Reviewer's report

Title: Non-Small Cell Lung Cancer with EML4-ALK Translocation in Chinese Male Never-Smokers is Characterized with Early-Onset and Less-Differentiation

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Reviewer: Maria Wong

Reviewer's report:

This manuscript reports EML4-ALK translocations in 95 primary lung cancers from Chinese male never smokers. Multiple analysis methods including RT-PCR-sequencing, FISH and immunohistochemistry were used. The authors found EML4-ALK translocations in 8/95 (8.42%) of the study subjects including 6 adenocarcinomas and 2 squamous cell carcinomas. Amongst the 8 positive cases, only 1 case showed well-differentiation. The mean age of patients was 50.63. Comparing with 5 other series of Chinese patients, the authors found male never-smokers in their series showed higher EML4-ALK translocation frequencies than Chinese males and smokers in other reported series.

The relatively large case number and the unusual subgroup of male never-smokers are merits of this study, providing data that supplement a gap in other studies that usually include much fewer male never smoking subjects.

Major compulsory revision:

1. One of the main correlates found in this study – that EML4-ALK translocations are more common in “less differentiated” tumors should not be emphasized and thus it is not advisable to include this term in the title. Tumor differentiation is a very subjective morphological feature. The criteria for defining “well”, “moderate” or “poor” differentiation are not stated in the manuscript and there is no pathologist in the authorship to ensure consistent criteria are used throughout the entire cohort. The number of cases in the respective subgroups is also not balanced. Thus the significance of “tumor differentiation” is unclear. The term “less differentiation” is also not an established pathological term. These limitations should also be discussed.

2. The optimal approach for EML4-ALK testing is not universally established. Since 3 different methods of analyses were used in this study, the authors should state clearly the criteria for calling a case “positive”, whether only one test was determinant or an agreement of all 3 methods was required.

Minor essential revisions:

1. The specific clone name of antibody used for IHC is required.
2. Genomic DNA is not used in the testing and this should be amended in the “Methodology”.
3. The reference numbers (particularly studies quoted for clinicopathological
comparison) used in the text and table are inconsistent and needs to be unified.

4. The study

Discretionary revision

The finding of around 8% of EML4-ALK translocation is similar to reported frequencies in studies of non-selective patients, inferring gender differences probably plays a limited role in the occurrence of the translocation. It is a pity this study has not included females or male smokers to enable regression analysis which is needed to delineate the effects of these factors. The term “meta-analysis” is wrongly used as strict statistical methodology is required for this type of analysis but is not utilized in this study. It is advisable to emphasize these points in the “Discussion” as limitations of this study.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I have no competing interests with regard to this study.