Reviewer's report

Title: Chemotherapy weakly contributes to predicted neoantigen expression in ovarian cancer

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Reviewer: Vinay Varadan

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In this study, the authors seek to assess the effect of chemotherapy on somatic mutations and computationally derived expressed neoantigens using pre- and post-treatment ovarian cancer tissue samples. In addition, they use previously generated data from preclinical model systems to assess for therapy-induced mutational signatures. The overall study is of biological and clinical interest given the likely mutagenic effects of platinum-based therapies. While it is unclear whether the results from the preclinical model data are sufficiently generalizable, and additional details in the methods are required before the manuscript can be published, the results of this study provide can motivate and inform the design of future studies, thus meriting publication.

- Given that the observed effects of chemotherapy on C. Elegans are quite different as compared to G. Gallus, it is unclear whether these are the optimal preclinical model systems to explore the effects of chemotherapy, especially in the context of cancer cells. The use of preclinical model systems, however, is essential to ascertain whether the post-therapy mutational signatures are the result of clonal selection or indeed suggest therapy-associated mutagenic processes. Thus, the authors may wish to include a more in-depth discussion about whether the use of mammalian cancer and/or non-cancer cell lines would be useful in determining the mutational signatures associated with chemotherapy. This is particularly important given that the signatures identified in the preclinical models were not consistent with the tumor-derived data.

- The Varcode pipeline does not appear to be previously published. Is there a reason why the authors chose this pipeline as opposed to publicly-available published approaches? Also, it is unclear whether Varcode accounts for every transcript in a given gene since the effects of mutations could vary depending on the transcript. This needs to be addressed/discussed.

- The authors need to provide more details in the methodology section of Mutational Signatures. For example, it is unclear how D(i,s) and H(s,j) are defined or estimated on Page 4, line 61; while some of these details are likely addressed in the deconstructSigs package, it should be explicitly mentioned here to ensure clarity.
- The authors recognize and discuss the challenge in determining whether mutational signatures are induced by chemotherapy or whether the inferred changes reflected clonal selection and/or heterogeneity. While better preclinical model systems may help address this issue, the authors may also wish to consider whether observed changes in pre/post treatment mutational signatures are dependent on the number of cycles received by the patient. For example, it may be that patients who received more number of cycles of chemotherapy are more likely to exhibit therapy-induced mutational signatures, as was found in sample AOCS-092-3-3 derived from a patient who received several lines of platinum chemotherapy. This needs to be explored/discussed.

- It is as yet unclear from this study whether the predicted 16% of expressed neoantigens likely attributable to chemotherapy would be sufficient to elicit a sustained immune response. Given that the RNA sequencing data can reveal changes in the levels of infiltrating immune cell subsets, it would be useful to explore whether increased neoantigen expression is associated with an increase in immune cell infiltration post-treatment in this cohort. While the association in itself is not evidence of causation, it could provide input for follow-up studies.

**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

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