

Klinik für Dermatologie

**Dermatologisches Zentrum Buxtehude**

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**EJC Editorial Office**

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**Response to reviewer’s comments**

Dear EJC: Skin Cancer editorial board,

Please find our response to the reviewer’s comments below:

1. *The authors used conventional RECIST to split the cohort into responders versus non-responders. I assume this is based on initial response to ICI. However, some investigators examine a longer term response definition in order to capture durable responders. Did the authors consider this in their study design? This should be discussed in greater detail.*

Classification of responders and non-resonders was based on initial response data. Longer term response has not been considered in this “proof-of-principle” investigation because data have not (yet) been available for the majority of patients.

*2. Why is data regarding prior BRAFi treatment missing in such a high proportion of the patients (21%, Table 1)?*

The patient’s treatment history has not been available for these cases (blood samples have been taken from other hospitals sample banks, with no documentation of BRAFi treatment) in our retrospective analysis.

*3. Given the relatively small N and the statistical techniques utilized, the potential for overfitting should be discussed.*

That is a valid point, which we have addressed in the discussion.

*4. How well does a model incorporating available markers and clinical features but without miRNAs perform? It is important to determine the additive benefit of including the miRNAs.*

It does perform worse but is included in the model comparison now to see the added benefit of the miRNAs.

*5. The performance of including all miRNAs is shown. What is the AUC if only the significant miR markers are included in the model?*

It does perform worse but is included in the model comparison now to see the added benefit of the miRNAs.

*6. BRAF mutation status-a PCR-based assay is reported. Did the patients not undergo NGS or a comparable clinically available assay?*

The PCR is just a necessary step in preparation for an accredited pyrosequencing pipeline. The mutation status is determined via pyrosequencing. This is a routine BRAF status analysis we perform for the adjacent dermatology department.

*7. Discussion section- the other studies that have used miRs to identify ICI responders should be presented and discussed.*

Response to editor:

*1. Please may we ask that the highlights in this submission are reduced to meet the journal's criteria of 3-5 bullet points with each bullet not exceeding 85 characters including spaces.*

Done.

*2. Please remove the graphical abstract from the manuscript document and upload as a separate item in the submission.*

Done.

*3. The journal's guide for authors advises that Original research articles have a limit of 2,500 words and no more than 40 references. Would you please reduce accordingly.*

Will this guideline be strictly enforced? We tried to summarize and remove some text but as it is a complex topic with development of a new machine learning pipeline and comprehensive model evaluation, we did not meet the 2500 word threshold. However, in other publications we saw that an article with 3700 words (https://www.ejcskn.com/article/S2772-6118(24)00006-5/fulltext) was also accepted.

*4. Please include the all-author conflict-of-interest statement as a separate upload document, the conflict-of-interest detail is not required in the manuscript document.*

Done.

*5. Please remove the supplementary material from the manuscript document and upload as separate items in the submission.*

Done.

Sincerely,

Dr. Marc Bender