Sir,

We would like to draw your attention to certain issues with the paper by Frass *et al.* about adjunct homeopathic treatment of Non-Small Cell Lung Cancer patients [1]. We have reviewed the paper and the information available on clinicaltrials.gov [2] including the history of changes and have some serious concerns that the results are a product of strong biases arising from modifications of the study parameters (see Tab. 1).

The authors did not indicate any of these substantial modifications of their study-parameters in their paper.

The protocol was uploaded to the register on Sep.19, 2019, about two months after data collection was completed where further modifications were introduced (follow-up time for quality of life (QoL) which is the primary endpoint, number of included cancer types). Oddly enough the date given in this document is Jan 10, 2011, a full year before the study was first registered on Jan 13, 2012. This seems misleading, because the final paper does reflect the parameters that were disclosed in the protocol while the data used during first registration do not.

In the published paper the authors describe 20 exclusion criteria while only one was given in the first registration and none was introduced during any of the seven modifications of the registration data that followed until the final results were uploaded. This raises serious concerns about selection bias

The inferior survival of the placebo group derives from an unusually high number of deaths within the first nine weeks alone while the treatment groups performed comparably afterwards. This might be the result of some selection bias.

The Consort diagram (Fig 3 of the original paper) seems incomplete and misleading. Not only compared to Fig. 2 (see below) data seem to be missing. The authors felt inclined to additionally introduce 19 exclusion criteria while the trial was under way but oddly enough none of the 158 patients assessed for eligibility seems to have met any. Only after randomisation were eight patients excluded: all due to the same criterion of “sensitizing EGFR mutations or ALK translocations”.

The authors reduced the follow up time of two years for QoL to only 18 weeks which raises concerns about incomplete reporting.

Fig 2 of the original publication indicates that there was a group of patients that “refused to participate”, but somehow gave their informed consent to receive verum. Their number is not included in the Consort diagram nor is it given in the text of the paper. In fact, data of these patients would be important to assess the overall effect of the adjunct treatment.

We conclude, that the outstanding results of the study may well be due to some serious bias arising from the apparently numerous but undisclosed modifications of the protocol while the study was under way. The authors’ conclusion about the positive influence of the additional homeopathic treatment on the patients’ QoL and survival is unjustified until they are confirmed by an independent and rigorous replication.

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References

[1] Frass M, Lechleitner P, Gründling C et al. Homeopathic Treatment as an Add-On Therapy May Improve Quality of Life and Prolong Survival in Patients with Non-Small Cell Lung Cancer: A Prospective, Randomized, Placebo-Controlled, Double-Blind, Three-Arm, Multicenter Study. The Oncologist 2020;25:e1930–e1955

[2] https://clinicaltrials.gov/ct2/show/NCT01509612