Reviewer’s report

Title: Genomic profiling in ovarian cancer retreated with platinum based chemotherapy presented homologous recombination deficiency and copy number imbalances of CCNE1 and RB1 genes

Version: 0 Date: 27 Nov 2018

Reviewer: Kirsten Timms

Reviewer's report:

The manuscript describes an analysis of several previously described biomarkers for response to DNA damaging agents in a small cohort of platinum resistant ovarian cancer. While the cohort is small and it's size limits the conclusions that can reliably be drawn, the content of the study is of interest due to ongoing clinical trials of PARP inhibitors in this treatment setting. The following concerns should be addressed by the authors:

1. The methods which describe the analysis performed and algorithms utilized in order to generate the 3 HRD scores described in the manuscript need to be more comprehensive. Currently the authors provide only a reference to a previously published manuscript (Telli et al., 2016), however the assay described in that manuscript (next-gen sequencing based) is substantially different from the assay used in the current study (SNP microarray). Given that the authors have utilized thresholds developed by Telli et al. for use with their assay it is important to understand whether HRD scores generated by the two assays are comparable. Any variation in scores between the two methods would result in false negative or false positive samples within the current study. The description of the analyses performed in order to calculate the HRD scores are not comprehensive enough for a reader to be able to assess whether this is the case.

2. One interesting observation from the current manuscript is the high rate of CCNE1 amplification in this cohort, and the overlap of CCNE1 amplification with BRCA1/2 mutations. Previous studies have reported CCNE1 amplification at lower rates, and that CCNE1 amplification and BRCA1/2 mutations are mutually exclusive (Cancer Genome Atlas Network, 2011; Ciriello et al., 2012; Etemadmoghadam et al., 2013). In a recent publication (Stronach et al., Mol Cancer Res, 2018) analysis of HRD scores, BRCA1/2 mutation status, and CCNE1 amplification in a cohort of 250 ovarian tumors reported that CCNE1 amplification and BRCA1/2 mutants were again mutually exclusive, and that there was a highly significant association between CCNE1 amplification and low HRD scores (<42). The authors of the current study should discuss possible reasons why the previously reported relationship between CCNE1 amplification and BRCA1/2 mutation status does not
appear to hold true in this cohort, and in addition should provide an analysis of the relationship between CCNE1 amplification and the HRD scores which they have calculated.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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I am an inventor on patents submitted for some of the homologous recombination scores utilized in this study.

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