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Review Comments

Reviewer A

The authors nicely review all the different immune checkpoint inhibitors used in early stage TNBC. The discussion section was excellent and very thorough. Few comments below:

We would like to thank Reviewer A for taking the time to provide us with valuable feedback.

Introduction:
Comment: 1- Lines 37-38: If the review is about early stage TNBC, I would omit discussing survival in regards to metastatic disease ie consider removing sentence "Given the paucity of proven therapeutic options in TNBC, the median survival from the time of diagnosis of metastases is only 13.3 38 months, with first line treatment working for a median of 11.9 weeks (4,5)"

Response: Thank you for the suggestion. This sentence was removed.

Comment 2- Lines 50-51: Line "(with the percentage of patients with high mutational burden varying from 3.7% 51 - 37% depending on the definition used)" is unnecessary to the point you are trying to make.

Response: Thank you for the suggestion. This sentence was removed.

Comment 3- Lines 52-53, given the timing of this publication and the newly FDA approved pembrolizumab, I would consider adding the Pembrolizumab data here as well.

Response: We would like to thank the Reviewer for pointing this out. We have now made reference to KEYNOTE 355 pembrolizumab data.

Comment: Results:
Although authors mentioned toxicity in their introduction, the results section had no mention of toxicities. One of the biggest components of why immunotherapy is not

yet approved in the early setting is the possibility of having long term toxicities in a patient population being treated for a curative intent. Therefore, I suggest the authors may want to add a toxicities section to reflect the frequency and severity of the toxicities experienced in these trials.

Response: We would like to thank Reviewer A for their feedback. We have added two columns to Table 1, one for grade 3-4 adverse events and one for SAEs in each treatment arm. This data has been integrated into the summary of each trial as well as in the discussion.

Discussion;
Comment: 1- Lines 178-179 – This doesn't hold true in the neoadjuvant setting, BRCA status was not shown to have improved response to carboplatin in the early TNBC. Interestingly, the effect of adding carboplatin was most pronounced in those with wild-type BRCA compared with those with a germline mutation in BRCA. (worth mentioning)

Response: We would like to thank the reviewer for clarifying the data. We have added a new paragraph on page 8, Lines 442-460 to summarize the gBRCA subgroup analyses from GeparSixto and BrighTNess and also discussed the INFORM trial data and provide a hypothesis as to the lack of additional benefit from carboplatin in the gBRCA cohort.

Title:
Comment: 1- If you are only discussing checkpoint inhibitors then you should change title to "Check point inhibitors in early TNBC". There are trials with other immunotherapy in the neoadjuvant setting such as TLR-9 agonist with pembrolizumab. So if you don't plan to discuss all kinds of immunotherapy, being more specific is better.

Response: Thank you for this suggestion. We have changed our title to more accurately reflect our primary focus on immune checkpoint inhibitor studies.

Comment: 2- I recommend removing "right drug at the right time" as it makes the title appear less professional and might be confusing to the reader.

Response: Thank you for the suggestion. This has been removed from the title.

Reviewer B

Overall, the paper was a good summary of immune checkpoint inhibition therapy in early stage TNBC. The literature search was thorough and provided enough relevant

details about each clinical trial.

We would like to thank Reviewer B for taking the time to provide us with valuable feedback.

Some Feedback:
Comment: 1- Line 73-74- It says that the investigational arm had n=69 but the number of patients in the TNBC subgroup was only 29 so the phrasing is slightly misleading.

Response: Thank you for pointing this out. We have corrected the sample size to reflect only the TNBC subgroup.

Comment: 2- The summary table was a concise and clear way of presenting the information from all the trials. I would maybe add a column about any immune-related adverse events and mention it a bit more in the main text.

Response: We would like to thank the reviewer for their suggestion. We have included rate of grade 3-4 AEs and rate of SAE (where available) for each treatment arm to the table.

Comment: 3- Could also mention current uses of immune checkpoint inhibitors in the breast cancer setting in general (Atezolizumab (anti-PD-L1) for advanced TNBC, Pembrolizumab (anti-PD-1) in combo with chemo for advanced TNBC- recently FDA-approved).

Response: Thank you for the suggestions. In the introduction, we had mentioned atezolizumab plus nab-paclitaxel for advanced TNBC, and we have now also made reference to pembrolizumab in the first line advanced setting given its recent FDA accelerated approval status.

Comment: Grammar/Spelling:
- Typo?- random letter “q” on lines 92, 132 etc.
- Consistency would be good - e.g. some places s

Response: Thank you for pointing this out. We have replaced “q” with “every” to make it clear to the reader. We have reviewed the paper in detail and have corrected any minor spelling or grammatical errors.

Reviewer C

Comment: The manuscript goes over a handful (seven to be precise) of clinical trails. There is a lack of depth and does not go to into the molecular or clinical futuristic

insights. Other than immunohistochemistry testing of PD-1/PD-L1 (which in itself has limited value) to determine application of immune checkpoint inhibitor therapy, there is no other direction envisioned in the manuscript.
There are several TNBC specific neoantigens, biomarkers under research. ALSO, the applicability of cancer vaccines, CAR-T cells and several other personalized approaches are under intense study. None these were touched upon in the review article.

Response: *We would like to thank Reviewer C for taking the time to review this manuscript and for their valuable feedback. Unfortunately, given that there will be separate manuscripts in this series dedicated to biomarkers in triple negative breast cancer and novel therapies in triple negative breast cancer, we have narrowed the scope of this paper to immune checkpoint inhibitors. We have therefore updated the title of our paper to more accurately reflect this and we have specified in our introduction that this paper focuses only on the immune checkpoint trials. We have, however, alluded to the categories of biomarkers and therapies mentioned in the final paragraph of the paper (under Future directions).*