Peer Review File

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Reviewer A:

Comment 1: With the different PARP inhibitors shown to be effective against HRR mutation prostate cancer, we would like to know the pharmacological differences among them. Please discuss briefly about the manner in which these PARP inhibitors perturb PARP-1 allostery, in term of the side effects (PMID 33674152, 32241924).

Reply 1: We thank the reviewer for this suggestion. We have added discussion on the mechanism of action of PARP inhibitors and included the suggested articles.

Changes in the text: Added discussion of the mechanism of action of PARP inhibitors (see lines 61-89)

Comment 2: Please also discuss about mechanisms of resistance to PARP inhibitors, which have been reported recently (PMID 37174127).

Reply 2: We thank the reviewer for this comment. We have added a discussion on the proposed mechanisms of resistance to PARP inhibitors and included the suggested reference.

Changes in the text: Added discussion on mechanism of resistance to PARP inhibitors (see lines 91-105)

Comment 3: The authors should discuss about pulmonary embolism events which have been observed in PROpel study.
Reply 3: We thank the reviewer for this suggestion. We have added mention of pulmonary embolism from the PROpel trial and included the rates of pulmonary embolism observed in the adverse events table.
Changes in the text: Added discussion on pulmonary embolism events and added pulmonary embolism as a complication to the adverse events table (see table 3, lines 228-236)

Comment 4: In lane 103 “the” should be “The”.
Reply 4: We thank the reviewer for bringing this to our attention. We have edited the appropriate text.
Changes in the text: “the” changed to “The” (See line 164)

Comment 5: In lane 111 “88(62%) should be deleted.
Reply 5: We thank the reviewer for bringing this to our attention. We have edited the appropriate text.
Changes in the text: Deleted “88(62%)” (See line 174)

Comment 6: In table 1 character font should be standardized.
Reply 6: We thank the reviewer for bringing this to our attention. We have edited the appropriate text.
Changes in the text: Standardized font in table 1 (See table 1)

Comment 7: In table 3 “PROFOUND phase 2” should be “PROFOUND phase3”.
Reply 7: We thank the reviewer for bringing this to our attention. We have edited the appropriate text
Changes in the text: “PROFOUND phase 2” changed to “PROFOUND phase3” (see table 3)

Reviewer B:

Comment 1: In title, I would use "Castration Resistant" instead of "Castrate Resistant"
Reply 1: We thank the reviewer for this suggestion. We have edited the title accordingly.
Changes in the text: Changed “castrate” to “castration” (see line 2)

Comment 2: Niraparib trial -- "GALAHAD" not GALHAD
Reply 2: We thank the reviewer for bringing this to out attention. We have edited the text where appropriate.
Changes in the text: “GALHAD” changed to “GALAHAD” throughout text and tables.

Comment 3: PROfound trial, if you use the study authors capitalization, was PROfound not PROFOUND

Reply 3: We thank the reviewer for bringing this to out attention. We have edited the text where appropriate.
Changes in the text: “PROFOUND” changed to “PROfound” throughout text and tables.

Comment 4: . Line 58 "BRCA mutation housing patients" is odd, would rephrase
Reply 4: We thank the reviewer for this suggestion. We have edited the text accordingly.
Changes in the text: "BRCA mutation housing patients" changed to “patients with BRCA mutations” (see line 118-119)

Comment 5: Line 63 -- in the discussion of OS, need to explicitly state that the data are immature.
Reply X: We thank the reviewer for this comment. We have added mention of data immaturity in the text.
Changes in the text: Added “immature study data” when discussing results (see line 124)

Comment 6: discussion of Talapro-1 is missing. The phase 2 data for niraparib is included, I certainly would also include the phase 2 data for talazoparib.
Reply 6: We thank the reviewer for this comment. We have added discussion on talazoparib to the article where appropriate. (see lines 176-191)
Changes in the text: Section on talazoparib added under subheading “ Summary of TRITON3 results in comparion to similar clinical trial”. Added TALAPRO-1 information into tables 1 and 3.

Comment 7: Line 102: I would include details about the study (dosing, etc)
Reply 7: We thank the reviewer for this comment. We have added additional details about the study.
Changes in the text: Added additional details about the GALAHAD trial (see lines 164-168)

Comment 8: Line 130: olaparib and abiraterone also included prednisone
Reply 8: We thank the reviewer for this comment. We have added mention of the prednisone in addition to Olaparib and abiraterone.
Changes in the text: Added “plus prednisone” along with the olaparib and abiraterone treatment regimen (see line 211)

Comment 9: Line 139: clarify statement that whole population demonstrated OS improvement but inconsistent with BRCA1/2 population? BRCA1/2 drives all this data.
Reply 9:We thank the reviewer for this comment. We have added clarification in the manuscript.
Changes in the text: Clarified this statement in the manuscript (see line 222-223)

Comment 10: Conclusions can be updated given the recent FDA approvals of all 3 PARP combinations.
Reply 10: We thank the reviewer for their comment. We have updated the conclusion section to reflect current FDA approvals for combination therapies.
Changes in the text: Added mention and references to updated FDA approvals for (see lines 249-255)

Comment 11: Line 152: I didn't see any discussion to support the conclusion statement that greatest benefit is in germline DNA repair mutations
Reply 11: We thank the reviewer for this feedback. We have clarified this statement in the conclusions section.
Changes in the text: Clarified statement in conclusion section regarding greater efficacy of PARP inhibitors for those with specific mutations (see line 245-247)

Comment 12: Table 1: gene list for PROfound is incomplete
Reply 12: We thank the reviewer for this comment. We have added the comprehensive gene list for all trials included in table 1.
Changes in the text: Added comprehensive gene lists for all trials (see table 1)

Comment 13: Table 1: disease state is oddly differently described (histologically confirmed etc) -- I'm sure this was the same between trials...
Reply 13: We thank the reviewer for this comment. We have more uniformly described the diseases state of the trials included
Changes in the text: More uniform description of disease state added to table 1 (see table 1)

Comment 14: Figure 1 adds little. Presenting PFS in bar graphs is odd. Discussion in the text is probably adequate.
Reply 14: We thank the reviewer for this suggestion. We have removed figure 1 from the manuscript.
Changes in the text: Deleted figure 1 and removed mention of figure 1 from the text.

Reviewer C:

Comment 1: The authors do not describe the other studies with PARP inhibitors performed in patients with prostate cancer and in particular the studies TOPARP A, TOPARP B, TALAPRO 1 e TRITON 2. This work only describes the results of the studies without providing a critical comment. It lacks also an adequate description of the studies of PARPi + ARPI combination which represents the latest novelty in the treatment of patients with metastatic prostate cancer. Finally, this work adds nothing to the knowledge already available on the use of PARP inhibitors in patients with prostate cancer.

Reply 1: We thank the reviewer for their comment. Although there is a wealth of recently emerging information on the use of PARP inhibitors in prostate cancer treatment, this review was specifically requested to comment on the TRITON-3 phase the trial and those most similar to it. As such, we've focused primarily on the most current or advanced data on the various PARP inhibitors, but could not encompass all data available. We do agree the inclusion of TALAPRO-1 would benefit this manuscript and have thus included a section on it, as well as adding it to the relevant tables.
Changes in the text: Added section describing TALAPRO-1 and talazoparib, included in tables.