Reviewer’s report

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

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Reviewer: Alexandra Léary

Reviewer's report:

This is a very interesting study addressing for the first time the mutation or neoantigen load in treated ovarian cancer. At diagnosis the mutation load is known to be in the low-mid range, however given the chemosensitivity and frequent DNA repair defects of HGOC, treatment may have been expected to have an important mutagenic impact in these tumors, thus potentially increasing mutation and neoag load and increasing sensitivity to immune therapies.

The major comment is regarding one of the main take-home point as stated in the abstract 'relapse samples collected after chemotherapy harbored a median of 90% more expressed neoantigens than untreated primary samples'. However this figure is actually referring to the comparison between the number of neoAg in 75 primary tumor samples, and 6 relapsed samples. I am concerned that this is clearly unbalanced even if statistically significant? Here the point of view of a statistician would be useful. In addition 5 of 6 relapsed samples were obtained post-mortem. This in itself may introduce significant bias accounting for increased mutation load and NeoAg #, whatever happened before death (cachexia, infection, etc) may be more likely to account for increased mutations. Finally, the 6 relapsed samples actually come from 5 metastases from only 2 patients and 1 relapsed sample from another - Is it appropriate to count multiple mets from the same patient? In this regard, it may be useful to know how similar are mutation numbers from anatomically distinct metastases samples from the same patient?

It is interesting that such a low percentage of mutations are assigned to chemotherapy signatures. Rather most are present in the primary and attributable to non-cytotoxic mediated signatures. However it would be useful then to have an idea of the interval between last chemotherapy and sample procurement. Might not that have an impact? In such genomically unstable tumors, a mutational signature may not always persist for long. This could be particularly relevant when evaluating the relapsed tumor samples (5/6 obtained post-mortem), how distant was the last chemotherapy. Can the authors correlate the number of mutations attributable to chemotherapy signatures in relapsed samples to time interval since end of chemotherapy? For ex the outlier, AOCS09233 had the highest, was she still under chemotherapy when sample taken?
Minor comments:

Abstract: in the methods, the sample numbers don't fit with what is in the manuscript. The abstract mentions 12 primary and relapsed samples, and additional 16 post treatment only. But in the results and methods in text it is 75 primary untreated and 35 relapsed?

In results of abstract 'in analysis stratified for tissue type, relapsed samples expressed 90% more Neoag,' actually that is the results only for primary vs relapsed tumors, not results for the whole sample set stratified for tissue type.

A flowchart of the samples used could be provided in additional figures rather than referring to additional file 1 which is difficult to read.

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

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.
No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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