Peer Review File

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Review Comments

Reviewer A

It was a pleasure to review the article titled "Combining PARP inhibitors and platinum-based chemotherapy in metastatic triple negative and/or BRCA-associated breast cancer" by Consolacion Molto and Eitan Amir.

Below considerations aims to constructively make suggestions to potentially improve the manuscript, that is already in very good quality.

Comment 1: Although the authors perfectly report the evidence and discuss few bias of the study, it would be very helpful if they could consider discussing how meaningful the results are, especially the 1.8m gain in mPFS.

Reply 1: While we did discuss the limited meaningfulness of the reported results, in response to this comment, we have revised the language to make this clearer. See page 4, line 98-99.

Changes in the text: “Irrespective of the statistical significance of these data which may have been limited by statistical power, neither the improvement in PFS nor in OS were of a clinically meaningful magnitude. Specifically, the gains reported failed to meet the threshold for clinically meaningful benefit defined by professional societies.”

Comment 2: Moreover, if this regimen would be feasible in practice, especially given the a significantly toxicity. I would equally encourage authors to review the literature and add studies that used the same classes of drugs.

Reply 2: We have expanded the section relating to other trials in this space. See page 4, line 92-96.

Changes in the text: Prior trials had shown that the addition of PARP inhibitors to chemotherapy increased response rate and had a modest

impact on PFS (9). One possible reason is the low statistical power in this group. The trial was designed with an expected total sample size of 63 *BRCA1/2* mutation carriers. However, only 37 patients were positive for germline *BRCA1/2* mutation. Another explanation is that in some trials, PARP inhibitors were continued after chemotherapy was stopped and PFS curves appeared to separate after participants stopped chemotherapy. This questions whether the observed effect reflects maintenance use of PARP inhibitors rather than the combination of PARP inhibitors with chemotherapy.

Reviewer B

In this article, the authors make a comment on the S1416 study, published in "Lancet" in February 2023. The manuscript is straightforward, well written, and concise and has clear results within the scope of a review article. Definitely deserves to be published and is a valuable contribution to the "Translational Cancer Research" journal. Some comments need to be addressed, based on my recommendations below.

Comment 1: [1] Lines 29-30:

"Regardless of germline or somatic BRCA mutation status, mTNBC can share characteristics with cancers which arise in patients with homologous recombination deficit (HRD).".

This part should be expanded with updated data. The authors should definitely add that when lacking homologous recombination DNA repair function, as in BRCA-mutant cells, DNA double-strand breaks will be processed by alternative but error-prone repair pathways, such as the non-homologous end joining repair (NHEJ), which lead to the accumulation of genomic instability and ultimately cancer cell death. NHEJ is faster than homologous recombination and mainly occurs in the G1 phase. Nevertheless, there is recent evidence that NHEJ functions throughout the cell cycle. Among proteins involved in the NHEJ, MRI/CYREN has dual role, as it stimulates NHEJ in the G1 phase of the cell cycle, while it inhibits the pathway in the S and G2 phases.

Recommended reference: Boussios S, et al. BRCA Mutations in Ovarian and Prostate Cancer: Bench to Bedside. Cancers (Basel). 2022;14:3888.

Reply 1: We have added reference to repair mechanisms to the Introduction section. See page 2, Lines 32-33.

Changes in the text:

Regardless of germline or somatic *BRCA* mutation status, mTNBC can share characteristics with cancers which arise in patients with homologous recombination deficit (HRD). In this setting which has been termed BRCAness (2), DNA double strand breaks are repaired by more error-prone pathways such as non-homologous end joining repair. This supports the study of drugs targeting HRD in mTNBC.

Comment 2: [2] Lines 69-70:

"The impact of exposure to immunotherapy on benefit from PARP inhibitors remains unknown.".

The authors should also mention that apart from the higher neo-antigen load of BRCA1/2, and wild-type BRCA1/2 homologous recombination (HR) deficiency tumours as compared to the HR-proficient cancers, there is evidence that BRCA deficiency may induce a STING-dependent innate immune response, by inducing type I interferon and pro-inflammatory cytokine production. Interestingly enough, clinical models have also demonstrated that PARP inhibition inactivate GSK3 and upregulate PD-L1 in a dose-dependent manner. Consequently, T-cell activation is being suppressed, resulting in enhanced cancer cell apoptosis.

Recommended reference: Revythis A, et al. Recent Insights into PARP and Immuno-Checkpoint Inhibitors in Epithelial Ovarian Cancer. Int J Environ Res Public Health. 2022;19(14):8577.

Reply 2: We have revised the language to focus attention away from the benefit of immunotherapy in BRCA1/2 mutated breast cancer (which is not within scope for this Editorial), but to discuss that benefit from PARP inhibition after prior receipt of immunotherapy is unknown. See page 3, lines 74-75

Changes in the text: The impact of prior treatment with immunotherapy

on benefit from PARP inhibitors delivered in later lines remains unknown.

Comment 3: [3] Lines 71-72:
"As expected, the addition of veliparib did increase toxicity consistent with the known adverse event profile of PARP inhibitors.".
Veliparib is the smallest PARP inhibitor. The authors should mention that the differences in size and rigidity among PARP inhibitors are hypothesized to be the basis for the distinct behavior of each drug to prevent the release of bound PARP1/2 from chromatin. During this process, known as "PARP trapping", PARP1 or PARP2 become trapped in DNA damage sites and prevent the recruitment of additional DNA repair proteins. It appears that the cytotoxic mechanism as it relates to PARP trapping may be dependent on the use of PARP inhibitors in monotherapy or combination therapy. PARP trapping is associated with high myelosuppression, which results in variation of the recommended doses across PARP inhibitors.
Recommended reference: Shah S, et al. BRCA Mutations in Prostate Cancer: Assessment, Implications and Treatment Considerations. Int J Mol Sci. 2021;22(23):12628.
Reply 3: The differential toxicity of different PARP inhibitors is not within scope of this Editorial. We have therefore revised the language to focus on veliparib alone rather than PARP inhibitors as a class. See page 3 lines 76-77.
Changes in the text: As expected, the addition of veliparib did increase toxicity consistent with the known adverse event profile of this drug.