Peer Review File

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Reviewer A

Well summarized results of TRITON-2.
-Comment 1: Consider a table summarizing the results
Response: We have added a table summarizing the results on page 11.

-Comment 2: Insights into each of the response rates for BRCA2 or BRCA1 patients and duration of response would be worthwhile.
Response: We thank the reviewer for this suggestion. We have added the following to page 4: "A superior response was observed among *BRCA2* patients (48% versus 30% for *BRCA1*), which is potentially secondary to an increased frequency of biallelic mutations among *BRCA2* patients and a greater coexistence of *TP53* mutations among *BRCA1*-mutated men. (12)". We have also added the following reference:
12. Taza F, Holler AE, Fu W, et al. Differential Activity of PARP Inhibitors in BRCA1- Versus BRCA2-Altered Metastatic Castration-Resistant Prostate Cancer. JCO Precis Oncol 2021;5:PO.21.00070.

-Comment 3: Worth mentioning if responses were noted in measurable disease patients and symptomatic patients
Response: We thank the reviewer for this comment. In this TRITON 2 report, the objective responses were limited to patients with measurable disease at baseline. Accordingly, we have clarified this on page 4: "A confirmed objective response was observed in 46% of *BRCA* patients **with measurable disease**". The investigators did not report in this manuscript whether responses differed by patient symptomatology.

-Comment 4: Toxicities should be expanded upon with the possibility of MDS or longer-term bone marrow failure with earlier use of PARP inhibitors.
Response: We have added the following to page 4: "While not reported in the TRITON2 overall safety population, known potential long-term sequalae of these agents, particularly if used in earlier settings, include myelodysplastic syndrome and bone marrow failure (13)."

-Comment 5: Please mention the false positive rate due to CHIP with doing circulating tumor DNA testing for mutations.
Response: We have added the following to page 6: "and potential false positive results secondary to clonal hematopoiesis of indeterminate potential (CHIP)."

Reviewer B

This editorial addresses an overview of the evolving landscape of treatment options for metastatic castrate-resistant prostate cancer (mCRPC), focusing on the emergence of Poly-ADP ribose polymerase inhibitors (PARPi) and challenges associated with genetic testing in clinical practice. It highlights trial data from TRITON2 on rucaparib specifically and discusses alternative treatment options for mCRPC patients. Overall, this editorial contributes a valuable overview approach to mCRPC patient management considering the expanding array of available therapies and diagnostic challenges. I found the editorial to be well-written and clear. This editorial presents a rather interesting concept that is of interest in the field. The conclusions align with the review actual findings. Once the minor revisions are addressed, the revised editorial becomes acceptable for publication.

1. Discussion: Please revise or edit line 99 as follows: "While obtaining genetic testing from a fresh metastatic tumor biopsy is considered optimal, it is often unavailable."
2. I suggest maintaining consistency in the formatting of the letters in the figure, as the alteration is noticeable in "Niraparib + enzalutamide..."
3. In Supplementary Figure 1, there are misspellings in "Supuleucel-T" and "Olaprib + Abiraterone." Please correct them to "Sipuleucel-T" and "Olaparib+ abiraterone for.."

Response: We thank the reviewer for these comments. We have made all the suggested changes.

Reviewer C

Great commentary
only thing I would add is a table or a cartoon with upcoming trials and the disease space that they fit into... that would be extremely useful to show the earlier stage in which each trial would advance rucaparib use

Response: We thank the reviewer for the complementary feedback. We chose to highlight a few notable studies in our commentary: “Ongoing phase III trials in the metastatic hormone sensitive prostate cancer (mHSPC) space include…the NADIR (NCT04037254) three-arm trial is comparing radiotherapy + androgen deprivation therapy (ADT) to each of niraparib alone and niraparib+ radiotherapy/ADT.”

A review of clinicaltrials.gov (2/25/2024) demonstrated that currently there are:

- 51 studies for olaparib in prostate cancer
- 23 studies for niraparib
- 20 studies for talazoparib
- 15 studies for rucaparib

As such, it would be extremely challenging to fit these into a table or a caricature, and thus we chose to highlight the select few in the commentary. We hope this is satisfactory.