Peer Review File

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Reviewer A

Overall good review of the current literature based on the most up to date data.

- Do not need to include the section describing BRCAwt and other HRD..... The HRP group comprised those without any evidence of HRD. You did not use the classification anywhere in paper.

Among the studies included in the meta-analysis were "BRCA wild-type and other HRD" subgroup, such as PAOLA, PRIMA, ATHENA-MONO, ARIEL 3, NOVA, and Study 19. This subgroup comprises gBRCA wild-type/sBRCA wild-type patients with another HRD biomarker - gLOH or myChoice -. An HRP subgroup represents the BRCAwt group or the patients without HRD biomarkers. This paper has been rewritten to Non-BRCA HRD (patients with BRCA wild-type (wt) and HRD biomarker as gLOH or myChoice®).

- Instead of BRCAmut --> use BRCAm

The change has been made.

- Based on the difference typically seen in patients with newly diagnosed and recurrent disease; should separate out these patients in your analysis and description so that it shows what true response would be in the recurrent setting.

We did not conduct a separate analysis restricted to the recurrence setting as this was recently reported by another group – lines 135-136.

Reference:

Lee, C.K.; Friedlander, M.L.; Tjokrowidjaja, A.; Ledermann, J.A.; Coleman, R.L.; Mirza, M.R.; Matulonis, U.A.; Pujade-Lauraine, E.; Bloomfield, R.; Goble, S.; et al. Molecular and clinical predictors of improvement in progression-free survival with maintenance PARP inhibitor therapy in women with platinum-sensitive, recurrent ovarian cancer: A meta-analysis. *Cancer* **2021**, doi:10.1002/cncr.33517.

- Need to discuss that PAOLA-1 had bev combined with olaparib earlier in the paper. It is discussed briefly in the discussion but it's not truly PARPi maintenance alone and the comparison group also received maintenance. There was no true placebo arm in this trial. Thanks for the suggestion. This information is included. Lines 158-159.

- Need to discuss or acknowledge the recent letters to physicians removing indications for certain PARPi in the recurrent setting for HRP patients.

In recorrent setting, reports of detrimental overall survival in patients with mBRCAm or HRD from the ARIEL 4 (rucaparib), SOLO 3 (olaparib), and NOVA (niraparib) have led to treatment recommendation updates. PARPi monotherapy should not routinely be offered to patients who have recurrent platinum-sensitive cancer. It may be offered to patients who have not already received PARPi and who have responded to platinum-based therapy regardless of BRCA mutation status. PARPi monotherapy is not recommended for patients with either BRCA

wild-type or platinum-resistant recurrent.

References:

Tew WP, Lacchetti C, Kohn EC, PARP Inhibitors in the Management of Ovarian Cancer Guideline Expert Panel. Poly(ADP-Ribose) Polymerase Inhibitors in the Management of Ovarian Cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol*. 2022;40(33):3878-3881. doi:10.1200/JCO.22.01934

Reviewer B

In this article, the authors present an up-to-date meta-analysis of the various HRD biomarkers studied in the first and second line randomized clinical trials and their association with survival in patients with ovarian cancers treated with PARP inhibitors. The manuscript is straightforward, well written, and concise and has clear results within the scope of a meta-analysis. Definitely deserves to be published and is a valuable contribution to the "Chinese Clinical Oncology" journal. Some comments need to be addressed before publication.

Comment 1: [1] "Introduction", Lines 7-8:

"High-grade serous ovarian cancer (HGSOC) is the most common and most aggressive subtype.2".

At that point, the authors should clarify that 90% of ovarian cancer are of an epithelial cell type and comprise multiple histologic types, with various specific molecular changes, clinical behaviours, and treatment outcomes. The remaining 10% are non-epithelial ovarian cancers, which include mainly germ cell tumours and sex cord-stromal tumours, which are characterized by a more favourable prognosis.

Recommended reference: Cheung A, et al. Non-Epithelial Ovarian Cancers: How Much Do We Really Know? Int J Environ Res Public Health. 2022;19(3):1106.

Reply 1: We have modified our text as advised (see Page 2, line 47-50).

Changes in the text: High-grade serous ovarian cancer (HGSOC) is the most common (90%) and aggressive subtype, which retains a poor prognosis. However, epithelial ovarian cancer is a heterogeneous disease that includes several histotypes such as non-epithelial ovarian cancer (10%) based on molecular changes, clinical behavior and treatment.

Comment 2: [2] "Introduction", Lines 8-9:

"Patients with these tumors are commonly diagnosed at stages III (51%) or IV (29%) and their 5-year survival rates in the of 42% and 26% in the United States (US), respectively.3".

The authors should report that there are still no effective tools for general population screening. This is also reflected economically and cost-effective strategies for early detection and prevention of ovarian cancer have been investigated over the last decade. The cost of treatment per patient with ovarian cancer remains the highest among all cancer types. The average initial cost in the first year can amount to around USD 80,000, whereas the final year cost may increase to USD 100,000.

Recommended reference: Ghose A, et al. Hereditary Ovarian Cancer: Towards a Cost-Effective Prevention Strategy. Int J Environ Res Public Health. 2022;19(19):12057.

Reply 2: We have modified our text as advised (see Page 2, line 50-55).

Changes in the text: The cost of treatment per patient with ovarian cancer remains the highest among all cancer types, with an average initial cost in the first year of around USD 80,000 and the final year cost potentially increasing to USD 100,000. Despite efforts to develop effective tools for general population screening, patients with these tumors are commonly diagnosed at stages III (51%) or IV (29%) and their 5-year survival rates in the of 42% and 26% in the United States (US), respectively;

Comment 3: [3] "Introduction", Lines 6-8:

"Interestingly, some BRCA wild-type patients may also benefit from PARPi therapy, posing the question of whether we can identify biomarkers of HRD that goes beyond BRCA mutations.".

A comment should be made specifically about synthetic lethality that could also be used in tumours which share molecular features of BRCA mutated tumours—known as "BRCAness". Therefore, mutation of genes beyond BRCA in the homologous recombination pathway expands the indication of PARP inhibitors. The broader use of synthetic lethality targeting the homologous recombination pathway is still being investigated.

Recommended reference: Shah S, et al. Epithelial Ovarian Cancer: Providing Evidence of Predisposition Genes. Int J Environ Res Public Health. 2022;19(13):8113.

Reply 3: We have modified our text as advised (see Page 2, line 55-57).

Changes in the text: PARPi therapy may benefit some patients with wild-type BRCA, which raises the question of identifying HRD biomarkers beyond BRCA mutations. In addition, synthetic lethality can be used in tumors with similar molecular characteristics to BRCA-muted tumors, referred to as "BRCAness". Mutations in genes outside of BRCA in the homologous recombination pathway may expand the indication for the use of a PARP inhibitor, although this is still being studied.

Comment 4: [4] "Introduction", Lines 0-1:

"In fact, PARPi have been approved with a similar indication for patients with prostate cancer who carry a mutation in a HRR gene.14".

The authors should mention that up to 8% of non-metastatic prostate cancer patients may respond to PARP inhibitors, irrespective of the fact that the HRD is not derived from BRCA mutations. This may be related to the CDH1 gene loss or inactivation of the SPOP gene, which represent early events in carcinogenesis.

Recommended reference: Boussios S, et al. BRCA Mutations in Ovarian and Prostate Cancer: Bench to Bedside. Cancers (Basel). 2022;14(16):3888.

Reply 4: We have modified our text as advised (see Page 3, line 77-80).

Changes in the text: In fact, PARPi have been approved with a similar indication for patients with prostate cancer who carry a mutation in HRR gene. However, it is worth noting that up to 8% of non-metastatic prostate cancer patients may respond to PARP inhibitors, regardless of whether the HRR deficiency is caused by a BRCA mutation. This suggests that other genetic alterations may render prostate cancer cells susceptible to PARP inhibition. For example, early events in prostate cancer development, such as CDH1 gene loss or inactivation of the SPOP

gene, may also increase sensitivity to PARPi.

Comment 5: [5] "Discussion", Lines 2-4:
"A possible explanation is that PARPi can promote anti-tumor activity by mechanisms other than homologous recombination deficiency, such as a microenvironment reshaping towards immune activation via macrophage activity 30.".
This is a good point and it should be mentioned the therapeutic strategy of the combinations of PARP inhibitors with immunotherapies, such as anti-CTLA-4 and PD-1/PD-L1 that has partly been based on the hypothesis that BRCA1/2, and wild-type BRCA1/2 HRD tumours display a higher neo-antigen load than homologous recombination-proficient cancers, producing more effective anti-tumour immune response. In addition, 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 5: We have modified our text as advised (see Page 8, line 221-226).
Changes in the text: A possible explanation is that PARPi can promote anti-tumor activity by mechanisms other than homologous recombination deficiency, such as a microenvironment reshaping towards immune activation via macrophage activity. Moreover, preclinical models support a therapeutical synergism between PARPi and immune checkpoint inhibitors, notably anti-PD-1/PD-L1 and anti-CTLA-4 which induces a PARPi sensitization and provokes a major antitumor immune response than either drug alone;

Comment 6: [6] "Discussion", Lines 4-5:
"It is also very likely that the methods currently available in clinical practice cannot capture all the features associated with HRD".
At that point, the authors should mention that technologies of proteomics, such as mass spectrometry and protein array analysis, have advanced the dissection of the underlying molecular signaling events and the proteomic characterization of ovarian cancer. Proteomics analysis of ovarian cancer, as well as their adaptive responses to therapy, can uncover new therapeutic choices, which can reduce the emergence of drug resistance and potentially improve patient outcomes.
Recommended reference: Ghose A, et al. Applications of Proteomics in Ovarian Cancer: Dawn of a New Era. Proteomes. 2022; 10, 16.
Reply 6: We have modified our text as advised (see Page 8, line 226-228).
Changes in the text: Recent advancements in proteomics, including mass spectrometry and protein array analysis, have significantly contributed to a deeper understanding of the molecular signaling events and proteomic characterization of ovarian cancer.