Author's response to reviews

**Title:** Comparative efficacy and safety of second-line treatments for advanced non-small-cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network meta-analyses

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**Author's response to reviews:**

Response to the reviewer 1

Reviewer #1: This is a systematic review incorporating network meta-analysis of efficacy and safety of second-line treatments for advanced non-small-cell lung cancer with wild-type or unknown status for EGFR mutations. The conclusions were proper in the second-line treatment for NSCLC. These evidences had been recognized well from the results of the pivotal phase III studies. In this view, a new network meta-analysis did not show a good value. This work is considered as complementary to the results of the pivotal phase III studies. In discussion part, the last paragraph is out of focus in this paper. Please delete it.

**Answer:**

We agree with the reviewer that our results are consistent with the results of the pivotal phase III trials. However, on the top of what is already known we provide results for comparisons that have never been assessed in RCTs (for instance comparisons between immunotherapy and other approved second-line treatments such as docetaxel+ramucirumab, docetaxel+nintedanib or even between immunotherapy drugs). To date, new treatments have only been compared directly to one alternative drug (mostly docetaxel and erlotinib). It is rather important to infer also on comparisons against other approved treatments to confirm their superiority; for instance, assessing whether immunotherapies are better than the combination of docetaxel+ramucirumab
or not. Finally, our network meta-analysis revealed that some combinations of old treatments (e.g. pemetrexed+erlotinib) appear to be comparable with the new drugs in terms of efficacy, although they are not regularly considered in clinical practice possibly due to lack of sponsoring by a single pharmaceutical company.

To highlight the importance of our findings, we wrote in the discussion (second point of paragraph 2):

“Our NMA also provides the most up-to-date evidence synthesis results with last search date on June 6, 2017. Considering all the available evidence on any treatment for NSCLC that has appeared in the literature allowed us to: 1) confirm the superiority of immunotherapies over all other treatments; 2) reveal highly efficacious treatment combinations (such as the combination pemetrexed+erlotinib) which can be considered as equivalent alternatives to the new drugs although they are underrepresented in trials partly due to contradicting interests of the two pharmaceutical companies that market the two drugs; 3) investigate subgroups of patients considering histologic subtypes, such as the superiority of immunotherapies over the combination of docetaxel+ramucirumab for NSCC, and ethnicity.“

We deleted the last paragraph of the discussion as suggested by the reviewer.

Response to the reviewer 2

Reviewer #2: Overall well done systematic review and NMA. The authors did most steps with rigor and did a lot of work. I cannot verify data extracted from original studies but do not see reasons to doubt the findings. I have several major concern that authors need to address:

In the abstract you say twice: "similar results were found for drug X". I don't know what this means. Be more specific in stating explicitly what these "similar results are (even if you don't put numbers).

Answer: We agree the reviewer and we rephrased the abstract as follows:

“For OS, nivolumab was more effective than docetaxel (hazard ratio 0.69, 95% credible interval 0.56-0.83), pemetrexed (0.67, 0.52-0.83), erlotinib (0.68, 0.53-0.86) and gefitinib (0.66, 0.53-0.83). Pembrolizumab, atezolizumab and pemetrexed+erlotinib were also significantly more effective than docetaxel, pemetrexed, erlotinib and gefitinib. For PFS, erlotinib+cabozantinib was more effective than docetaxel (HR 0.39, 95% CrI 0.18-0.84), pemetrexed (0.38, 0.18-0.82), erlotinib (0.37, 0.18-0.78) and gefitinib (0.38, 0.18-0.82). Cabozantinib and pemetrexed+erlotinib were also significantly more effective than the four recommended treatments.”

We have also re-phrased the results section of the manuscript accordingly.
In the abstract, reader cannot tell whether the difference between drugs is trivial or important. You state that drug X is superior but by how much? Does it extend survival by a day, a month or a year? HRs are insufficient. Please see published well-conducted network meta-analyses and add some assessment of the absolute difference between drugs. Otherwise, clinicians cannot act on this evidence. So, do we trust these results? I don't see a rating of the certainty in the results. Read about GRADE and provide such ratings.

Answer:

We agree with the reviewer that HRs might be difficult to be understandable by patients. Nevertheless, this is the typical way that oncologists report the results of such outcomes.

To our knowledge all published network meta-analyses performed in oncology (including Cochrane reviews) assessed and reported overall survival and progression free survival using hazard ratios. If the reviewer is aware of any network meta-analysis on survival outcomes using absolute measures, we are happy to follow their approach.

We also included a detailed assessment of the credibility of the evidence based on the extension of the GRADE system for network meta-analysis suggested by Salanti G et al. Evaluating the quality of evidence from a network meta-analysis. PloS One. 2014;9(7): e99682. The results of our assessment are presented in the respective section “Reporting bias and credibility of the evidence“ in the manuscript and in our discussion (third point of the second paragraph). We also provided our detailed assessment in Appendix Figure 7 (p 122-135 of Supplementary appendix figures).

We wrote in the section “Reporting bias and credibility of the evidence “:

“The GRADE evaluation suggests that the available evidence is of moderate credibility for the majority of the comparisons with respect to OS. For comparisons between immunotherapies and the combination pemetrexed+erlotinib against the four recommended treatments, information come from low risk of bias trials with a contribution varying from 60% to 100%. On the contrary, for comparisons including either cabozantinib alone or in combination with erlotinib, information come mainly from moderate risk of bias trials. Less confidence can be placed on the results for PFS as most comparisons were rated at low or very low credibility. “

in the discussion (third point of the second paragraph):

“We also performed a detailed assessment of the credibility of the evidence to critically appraise our results. With respect to the five most efficacious treatments for OS, the level of evidence was higher (i.e. moderate) for nivolumab, pembrolizumab, atezolizumab and pemetrexed+erlotinib when compared to the four recommended treatments than for erlotinib+cabozantinib for which the level of evidence was low. For PFS, most comparisons were rated at low or very low credibility mainly due to lack of blinding and absence of independent clinical endpoint adjudication committee to assess subjective outcomes that led to very serious concerns for study limitation for many comparisons. “
Don't use the terms "trial" and "study" interchangeably.

Answer: We now use only the term “trial” throughout the manuscript.

On page 10 you use the term "sponsored treatment”. This is not a common terminology, please reword.

Answer: We added a definition of this term in the manuscript. When a trial is supported by a pharmaceutical company and the experimental treatment is developed by the same company, we considered this drug as a “sponsored treatment”. For instance, the Checkmate trials were supported by Bristol-Myers Squibb which developed the experimental treatment nivolumab assessed in these trials, so we considered nivolumab as a “sponsored treatment”.

We added in the “Reporting bias and credibility of the evidence” section:

“We defined a drug as being “sponsored” if the drug was developed and marketed by the pharmaceutical company who sponsored the trial.”

There is minimal mentioning of details of the Bayesian approach. Which priors used? Any sensitivity analyses done with different priors? There is tendency these days to get better estimates using empirical priors (see Rebecca Turner's Paper to get such priors).

Answer: We added the full WinBUGS codes we used in the Appendix 12 (page 67 of Supplementary appendix) as suggested by the reviewer. We are aware of the empirical distributions for heterogeneity suggested in the literature but to date such distributions have been provided only for binary and continuous outcomes, whereas our primary outcomes are survival endpoints. Hence, we only employed non-informative prior distributions.

The last 2 figures in the appendix (risk of bias and contribution matrix) need more explanation on how they were produced and what they mean (in a legend). Detailed explanation is needed.

Any comments about the difference between published and unpublished trials and the impact on publication bias? Other than the table in the appendix, did you suspect publication bias based on this, as opposed to doing funnel plots and asymmetry tests?

Answer: We now describe in detail in the appendix (Appendix Figure 7 p 122) what the two bar plots present and how they were produced. We also commented on the difference between published and unpublished studies in the discussion (first point of second paragraph).

We wrote in the discussion (first point of second paragraph):

“The unpublished trials were mainly phase III trials (9/15, 60%), they corresponded to negative trials assessing unsuccessfully licensed drugs or small trials (less than one hundred patients).
Including these trials decreased the risk of publication bias and increased the power of treatment categories analysis.”.

We had already provided funnel plots for the two primary outcomes. According to Appendix Figure 6 p 120, the funnel for overall survival seems symmetric but the funnel plot for progression-free survival suggests the presence of small-study effects. We have taken these findings into account in drafting the reporting bias section and in our GRADE evaluations Appendix Figure 7 p 122.

Response to the reviewer 3

Reviewer #3: The Authors present a network meta-analysis comparing the relative efficacy and safety of available treatments for second-line treatment of advanced NSCLC in patients with wild-type or unknown status for EGFR. This is one of the most comprehensive evidence synthesis that has been conducted to date in the field of the second-line treatment of lung cancer. The results indicate that nivolumab, pembrolizumab and erlotinib+cabozantinib are the most effective second-line treatments for NSCLC in terms of OS and the findings of the Authors also highlight the need for improvement in reporting of safety outcomes and quality of life. The results are interesting and well presented.

Answer: We thank the reviewer for his comment on our manuscript. We also believe that the update of our search with a last search date on the 6th of June 2017 has further strengthened our findings.

Editorial Requests

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1. PRISMA checklist

Please use attached PRISMA checklist, when performing revisions and add any missing information as required by PRISMA guidelines. Please submit completed PRISMA checklist together with your revised manuscript.

2. Search update

We noticed that the search was done up to May 2, 2016. As therapeutic landscape in NSCLC is a fast-moving field, please consider updating your search.

Answer: We updated our search up to 6 June 2017 as suggested by the editorial board. We added 63 records including 4 new trials and additional results for 18 trials. We now included 102 eligible RCTs (311 reports) of second-line treatments for advanced NSCLC with wild-type or unknown status for EGFR.

3. Declarations

Please add these sections: Availability of data and materials and Authors' Contributions (text format).

For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must confirm this under this sub-heading and also provide their reasons. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page:

http://www.biomedcentral.com/submissions/editorial-policies#availability+of+data+and+materials

Answer: We added the required sections at the end of the manuscript.

We wrote: “Availability of data and materials and Authors' Contributions

All the data supporting our findings are presented in Appendix 7: Identified reports for the eligible trials (p 22-42), Appendix 8: Characteristics of the 102 individual trials (p 43-49), Appendix 9: Results of individual trials (p 50-59), Appendix 4: Risk of bias assessment (p 10-18).

PC was involved in the study conception, selection of trials, data extraction, data analysis, interpretation of results, and drafting the manuscript. AC was involved in the data analysis, interpretation of results, and drafting the manuscript. AY was involved in the selection of trials and data extraction. NA was involved in the data analysis. LT was involved in the study conception, selection of trials, data extraction, interpretation of results, and drafting the manuscript. JC and PR was involved in the study conception, interpretation of results, and drafting the manuscript. All authors read and approved the final manuscript.”