Author’s response to reviews

Title: The predictive value of microRNA-126 in relation to first line treatment with capecitabine and oxaliplatin in patients with metastatic colorectal cancer

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Author’s response to reviews:

To the Editor

Attached please find our revised manuscript:

”The predictive value of microRNA-126 in relation to first line treatment with capecitabine and oxaliplatin in patients with metastatic colorectal cancer”.

We have carefully considered all comments from the referees and hope you will now find the manuscript suitable for publication in “BMC Cancer”. Coloured text has been used in the revised manuscript in case of changes from the original manuscript.

General comments:

We are very thankful for a thorough review of the original manuscript. Bellow please find our responses to the comments from the reviewers.

Response to reviewer 1:

1) About the visualization and scoring of microRNA-126 expression exemplified in Figure 1: Can the authors discuss why the expression level of microRNA-126 is not merely a reflection of differential amounts of vessels in the tumors.

This is a very relevant question. As far as we see it the present way of quantifying miRNA-126 expression serves to purposes. First, it allows a specific visualization of blood vessels (the endothelial cells) and by that it provides a semi-quantitative estimate of the amounts of vessels in the tumours. However, it represents more than just a two dimensional area estimate. The intensity of each signal is also added to the final data (the amount of probe-microRNA interaction in the endothelial cells). So each identified vessel does not just count as “one”, but is also weighted by the amount of microRNA-126 present.

If each vessel expresses similar amounts of microRNA-126 the discussion of its
role in vessel integrity might be less valid.

The answer to this question is in line with the above one. There are no solid data on how the expression of microRNA-126 may differ between vessels and under different conditions but the present results suggest that there is a considerable inter- and intra-tumour variation. Most importantly it is the suggested function of this miRNA more than its role as a specific endothelial cell marker that is interesting. As suggested in the references (12, 14-15) it influences the integrity of the blood vessels (high miRNA-126 – high integrity) and it may very well be this fact that explains the positive correlation to the response to chemotherapy seen in this study. This is already addressed in the original manuscript (page 9 line 24 – page 10 line 6).

2) Preferably you would like to have some more biological insight other than through speculation what would be the reason for the associations found.

In line with the above questions. We agree that more insight is awaited. The field of microRNA research and its clinical relevance is still in its early years and unfortunately, speculations based on in vitro findings is more or less what we can achieve at this moment. Further research is currently ongoing.

Response to reviewer 2:

1) To the patient table is referred first in the result section. The section of the study population in the methods will be easier to read with this table is referred here as well.

Agreed, it may be helpful to refer to the patient table at this time. A reference to Table 1 has been added to the methods section in the revised manuscript (page 4, line 11).

2) In the discussion a multivariate survival analysis adjusting for parameters of prognostic importance in stage I through III disease where introduced. The analyzed parameters and results should be explained in more detailed make this statement easier to understand.

This is a misunderstanding. As explained in the discussion section (page 10, line 11-13) we did not perform a multivariate survival analysis in this study because we did not find it justified to adjust for classical stage I-III prognostic markers in a smaller cohort of patients with stage IV disease. This section has been rephrased in the revised manuscript in order to avoid misunderstandings.

3) Some readers would be interested if the KRAS mutation status is analysed in this cohort and if so if there is a correlation with the miRNA-126 expression or response to administered therapy.

The KRAS mutation status was only available for 21 patients and hence, these data were not presented. For these 21 patients however, no statistical correlations with miRNA-126 expression or response were seen but this may very well be due to lack of statistical power.
This is a question worthy of further research.

I hope that you will find the present revision satisfactory I am looking forward to hearing from you. On behalf of the authors,

Yours sincerely
Torben Frøstrup Hansen
MD, PhD