Author's response to reviews

Title: Is there a role for the quantification of RRM1 and ERCC1 expression in Pancreatic Ductal Adenocarcinoma?

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Author's response to reviews: see over
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Dear Editor-in-chief

This is a cover letter for our manuscript titled as “Is There a Role for the Quantification of RRM1 and ERCC1 Expression in Pancreatic Ductal Adenocarcinoma?” We are very pleased to know that we have satisfactorily answered all the issues raised by one of the reviewers. We are submitting a revised manuscript and the response to the first referee’s comments (Dr Amir Sonnenblick) for your review. All changes could be tracked using the “Track Changes” tool of the Microsoft Word® software and all the modifications are highlighted or in different font color. Also enclosed is a point-by-point statement on how we have addressed the reviewer’s comments and suggestions.

If you have any questions regarding the contents or the format of his manuscript, please do not hesitate to contact me. All the authors have no conflict of interest to disclose.

Yours sincerely,

Matias E Valsecchi, MD, MS
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Dear Referee and Editor,

Please find below are our response to your comments.

1) – “The authors state that mRNA samples for ERCC1 and RRM1 were classified as “Low” or “High” expression according to cut off values pre-established by Response Genetics. However in Manuel Cobo study {21} only ERCC1 levels were evaluated and the tumors were form NSCLC origin. In Cobo study around 55% tumors were classified as "low" while in the present study almost 70%. This problem is clearly stated by the authors in the discussion ("Other sources of variability could be related to the cut off values used for PCR detection ....") while no solution was done to solve it. Perhaps "linear regression" or dichotomizing as high or low at the median ("as was done in the pioneering studies in lung) would address this problem.”

The cut-offs were established by Response Genetics using the same methodology that was applied to develop cut off values for NSCLC in the Cobo’s study, but using pancreatic cancer samples. The company used its own standards, its own samples and its own methodology to establish those cut off values. We only obtained a “high” or “low” value in reference to these pre-established values. The pancreatic cancer cases that were tested to establish those cuts-off values were not included in the current study and a clarifying sentence was previously added to the materials and methods section. In this revision, we added a second sentence (in full disclosure) describing that the patients' samples were sent by the investigators to Response Genetic to imply that the analysis was outsourced.

With that stated, we do agree with the reviewer regarding the fact that changes in the cut off values may have impact in the final results; yet for the current manuscript we respectfully believe this is beyond the scope of this study. In fact we attempted the reviewer’s suggest, but we do not have access to the values needed to perform linear regression or to dichotomize at the median, thus the reviewer’s concern can not be addressed in the current study. Of course, this is a limitation of the study and we have clearly expressed this in the beginning of the discussion section. Of note, we do believe that altering the cut off values would not significantly change the data and/or the conclusions herein.

Thank you.