Reviewer’s report

Title: Analysis of the Mitogen-activated protein kinase kinase 4 (MAP2K4) tumor suppressor gene in ovarian cancer

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Reviewer: Antoinette Hollestelle

Reviewer’s report:

In their manuscript “Analysis of the mitogen-activated protein kinase kinase 4 (MAP2K4) tumor suppressor gene in ovarian cancer”, Davis et al. present a comprehensive overview of MAP2K4 mutation, methylation and gene silencing analysis in human ovarian cancer.

Among 149 human ovarian cancer samples, the authors report one MAP2K4 mutation in addition to the four homozygous deletions they identified in an earlier study. Interestingly, these were all identified in high grade ovarian cancers. This is the largest complete mutation analysis effort of the MAP2K4 gene in ovarian cancers to date. Furthermore, the authors have investigated the methylation status of 39 ovarian cancers. In agreement with Spillman et al., the authors find no evidence for MAP2K4 promoter methylation. It is a pity, however, that the authors decided to test as little as 39 tumors, considering they had a relatively large (i.e. 161) sample set at their disposal. Next, the effect of MAP2K4 expression on clinical outcome was assessed in two data sets. In one dataset there was an association of low MAP2K4 expression with improved overall survival, but not progression free survival. Finally, the authors studied the effects of MAP2K4 silencing in two ovarian cell lines and observed a reduction in proliferation in one of the cell lines. Overall, this study is carried out well.

Minor essential revisions:

1. On page 10: In the TCGA public copy number dataset an additional three homozygous deletions were found among 157 ovarian cancers. Did these deletions specifically target the MAP2K4 gene or were other genes/miRNAs also targeted? Can the authors speculate a bit on whether it is likely that MAP2K4 is (partly) responsible for the 17p loss?

2. On page 11: Is it not contradictory that all five genetic changes were discovered in high grade tumors whereas reduced expression of MAP2K4 was associated with a better survival? How do the authors explain this apparent discrepancy? Is there information on the grade of those tumors or was this a selected sample set? Also, in literature there was a report on MAP2K4 expression being associated with a reduction in overt metastasis (Yamada et al.).

3. On page 12: The authors saw a reduction in cell numbers upon silencing MAP2K4 in one of the two ovarian cell lines. In contrast, the stable clones generated in the study of Yeasmin et al. did not show a reduction in cell proliferation. However, they did observe EMT-like changes. Did the authors
observe any morphological EMT-like changes in their system?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests