Peer Review File

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Reviewer A

1) Line 32-33: There are few drug options for advanced non-small cell lung cancer (NSCLC) after first-line and second-line treatment failure? in China?

Reply: The previous statement was unclear. The background section of the abstract has been revised to describe the importance of pharmacoeconomics in the treatment of advanced NSCLC. (see Page 2, line 26-29)

2) Line 34 The price of anlotinib in China fell this year. That's why the study was done.?

Reply: Yes. The change in price is one of the reasons why we conducted this study. We have modified our text as advised (see Page 2, line 34-36).

3) Present the results of OWSA and PSA in abstract since you refer the owsa and psa in methods.

Reply: Thank you for pointing this out. We have modified our text as advised (see Page 2-3, line 51-54).

4) why a Markov model was chosen?

Reply: The Markov model is currently one of the most commonly used pharmacoeconomic evaluation models in the field of advanced cancer. It can simulate and calculate the lifetime cost and health output of patients based on clinical trial results of drugs and cost data. Therefore, this study chose the Markov model.

5) Why A 5% discount rate per year was adopted for both the costs and outcomes, why 5%?

Reply: A 5% discount rate per year was adopted for both the costs and outcomes, which was recommended by China guidelines for pharmacoeconomic evaluations in 2020. We have modified our text as advised (see Page 5, line 144-145).

6) Line 150-154 please report the source of Utility values

Reply: We have modified our text as advised (see Page 6, line 176).

7) The % of pts who receive subsequent therapy?

Reply: According to the real-world data used in this article, approximately 59.3% of patients receive follow-up treatment after the progression of third line treatment (see Page 7, line 190-191).

8) Line 174 were obtained from other published studies or real-world data please add refs

Reply: We have modified our text as advised (see Page 7, line 201-202).

9) Are any differences between the current study and Huang study?

Reply: Huang's study was published in 2020 and used the previous price of anlotinib. Huang's study showed that anlotinib was not a cost-effective regimen as the third-line and later treatment for the patients with advanced non-small cell lung cancer from the Chinese societal perspective. After medical insurance negotiations and drug price adjustments, anlotinib was included in the medical insurance catalog. The newest price was applied in our study. Our results showed that after price adjustment, anlotinib has become cost-effective compared to placebo in advanced NSCLC (see Page 10, line 286-287).

10) Please provide the limitations of the study

Reply: Thank you for pointing this out. The present study had limitations. The efficacy data of this study was obtained from the ALTER 0303 trial. However, there were still differences between the clinical trial and the real world, leading to potential uncertainty in the extrapolation of research results in the real world. Besides that, individual patient data from the ALTER 0303 study were unavailable, and we used the KM survival curve reported in the ALTER 0303 trial to reconstruct individual data. Although this is currently the most common method in the field of pharmacoeconomics, there may still be differences with real individual patient data, leading to some bias in the research results. We have modified our text as advised (see Page10, line 294-308).

Reviewer B

Smart and interesting. The topic of costs is extremely important for the sustainability of the system, especially concerning the cancer world (Lancet Reg Health Eur 2021;3:100060). I personally find it smart to shift attention to subsequent lines and to what has already been demonstrated with immunotherapy (in particular in NSCLC) in terms of cost-effectiveness (Clin Lung Cancer 2017;18:e363-e365). This should be stressed in the discussion citing the papers above.

Reply: Thank you for your positive feedback. We agree with the reviewer's comments. The health expenditure on cancer care has been a global concern. It is important to strike a balance between the costs of treatment and the added value represented by the improvement of the clinical parameters of interest. The third-line treatment options for advanced NSCLC include immunotherapy, chemotherapy, other anti angiogenic therapies, or participation in clinical trials. Among them, the cost-effectiveness of immunotherapy in the treatment of advanced

NSCLC has received considerable attention. We have modified our text as advised (see Page 9, line 261-264; Page 10, line 300-302; Page 12-13, line 392-400).

Reviewer C

1) First, the abstract needs some revisions. The background did not emphasize the importance of cost-effectiveness data for assessing an anticancer drug and what the potential clinical significance of this research focus is. In the methods, the authors need to describe how the effectiveness and cost data were calculated and how the sensitivity analysis was performed. The results need to report the findings from the sensitivity analysis. The conclusion needs comments for the clinical implications of the findings, not to repeat the main findings again.
   Reply: We have modified our text as advised (see Page 2-3, line 25-62).

2) Second, in the introduction of the main text, the authors need to have some reviews on the importance of the evaluation of the cost-effectiveness data and the progress in the methodology of the assessment of cost-effectiveness. In this part, the authors need to explain why the clinical data from ALTER0303 can be used to as the basis for cost-effectiveness analysis, because in general the sample in clinical trials is highly selective, making the findings from such studies difficult the generalize to the real-world patients.

Reply: Pharmacoeconomics has been used in health decisions, especially the drug price negotiation policy to adjust the National Reimbursement Drug Lists (NRDL), in China since 2017. ALTER0303 trial was currently the highest quality clinical study published for the use of anlotinib in Chinese patients with advanced NSCLC. The enrolled patients of ALTER0303 were basically consistent with the target patient population of this study, so our study conducted pharmacoeconomic evaluation based on the ALTER0303 trial. We have modified our text as advised (see Page 4, line 108-112; Page 5, line 126-130).

3) Third, in the methodology, the controls from the ALTER0303 trial are receiving placebo treatment, but the results would be more clinically relevant if the comparators are other anticancer drugs.

Reply: The present study had limitations. The efficacy data of this study was obtained from the ALTER0303 trial. However, there were still differences between the clinical trial and the real world, leading to potential uncertainty in the extrapolation of research results in the real world. For example, the control group patients in ALTER0303 trial were treated with placebo. However, in the real world, the third-line treatment options for advanced NSCLC include immunotherapy, chemotherapy, other anti angiogenic therapies, or participation in clinical trials. Our next research plan is to collect real-world data and further investigate the cost-

effectiveness of different treatments for advanced NSCLC. We have modified our text as advised in discussion (see Page 10, line 294-308).

4) Finally, please consider to cite several related papers: 1. Zhao Y, Wang Q, Zhang L, Shi J, Wang Z, Cheng Y, He J, Shi Y, Chen W, Luo Y, Wu L, Wang X, Nan K, Jin F, Dong J, Li B, Yamaguchi F, Breadner D, Nagano T, Tanaka F, Husain H, Li K, Han B. The efficacy of anlotinib as third-line treatment for non-small cell lung cancer by EGFR mutation status: a subgroup analysis of the ALTER0303 randomized phase 3 study. Transl Lung Cancer Res 2022;11(5):776-785. doi: 10.21037/tlcr-22-320. 2. Remon J, Esteller L, Hendriks LEL. Mechanisms of resistance after crizotinib or second-generation ALK therapy in advanced non-small cell lung cancer. Precis Cancer Med 2022;5:4. 3. Indini A, Rijavec E, Bareggi C, Grossi F. Immunotherapy for locally advanced non-small cell lung cancer: current evidence and future perspectives. Curr Chall Thorac Surg 2021;3:25.

Reply: We have added the references to the revised manuscript. (see Page9, line 258-259; Page9, line 256-257; Page9, line252).