Review of: "Classification and regression tree for estimating predictive markers to detect T790M mutations after acquired resistance to first line EGFR-TKI: HOPE-002"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

In this paper the authors evaluated predictive markers for the detection of T790M mutation in the patients with NSCLC treated with EGFR-TKIs. The theme of this study is important. The analysis of this research has a certain value. However, several points need to be clarified.

Major points:

1. For generalizaion, I am wondering how this result can be applicable for other patients' population than this specific patient cohort. This data may be better to be tested with other patient cohort, i.e. 'validation set'.
2. What these factors means, such as age, CYF, LDH, etc. for the markers for T790M? Why these factors induce T790M? Are there any rationale? For example, if a patient is older than 75 or 77, should we give up detecting T790M?
3. Introduction: 'we aimed to increase rates of T790M' > I think in this study, the authors cannot increase the rate of T790M because this study is not prospective but retrospective. The aim of this study may be 'search for prediction markers' and 'to make prediction models' for the future study.
4. Results: A total of 289 patients were enrolled and 287 eligible. What were the eligibility criteria? If 287 were eligible, all the results should be shown with n=287 (Figure 3 and 4).
5. For understanding of the possible confounding factors regarding Figure4, background patients' characteristics should be shown with afatinib group and 1st-G EGFR-TKI group.
6. From Table2, frequency of T790M mutation is numerically higher in erlotinib group. This may suggest 1st-G EGFR-TKI may not be equal. Additional analysis may be needed with out combining gefitinib and erlotinib in Figure4
7. Discussion: The authors mentioned 'Therefore, the use of osimertinib as first-line treatment' 'remains controversial'. But the reason is weak. Better prognosis of the patients with acquired T790M is just one aspect. Detection rate may vary. There is no comparison between 1st-line osimertinib and 1st-line 1G-EGFR-TKI in this study. I want to read more precisely description and explanation regarding the result and discussion of this study.
8. In this study, many factors were at the time of starting 1st-line EGFR-TKI but not at the time of 1st-line

EGFR-TKI failure. Some factors (such as tumor volume, metastatic sites, etc.) at the time of EGFR-TKI failure may be more important. Can the authors compare such factors?

Minor Points:

1. Abstract, Methods: ‘first-line drugs’ > It may be better to say more specifically like ‘first-line EGFR-TKIs’, because in clinical settings, some patients can be treated by ‘first-line drugs’ such as platinum-doubles other than EGFR-TKIs.
2. Abstract: Please add patients number.
3. Introduction: Please explain evidence level ‘B’ and strength of recommendation ‘1’.
4. Introduction: ‘There are two main first-line strategies’ > The current description is not easy to follow. I think there are three possible patterns, fist-line osimertinib, first line EGFR-TKI followed by osimertinib with T790M, and first line EGFR-TKI followed by non-EGFR-TKI therapy without T790M. Please explain more exclusively.