Author's response to reviews

Title: MEK1 is associated with carboplatin resistance and is a prognostic biomarker in epithelial ovarian cancer

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Author's response to reviews: see over
Dear Editors,

Thank you for the opportunity to revise our manuscript in response to the reviewers’ comments.

Please find below a point-by-point answer to each question that was raised:

**Reviewer's report**

*Title: MEK1 is associated with carboplatin resistance and is a prognostic biomarker in epithelial ovarian cancer*

*Reviewer: Alister Ward*

We agree with the reviewer regarding the potential of multiple pathways to mediate the effect of MEK1 inhibition in carboplatin resistance. Now, we have utilized the available genomic data to identify which previously described resistance mechanisms have relevance to MEK1 (for references see [1-5]). In this, we computed correlation between MEK1 and ERCC1, a metagene comprising of the mean expression of major genes included in the AKT pathway (AKT1, PI3KCA, MDM2, MTOR) and a metagene for a set of EMT inducers (including CDH1, SNAI1, SNAI2, ZEB1, ZEB2, E47, KLF8, TWIST, TCF4, SIX1, FOXC2). Interestingly only the AKT pathway showed significant correlation with MEK1. We have to mention that none of the previous studies investigated the potential role of MEK1 in clinical resistance - these studies used cell-line based approach only. We added detailed description of this analysis to the Methods and Results sections of the manuscript and have also modified the Discussion.
The authors should re-check the statistical analyses. The indicated statistical significance for some of the samples in Figure 2 panel B appears questionable, given the small change and relatively large error bars.

We have reanalysed the results throughout the manuscript. We used unpaired one-tailed T-test to compute the significance in the experiments displayed in Figure 2/B and we have increased the significance level for the combination of drug silencing and drug treatment. This resulted in less significant genes (four out of eight - FUBP1 was not significant in this setting). However, the overall message of the manuscript was not altered, and MEK1 remained the most powerful biomarker candidate. We have corrected Figure 2 and the manuscript text at multiple locations.

- Minor Essential Revisions
The authors should correct the minor typographical errors in the manuscript.

We have checked the manuscript and corrected the text at multiple locations.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer: Yong Han
In this paper, the authors showed that MEK1 is associated with carboplatin resistance and is a prognostic biomarker in epithelial ovarian cancer. Besides, they also demonstrated that the selective MEK1 inhibitor PD0325901 and carboplatin have synergistic effect when treatment in combination. Thus, the authors suggest that MEK1 is a promising prognostic biomarker candidate correlated to response to platinum based chemotherapy in ovarian cancer. These findings are of potential clinical impact and the data presented may be of interest to some clinicians. However, several minor modifications are still needed.

1. “Figure 3” mentioned in the Result section does not exist (line252, 259 and 262).

Unfortunately, Figure 3 was missing in our previous submission. We have now corrected this and added Figure 3 to the current version of our manuscript.

2. “Figure 4” mentioned in the Result section refers to “Figure 3” which was displayed in the Figure section (line269, 275).

This was a consequence of the missing figure, and now it is corrected.

3. The authors should upload new “Figure 3” and modify Figure 3 & Figure 4 related descriptions in the main text.

We have added all figures and modified the text at multiple locations.

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

We have highlighted all changes in the new manuscript using yellow background.
Finally, we have corrected the formatting of the manuscript according to the journal guidelines. We added a description of the supplemental material to the end of our manuscript, and also made minor changes in our supplemental files to improve clarity.

We hope that we have sufficiently addressed criticisms and comments and that our manuscript will now be eligible for publication.

Yours truly,
Balázs Győrffy