PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness analysis of pembrolizumab plus chemotherapy for previously untreated metastatic non-small-cell lung cancer in the United States
AUTHORS	Zeng, Xiaohui; Wan, Xiaomin; Peng, Liubao; Peng, Ye; Ma, Fang; Liu, Qiao; Tan, Chongqing

VERSION 1 – REVIEW

REVIEWER	David W. Hutton University of Michigan United States of America
REVIEW RETURNED	08-May-2019

GENERAL COMMENTS	Cost-effectiveness analysis of pembrolizumab plus chemotherapy for previously untreated metastatic non-small-cell lung cancer in the United States Overall, this is a nice study. The model health states are appropriate and it appears the methods to take the trial results and use them in the model are reasonable. The most important cost categories appear to be incorporated and the utilities seem reasonable. The analysis and the results are well-presented. I appreciate the CHEERS checklist. I do have some minor comments: p2, line 64 says: "Immune checkpoint inhibitors showed higher efficacy and less toxicity compared to other [3]." Did the authors mean to say, "Immune checkpoint inhibitors showed higher efficacy and less toxicity compared to other therapies[3]." p3 line 68 I would say approved instead of ratified The wording in the discussion could be improved for readability. for example: p 6 "These results showed that the cost-effectiveness probability of pembrolizumab plus chemotherapy was 0% under the condition of a WTP threshold of $130,000/QALY" and "There were many published study estimated the cost-effectiveness of pembrolizumab monotherapy as first-line setting for advanced NSCLC across multiple countries"

	Figure 2: I would replace the TreeAge labels with more meaningful names (e.g. "cPFS_Pem" is "Cost in PFS with Pembrolizumab") Somewhat more substantive comments: Methods: When calculating the probabilities you say that you did a good fit. It would be nice to see graphically that your fit with the Weibull and exponential fits matched the trial data. This could maybe be an appendix graph. Results/Sensitivity: Your analysis shows that pembolizumab is not cost-effective at a threshold of $100,000/QALY. That is very nice to know. $100,000/QALY is probably a reasonable threshold. But, there is no hard consensus on this and there are some that might argue that is not appropriate or that there are other reasonable thresholds for the United States(e.g. see: "What is the Price of Life and Why Doesn't It Increase at the Rate of Inflation", Ubel, Hirth, Chernew. Arch Inter Med, 2003 or "Updating cost-effectiveness-the curious resiliance of the $50,000-per-QALY threshold" Neumann, Cohen, Weinstin, NEJM, 2014) A sensitivity analysis showing the incremental cost-effectiveness ratio based on varying the price per mg of pembrolizumab would be valuable. You could show the various prices at which pemborlizumab could be considered cost-effective (based on various thresholds readers may have in mind). To answer this question, you may need to disaggregate the cPFS_Pem (and cPD_Pla) variables to be a function of the cost per mg of pembrolizumab. Discussion: I think the discussion could add additional nuance to how your study fits in with the existing literature. For example, your study is based on Keynote 189 and others used data from different trials (e.g that focused on PD-L1 positive patients). You are looking at first-line therapy and others might be looking at second-line therapy. Your study is focused on the US (which has different prices than in Switzerland, Australia, China, France, or Canada). How might these differences between the studies affect their cost-effectiveness conclusions?

REVIEWER	Ramses Sadek Augusta University, USA
REVIEW RETURNED	25-Jul-2019

GENERAL COMMENTS	Well written article. However, It would like to see a comparison with another treatment. Very difficult to put a dollar value for life but comparing the effect of treatment with another standard of care or competitor would be beneficial.

REVIEWER	Jian-Guo ZHOU Zunyi Medical University, China
REVIEW RETURNED	15-Sep-2019

GENERAL COMMENTS	1. The critical point is the author use Medicare database, but the authors did not show the licence of this databse. " The cost information was from Medicare in 2018."

	2. The US database is total difference of china policy, please give me a response. 3. The result of pembrolizumab Plus CT for naive IV NSCLC, but the result should give the subgroup by the NCCN or CSCO, ASCO guideline. 4. The difference of insurance between China and USA, should be discussed.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
First, we are pleased that the reviewer considers our article is a nice study.

1. p2, line 64 says:
"Immune checkpoint inhibitors showed higher efficacy and less toxicity compared to other [3]." Did the authors mean to say,
"Immune checkpoint inhibitors showed higher efficacy and less toxicity compared to other therapies[3]."
Reply: We apologize for our carelessness and the sentence have been revised;
“Immune checkpoint inhibitors showed higher efficacy and less toxicity compared to other.”
to;
“Immune checkpoint inhibitors showed higher efficacy and less toxicity compared to other therapies.”

2. p3 line 68
I would say approved instead of ratified
Reply: Edited as suggested.

3. The wording in the discussion could be improved for readability. for example:
p 6
"These results showed that the cost-effectiveness probability of pembrolizumab plus chemotherapy was 0% under the condition of a WTP threshold of $130,000/QALY"
and
"There were many published study estimated the cost-effectiveness of pembrolizumab monotherapy as first-line setting for advanced NSCLC across multiple countries"
Reply: We have revised the sentence;
“These results showed that the cost-effectiveness probability of pembrolizumab plus chemotherapy was 0% under the condition of a WTP threshold of $130,000/QALY”
to;
“The results showed that the probability of pembrolizumab plus chemotherapy being cost-effective was 0% at a WTP threshold of $130,000/QALY”
And;
“There were many published study estimated the cost-effectiveness of pembrolizumab monotherapy as first-line setting for advanced NSCLC across multiple countries”
to;
“There are many other studies that have analyzed the cost-effectiveness of pembrolizumab monotherapy for advanced NSCLC in different setting”

4. I would replace the TreeAge labels with more meaningful names (e.g. "cPFS_Pem" is "Cost in PFS with Pembrolizumab")
Reply: We have modified Figure 2 and replaced all TreeAge labels with more meaningful names.

5. Methods:
When calculating the probabilities you say that you did a good fit. It would be nice to see graphically that your fit with the Weibull and exponential fits matched the trial data. This could maybe be an appendix graph.
Reply: We thank the reviewer for the useful suggestion. We now add a supplementary appendix 1 and the sentence in the first paragraph of the results;
“Weibull and exponential models used to fit the survival curves from the clinical trial (supplementary appendix 1), which show that the decision analysis model established in this study can reflect the clinical effects very well.”

6. Results/Sensitivity: Your analysis shows that pembolizumab is not cost-effective at a threshold of $100,000/QALY. That is very nice to know. $100,000/QALY is probably a reasonable threshold. But, there is no hard consensus on this and there are some that might argue that is not appropriate or that there are other reasonable thresholds for the United States(e.g. see:
"What is the Price of Life and Why Doesn't It Increase at the Rate of Inflation", Ubel, Hirth, Chernew. Arch Inter Med, 2003
or
"Updating cost-effectiveness-the curious resiliance of the $50,000-per-QALY threshold" Neumann, Cohen, Weinstin, NEJM, 2014)
A sensitivity analysis showing the incremental cost-effectiveness ratio based on varying the price per mg of pembrolizumab would be valuable. You could show the various prices at which pemborlizumab could be considered cost-effective (based on various thresholds readers may have in mind).
To answer this question, you may need to disaggregate the cPFS_Pem (and cPD_Pla) variables to be a function of the cost per mg of pembrolizumab.
Reply: We thank the reviewer for the comment and suggestion. According to the suggestion of Neumann et al1, we set thresholds of $100,000 and $150,000 to explore the price at which pemborlizumab can be considered cost-effective. We now add Table 2 and the sentence in the first paragraph of the results;
“When pembrolizumab cost $12.05 and $31.38/mg , the ICERs approximated the WTP thresholds of $100,000 and $150,000/QALY, respectively (Table2).”

Reference:
1. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014; 371: 796-797.

7. Discussion:
I think the discussion could add additional nuance to how your study fits in with the existing literature. For example, your study is based on Keynote 189 and others used data from different trials (e.g that focused on PD-L1 positive patients).
You are looking at first-line therapy and others might be looking at second-line therapy. Your study is focused on the US (which has different prices than in Switzerland, Australia, China, France, or Canada). How might these differences between the studies affect their cost-effectiveness conclusions?
Reply: We thank the reviewer for the useful suggestion. We have updated the second paragraph of The Discussion section;
“There were many published study estimated the cost-effectiveness of pembrolizumab monotherapy as first-line setting for advanced NSCLC across multiple countries, with ICERs ranging from $52,000/QALY to $110,000/QALY, and if pembrolizumab monotherapy was used as a second-line treatment, the ICER was $168,619/QALY compared with docetaxel. As a second-line treatment compared with docetaxel, the value of another immunosuppressive agent (nivolumab) was also evaluated to have the ICERs of A$220,029/QALY, CHF177,478/QALY and $15,229/QALY, from the perspective of Australia, Swiss and Canada, respectively. Obviously the ICER we gained is

comparable with the previous published studies of immunosuppressive agents used for second-line treatment. These data provide reference value for evaluating the total cost of therapy and the value of regimens for advanced NSCLC."
to;
"There are many other studies that have analyzed the cost-effectiveness of pembrolizumab for advanced NSCLC in different setting. In the KEYNOTE-024 trial, pembrolizumab demonstrated the incremental survival benefits and better safety profile versus chemotherapy for first-line treatment of PD-L1 -positive (≥50%) metastatic NSCLC patients, Based on the KEYNOTE-024 trial, a US-based study found that pembrolizumab was cost effective, with an ICER of $97,621/QALY, a study by Georgieva et al. demonstrated that pembrolizumab monotherapy was cost-effective in the US but not the UK, a study by Hu X et al. conducted in the UK demonstrated that pembrolizumab plus chemotherapy was not cost-effective, with an ICER of £86,913/QALY, and a French study foud that pembrolizumab appears cost-effective. Our results differ from the above results may be due to different health systems and costs in different countries, which leads to different cost-effectiveness conclusions. Based on the KEYNOTE-010 trial, a study analysed the cost-effectiveness of pembrolizumab and docetaxel as second-line treatment for PD-L1 positive advanced NSCLC from the US third-party payer perspective. The results showed that the ICER was $168,619/QALY, which was cost-effective at a threshold of three times GDP per capita ($171,660). These data provide reference value for evaluating the total cost of therapy and the value of regimens for advanced NSCLC"

Reviewer: 2

1. Well written article. However, It would like to see a comparison with another treatment. Very difficult to put a dollar value for life but comparing the effect of treatment with another standard of care or competitor would be beneficial.
Reply: We thank the reviewer for the comment and suggestion. Our study directly compared pembrolizumab plus chemotherapy with chemotherapy according to the KEYNOTE-189 trial. Although there are other potential first-line treatments for advanced non-small cell lung cancer, our study did not indirectly compare them because of the lack of convincing trial data and robust head-to-head trial data. We now add the following text in the limitation (the forth paragraph of Discussion);
"Finally, Our study directly compared pembrolizumab plus chemotherapy with chemotherapy according to the KEYNOTE-189 trial. Although there are other potential first-line treatments for advanced non-small cell lung cancer, our study did not indirectly compare them because of the lack of convincing trial data and robust head-to-head trial data."

Reviewer: 3

1. The critical point is the author use Medicare database, but the authors did not show the licence of this databse. " The cost information was from Medicare in 2018."
Reply: We thank the reviewer for the comments. The Medicare database is freely available, similar to our previous research in which Medicare database was used to derive unit cost of drug1,2.
Reference:
1. Wan XM, Peng LB, Ma JA, et al. Economic evaluation of nivolumab as a second-line treatment for advanced renal cell carcinoma from US and Chinese perspectives. Cancer. 2017; 123(14):2634-2641.
2. Wan X, Luo X, Tan C, et al: First-line atezolizumab in addition to bevacizumab plus chemotherapy for metastatic, nonsquamous non-small cell lung cancer: A United States-based cost-effectiveness analysis. Cancer, 2019

2. The US database is total difference of china policy, please give me a response

Reply: We think there may be some misunderstandings here. Our research is conducted from the perspective of US payers, so there is no need to discuss them from the perspective of China.

3. The result of pembrolizumab Plus CT for naive IV NSCLC, but the result should give the subgroup by the NCCN or CSCO, ASCO guideline.
Reply: We thank the reviewer for the comment and suggestion. Most of the treatment of NCCN or CSCO, ASCO guidelines are similar but there are subtle differences. Therefore, the subgroup by NCCN or CSCO, ASCO is interesting to readers. However, due to the lack of robust trial data, we have not evaluated them. When more accurate trial data is available, further study can be made.

4. The difference of insurance between China and USA, should be discussed.
Reply: We think there may be some misunderstandings here. Our research is conducted from the perspective of the US payer, there is no need to discuss the differences between China and the United States.

VERSION 2 – REVIEW

REVIEWER	David Hutton University of Michigan
REVIEW RETURNED	23-Oct-2019

GENERAL COMMENTS	I am satisfied with the updates to the manuscript.

REVIEWER	Jianguo Zhou Universitätsklinikum Erlangen Department of Radiation Oncology Universitätsstr. 27, 91054, Erlangen, Germany
REVIEW RETURNED	17-Oct-2019

GENERAL COMMENTS	Release of SEER-Medicare data is project specific. You must have an approved application in order to access these files. You may only access these files to work on the project as it was described in the approved application. Any other analysis must be submitted as a new application with all the appropriate paperwork. No work can begin on any new aim/project until all approvals have been secured. Datasets containing any restricted variables may only be accessed to work on the project for which the release of the restricted variables was approved. These data cannot be used for any subsequent analysis. Please be aware that in compliance with CMS, we no longer release SEER-Medicare data outside the USA. please check this in the link:https://healthcaredelivery.cancer.gov/seermedicare/obtain/requests.html And, i just want the authors according Guideline to subgroup Analysis the Treatment line or histology or stage et al, but they did not work.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

1. Release of SEER-Medicare data is project specific. You must have an approved application in order to access these files. You may only access these files to work on the project as it was described in the approved application. Any other analysis must be submitted as a new application with all the appropriate paperwork. No work can begin on any new aim/project until all approvals have been secured.
Datasets containing any restricted variables may only be accessed to work on the project for which the release of the restricted variables was approved. These data cannot be used for any subsequent analysis.
Please be aware that in compliance with CMS, we no longer release SEER-Medicare data outside the USA.
please check this in the link:https://healthcaredelivery.cancer.gov/seermedicare/ obtain/requests.html
And, i just want the authors according Guideline to subgroup Analysis the Treatment line or histology or stage et al, but they did not work.
Reply: We thank the reviewer for the comments. The cost we used in our manuscript is not the SEER-Medicare data, but the publicly free data from the Center for Medicare & Medicaid Services; https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html
And we apologize that we did not understand the meaning of the review last time. Based on the forest plot in clinical trials, we have selected three subgroups for analysis and the results are shown in Supplementary appendix 2. We now add the following text in the results;
“The results of the subgroup analysis showed that pembrolizumab combined with chemotherapy was the most cost-effective (36%) for patients who had never smoked at a WTP threshold of $100,000. When the WTP threshold was $150,000, the probability of pembrolizumab combined with chemotherapy being cost-effective in the subgroup of never-smoking and female patients was 100% (Supplementary Appendix 2).”