Peer review file

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Reviewer A

Comment 1: In the authors cohort (n=40), there was no difference in overall survival between stage groups. This may mean the cohort does not represent the real-word NSCLC patients. I understand this could be due to the relatively small sample size, however the authors at least mention it as a limitation of the study.
Reply 1: We thank the reviewer for overall positive assessment of the manuscript. We agree, that a larger cohort size can potentially better represent the whole population, and we have added this to the discussion.
Changes in the text: p9, lines 243-244

Comment 2: I recommend the authors only state the objective result from analysis in results section. The authors' interpretations (e.g. page 6, line 171-173, 179-181, 191-192) should be presented in discussion section.
Reply 2: We have modified our text according to reviewer's suggestion.
Changes in the text: p9, lines 239, 241-244

Comment 3: Please show how the normal and tumor tissue samples were obtained (surgery? bronchoscopy? TBNA? etc.), as well as its breakdown.
Reply 3: We have added this information into Table 1.
Changes in the text: additional information added to Table 1

Comment 4: Please show how the authors set H-score above 170 as cutoff for MSI2 expression. Are there any rationales?
Reply 4: Median value of H-score of 170 was used as a cutoff for high MSI2 expression. The reason for this cutoff is because values above 170 represent top two quartiles of MSI2 expression H-scores. We have added this information to the text.
Changes in the text: p5, lines 134-136

Comment 5: Page 6, line190: statistically borderline -> without statistical difference
Reply 5: We have modified the text.
Changes in the text: p7, line 193

Comment 6: Table 1: Please show the numbers of patients for each clinical category, not just as percentages. For histology, I recommend the authors classify the diagnosis according to up-date WHO classification. Lymph Nodes -> N stage. For "targeted therapy", please show the details in footnote of the table. For "surgery in stage IV patient", please add the explanation.
Reply 6: We have added this information to the Table 1, and provided additional information requested in the footnotes.
Changes in the text: additional information added to Table 1

Reviewer B

Comment 1: On page 7 the authors state that the expression of MSI2 per IHC did not correlate with survival for stage II-III cases (lines 203-206). Also, there was no significant association of MSI2 expression with survival in stage I-II (lines 216-218), and only a marginal association for stage III (line 219). In contrast, in the Abstract the authors state that MSI2 expression correlated with a shorter PFS for all stages (line 44-46). This contradiction has to be corrected.
Reply 1: We thank reviewer for many positive comments. We apologize for giving a misleading information in the originally submitted manuscript. In the abstract we meant to state that MSI2 expression correlated with PFS at all stages (we added word “combined” to the abstract) which is also indicated in the manuscript (line 54). Additionally, we performed correlative analysis between MSI2 expression and OS and PFS by stage, and results are presented in the last part of Results section of the narrative.
Changes in the text: we added additional text in the abstract (p.2 line 54) and Results section (p7, line 192; p8, line 209, p.9 line 241-242,).

Comment 2: It would be helpful if the authors would describe the treatment of

patients in more detail in Table 1, i.e. what is "chemotherapy and targeted therapy" for stage I-III, was it an adjuvant TKI study? It would be better to state the number of patients that received each therapeutic sequence, e.g. xx% of patients surgery + adjuvant chemotherapy etc. Also, did none of the stage I-III patients receive radiotherapy/chemoradiotherapy? The 50% precentage of surgery for stage IV is relatively high: was ist palliative, or with curative intention for oligometastatic disease? Were the stage IV patients tested for EGFR and other actionable mutations (e.g.ALK). Do you have the results? Did they receive targeted therapies? What were the 50% targeted therapies mentioned: TKI for actioanble alterations, or erlotinib in later treatment lines, which was earlier given independent of the mutation status?
Reply 2: We certainly agree with the reviewer and we fulfilled the Table 1 with missing information. We stated number of patients with specific therapeutic sequence. We apologize for the oversight, and added chemoradiation patients (n=11). Surgery in stage IV patients was palliative. Specific TKIs were also indicated in the table, this were given after surgery as an adjuvant treatment. Additionally, we indicated treatment for certain categories in the footnotes, methods for samples collection, provided information regarding surgery treatment. None of the stage I-III patients in our cohort receive chemoradiation therapy.
Changes in the text: Modified Table 1.

Comment 3: Please also give the number of the ethical approval by the IRB (line 102).
Reply 3: We thank reviewer for pointing this, and we have provided IRB approval numbers in the text.
Changes in the text: added text p. 4, lines 108-111.

Reviewer C

Comment 1: The authors use multiple abbreviations. Possibly some of these could be eliminated.
Reply 1: We thank the Reviewer for the valuable comment. Indeed, common abbreviations are used in the text, and we have now carefully revised the narrative to

make sure that the acronyms are spelled at first appearance.
Changes in the text: added text p5, line 139; p9, line 228

Comment 2: I would consider revision of some phrases. For example, MSI2 “plays an important role”–. This expression does not convey much information. 3. The manuscript needs to be reviewed to correct some grammatical errors
Reply 2: We carefully revised the narrative to specify vague phrases and to correct any grammar issues.
Changes in the text: added text p9, line 225

Comment 3: The MSI2 protein levels are reported as an H-score. I am not familiar with this score. It would be useful if the authors would describe it in at least one sentence in the Methods. In addition, they should give the range of H-scores for lung cancer tissues and for healthy lungs in the Results.
Reply 3: We have added information regarding H-score quantitation supported by the reference in the methods section of the manuscript. H-score range of MSI2 levels in normal tissues is represented on Fig 1B (from 35 to 77) and we added this information to the Methods section.
Changes in the text: added text p.5, lines 130-136., additional reference #11.