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:

The authors' response letter has also been included as a supplementary file in order to provide the table.

August 23th 2017

Dear Dr Szyszka,

Thank you for considering our manuscript "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" (BMED-D-17-00543R1) as potentially acceptable for publication in BMC Medicine. We thank the reviewers and yourself for your comments.

We have addressed the reviewer’s additional comment and revised the paper accordingly.

You will find enclosed a revised version of our manuscript incorporating the latest amendments. We include 2 copies of the revised manuscript (clean version and version with changes tracked).
Response to reviewer 2

Reviewer #2: The authors have responded well to all our previous comments, except for providing clinicians with an estimate of the true absolute effect. I understand that oncologists are used to dealing with hazard ratios and I am not asking authors to do a network meta-analysis of absolute effects. All I am asking is to tell readers, on average, how many weeks do patients live more if they used the "superior" drug vs. the "less superior drug". This does not require statistical analysis, just a simple average across trials. Patients do not care about hazard ratios, they want to know how much longer will they live with this newer treatment (compared to the other treatments).

Answer:

We agree that this is an important issue for patients and we thank the reviewer for his comment. However, we performed a meta-analysis on aggregated data and therefore we are bound on the data reported in the published articles or posted results that we extracted. The measure of treatment effect most frequently reported in the included studies was the hazard ratio. This is not surprising as it remains the most widely used in oncology [1-2]. Thus, our network meta-analysis results were restricted to summary hazard ratios.

This raises more generally the complex issue of quantifying the benefit of a cancer treatment or even of any treatment on a survival outcome. Alternatives to the hazard ratio have been proposed, among which measures of absolute effects [3-4], but all have limitations.

Common alternatives are:

- The difference in median survival, but this has many limitations both from a clinical point of view (the median is only one point on a whole curve, it could not be attained in a particular group though this is unlikely in NSCLC, and the difference in medians has no interpretation from a patient perspective since it cannot be interpreted as the median of expected survival differences), and from a statistical point of view for meta-analysis (its variance is not easily obtained from the confidence interval, assuming the latter would be reported which is not always the case).

- The difference in restricted mean survival times RMST (area between the survival curves up to a pre-specified timepoint), which has been recently advocated in numerous articles [2, 5, 6]. It has the advantage of summarizing the curve instead of using a single point. But it necessitates determining a time horizon that should be common to all trials. In terms of interpretations, it is indeed interpretable as the difference in life expectancy at the pre-specified
time horizon. This makes it more useful from a public health or health economics perspective than purely a patient perspective.

- The difference in survival at a pre-specified timepoint (milestone analysis). This is likely the most relevant for patients, assuming we can determine an agreed timepoint (12 months, 24 months?), and that data would be reported for survival at this timepoint in all trials.

Both the difference in RMST and milestone analysis have been used for meta-analysis [7-9], though using individual patient data (or reconstructed individual patient data) for RMST. Note however that this approach has never been applied to date to network meta-analysis.

In our analysis using any of the aforementioned measures would be very complicated, albeit appealing. Without individual patient data (we obtained data from only two out of the 40 datasets that we requested to trial authors) this would require reconstructing individual patient data from the survival curves, which we already did for 10 trials not reporting hazard ratios. Nevertheless, such curves were not always available, in particular in abstracts or posted results. Therefore, how to answer the patient question “how much longer will they live with this newer treatment (compared to the other treatments)” is currently not solved and constitute a real research question.

To address the reviewer’s comment, we present below the data of trials comparing immunotherapy versus docetaxel to illustrate the magnitude of absolute benefits. We have also assessed the difference in RMST at 18 months, as well as the 1-year OS. In this way we can estimate that immunotherapy provide an increase of life expectancy at 18 months of about 1.5 months.

The table is provided in the supplementary file.

We now raise this issue at the end of our discussion in the manuscript and we report the gross estimate of the average survival benefit of immunotherapy drugs as compared to docetaxel. We wrote:

“Lastly, we performed a NMA on the hazard ratios, which remain the most widely used measure of treatment effect in oncology, although this measure is probably not the most informative for patients. Alternatives to the hazard ratio have been proposed, such as the difference in restricted mean survival times [Uno, Trinquart] or difference in survival rates at a pre-specified timepoint [Blumenthal]. However, these alternatives have never been applied to date to network meta-analysis, as several issues remain to be solved (such as the choice of the timepoint for defining the restricted mean survival or the survival rate). As requested by one reviewer, we have nevertheless assessed the difference in restricted mean survival at 18 months of immunotherapy versus docetaxel to illustrate the magnitude of absolute benefits (Appendix 13). Results show that immunotherapy compared to docetaxel should provide an increase of 18-month life expectancy of about 1.5 months.”
References


2. Royston P, Parmar MKB. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Medical Research Methodology 2013; 13:152


