconomic evaluation for malignant tumors. Thus, we chose this model for the analysis. Several articles applying this model are listed below:
1) Cost-Effectiveness Analysis of Brentuximab Vedotin With Chemotherapy in Newly Diagnosed Stage III and IV Hodgkin Lymphoma. J Clin Oncol. 2018 Oct 4;36(33):JCO1800122. doi: 10.1200/JCO.18.00122.
2) Cost-Effectiveness of Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2016 Mar 20;34(9):902-9.
3) Cost-Effectiveness of Immune Checkpoint Inhibition in BRAF Wild-Type Advanced Melanoma. J Clin Oncol. 2017 Apr 10;35(11):1194-1202.

4. Can you please explain how the Markov model based on short-term clinical trial data was extrapolated for 30-years? Extrapolation approaches may carry forward a period of relatively high mortality within the first year post-diagnosis or post-trial enrollment, and over-estimate mortality risks in later years when surviving patients are in remission or cured. Thanks.
Response: Thanks very much for your kind reminder.
The markov model is usually composed of basic elements such as markov health status, cycle, transition probability, health output and cost, etc. The markov model divides the disease process into multiple mutually exclusive health states. The tendency of a patient to make a transition from one state to another is described by the transition probabilities. When most of the subjects are in the absorption state or reach a preset number of cycles, the model is terminated and the final cost effectiveness is obtained. Transition probabilities of every state were calculated based on the

following equation: P (1 month) = 1-0.5(1/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).

5. How were costs of subsequent therapy following discontinuation of initial trial regimens accounted for? Did you account for supportive care costs? The possible states in your Markov model would likely yield different results for progression-free disease management costs and progressed disease management costs.
Response: Thanks for your question, which can promote us for further thinking and exploration.
(1) It is assumed that after tumor progression or drug intolerance, the follow-up treatment regimen is the same in both groups. Thus, the cost in both arms are the same. The cost after cancer progression were obtained from the previously published literature (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.).
(2) We fully agree with you and re-include the cost of supportive care and terminal cancer care. For more information about the cost, please see Table 1.

6. Do you plan on including the costs of Terminal Cancer Care?
Response: We fully agree with you and re-include the cost of supportive care and terminal cancer care. For more information about the cost, please see Table 1.
When the cost of supportive care and terminal cancer care were included, total costs incurred was US$45,861 in the pembrolizumab group and US$41,950 in the SOC group. These results led to a lower ICER US$65,186 per QALY, which was still higher than WTP.
Thank you again for your rigorous review.

Reviewer: 2
Reviewer Name
Qiu Li

Institution and Country
West China Hospital Sichuan University, China

Please state any competing interests or state ‘None declared’:
None.

Please leave your comments for the authors below

1. In this paper, there are serveral errors of academic term. eg, P7, "KEYNOTE-040 test" should be "KEYNOTE-040 trial"; P8 "US$37.787 " should be "US$37,787" ? etc.
Response: Thank you for bringing our attention to this error. We have corrected the two places you mentioned. In addition, we also checked the full text and corrected some minor mistakes. The correction part is highlighted in red.

2. The words and sentences should be brief in the whole manuscript.
Response: We have modified the words and sentences of the full text. We found some minor mistakes and changed some complex sentences to make them easy to understand. All changes are marked in red.

3. The time cost calculation is not well described.
Response: Thanks for your kinder reminder. Time cost has been re-described as “time cost was estimated at US$35.73 per day on the basis of the average monthly salary in China in 2018”. The corresponding changes are in Page 6, line 15-18 and Table 1.

4. The survival assumption in this study used equation, it is better to show the modeled survival curve compared with that in the trial.
Response: The modelled survival curves and survival curves in the trial in the both groups have been provided as supplementary data.

5. In this paper, several citations are not rigorous. eg, “All costs in the model were adjusted to US dollars based on the 2018 average exchange rate (US$ = CYN 6.6174) ”; "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"; "Similar economic assessments of pembrolizumab for the treatment of non-small cell lung cancer (NSCLC) in China consistently lead to the same conclusion.",etc. Here are no references.
Response: Thank you for the rigorous and professional review of the article. We have revised these details one by one.
(1) The sentence “All costs in the model were adjusted to US dollars based on the 2018 average exchange rate (US$ = CYN 6.6174)” has been revised as “All costs in the model were adjusted to US dollars based on the 2018 average exchange rate (US$ 1 = CNY 6.6174).” For more information, please see Page 6, line 21-23.
(2) The sentence "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" has been revised as “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.” For more information, please see Page 6, line 25-27.
(3) The reference literature of this sentence has been added to the article. Here are the details of the references: “Wan, N; Zhang, T.T.; Hua, S.H.; Lu, Z.L.; Ji, B.; Li, L.X.; Lu, L.Q.; Huang, W.J.; Jiang, J.; Li, J., Cost-effectiveness analysis of pembrolizumab plus chemotherapy with PD-L1 test for the first-line treatment of NSCLC. Cancer medicine 2020, 9 (5), 1683-1693.” For more information, please see Page 8, line 27.

VERSION 2 – REVIEW

REVIEWER	Qiu Li Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, China
REVIEW RETURNED	03-Nov-2020

GENERAL COMMENTS	This work is described clearly and well-done. The manuscript needs only some minor revisions before being accepted. P4: The added texts in red should have reference notes. P9: "An evaluation ... US$103,128 per QALY." in the manuscript. The reference should be "Liao W, et al. Cost-effectiveness analysis of first-line pembrolizumab treatment for PD-L1 positive, non-small cell lung cancer in China. Journal of medical economics 2019;22:344-349."