Peer Review File
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Reviewer A

The authors present a real-world analysis of outcomes in mHSPC patients receiving darolutamide. They demonstrate excellent tolerability of darolutamide and significant deep PSA responses in the early treatment period. While these results are not surprising, there is value to reporting real world evidence. However, there are several limitations that should be acknowledged and the following comments addressed.

- Current evidence only supports the use of darolutamide together with docetaxel chemotherapy. While ongoing studies are investigating the use of ADT+darolutamide, these have not yet been reported and this should be acknowledged in the manuscript.
Reply：Thank you for the advice. I added some description in Abstract and Introduction.
Changes in text: Page 2 line 40-41; Page 4 line 98, 99, 103.

- There is no mention of the addition of chemotherapy in mHSPC as a standard of care (or abiraterone) for completeness in the introduction
Reply：Thank you for the advice. I changes and added descrpition in Introduction. I also changed the citation for this part.
Changes in text: Page 4 line 98-99,103-105; Citation 5.

- Please confirm that patients receiving chemotherapy were excluded.
Reply：Thank you for the advice. I added the description in the method part.
Changes in text: Page 8 line 152.

- It is mentioned that some patients had ADT +Enza or Abi prior, why were they changed to darolutamide? This only mentioned in the discussion re: adverse events and the fact that daro could further reduce PSA levels has not been demonstrated in the study. In general this would not be considered second line if switching for toxicity.
Reply: Thank you for noticing that. These 4 patients were swithed to Daro from other NHT because of AE, and the PSA of these 4 patients was futher reducted as it has been demonstrated in that part. In Chinese clinical practice, some urologists do take this kind of switching as the secon-line in prostate cancer because the efficacy were further achived after switching. Nevertheless, changes these 4 patients to first-line won't change the results of DARO do further reduce PSA in the second-line of mHSPC. Still, your point is vital very much and helps us a lot.

- line 142 "patients had complications" should this be comorbidities? I presume this is at baseline rather than adverse events from the drug
Reply: Thank you for the correct word, I changed it with your recommedation.
Changes in text: Page 9 line 179.

- how many patients had denovo/synchronous metastatic disease vs metachronous.
Reply: It is such a great question that we were very much care about when collecting data. Unfortunately, nearly half of these 51 patients we cannot find out whether they were de novo or not, therefore we have to not present this baseline. Some of them are still in our follow-up for the PFS, we shall present this baseline information in the following paper.

- The paper would be more impactful if other real world cohorts were included, particularly those who were receiving chemotherapy (comparisons of outcomes but also toxicity would be interesting compared to abi/enza).
Reply: Thank you very much for the suggestion. That will also in anthor paper compared with abi, but the porpotion of patients using chemo in mHSPC is quite low, this cohort is very hard to establish in our 2 centers. But compared to Abi is in the “doing list”.

- further analysis to determine patient or disease characteristics that are associated with PSA decline would be of interest.
Reply: Thank you very much for the suggestion. We calculate the data set of GS≥8 and high tumor volume and added these in the section of previous viceral metastatsis.
Changes in text: Page 13 line 304-312.

- adverse reactions were only observed in 3 patients, however given this is relying on documentation in medical records, it is likely to be underreported. This should be highlighted as a limitation.
Reply: Thank you for the reminder. We added this in limitation.
Changes in text: Page 15 line 359.

- What was the median follow up of the study? Is there any data on CRPC rates as yet?
Reply: Thank you for asking. The median follow-up time was 9.3 months as it in the Results section. We are looking forward to report the PSA-PFS in the near future, but we haven’t get it now.

- Line 294- clarify "benefit to OS in patients with nonmetastatic CRPC in the mHSPC setting"- should be CRPC.
Reply: Thank you very much for the carefulness, totally my typo error.
Changes in text: Page 14 line 338.

- The conclusion that darolutamide is the safest among ARSIs is not explored by this study and should be removed, discussion about potential benefits including less BBB penetration and drug interactions are appropriate. However stating no drug interactions occurred is untrue unless all conmeds were assessed individually for interactions. Otherwise this should be reworded that no reported AEs related to drug interactions occurred.
Reply: Your point is vital. Daro reported to be the safest ARSIs is not by us in this article, so I added 1 reference as citation 38 to avoid the misunderstanding. And the DDI part was reivised as you suggested, more precisely. Thank you very much.
Changes in text: Citation 38; page 14 line 343, 347-348.

- The PSA reductions in those who have had prior ADT+ARSI should be in the results section rather than discussion.
Reply: At the beginning of writing, I agreed with you. However after we discussed with other authors who are more professional in statistics, we were agreed on apart from the main results, results from subgroups, due to the small number of other data, were lack of sufficient statistical significance. Therefore we decided to put them in discussion just to demonstrate the trends. Hope you could understand us.

- "trial" is misspelt as trail on several occasions.
Reply: Thank you very much for your kind reminder. I changed them all.
Changes in text: There are nine of typo error of trial in the text, in line 112, 213, 220,228,295,297,299,301.

- commenting on access to darolutamide in China is of interest, is it funded for use without chemo? in many countries it is not.
Reply: It is a great question and thank your for being so professional in clinical practice. It is not funded in this paper. In China, the reinbustment covering the use of darolutamide in mHSPC with chemo, but the chemo don't have to be decided to use or not wthin 6 weeks after the initiation of darolutamide. But in clinical pratice, the reinbustment cover differs from cities to cities, regions to regions. Some patients spent a few but some spent more. In these 2 centers, patients were from all over the country. But the worst situation we have clarified to patients before prescription. Unless patients accepted the cost of darolutamide coverd all by themselves, otherwise we would not prescribe for them.

Reviewer B

1) First, the title needs to indicate the combination of ADT and DARO, the outcome of PSA, and the clinical research design of this study, i.e., a real-world retrospective cohort study.
Reply: Thank you for the suggestion. I changed it to" Real-world retrospective study of PSA and safety assessment with darolutamide plus ADT for metastasis hormone—sensitive prostate cancer".
Changes in text: Page 1 line 1-3

2) Second, the abstract needs some revisions. The background did not analyze the clinical needs for real-world data and the knowledge gaps and limitations of prior studies. The methods need to describe the inclusion of subjects, details of the ADT and DARO treatment, and how the patients were followed up. The current conclusion needs to be tone down due to the lack of a control group receiving ADT alone and please accurately describe the treatment strategy of the combination of ADT and DARO, not DARO alone.
Reply: Very important opinions. I revised the abstract as you suggested. Thank you very much.
Changes in text: Page 3-4, line 33-66.

3) Third, in the introduction of the main text, the authors did not analyze the clinical needs for the real-world data on the efficacy of ADT + DARO. The authors also did not review the limitations and knowledge gaps of prior studies. Please clarify the potential clinical contributions of this study.

Reply: Great opinions of yours. I revised the introduction as you suggested. Thank you very much.

Changes in text: Page 6-7, line 98-128.

4) Fourth, in the methodology of the main text, please describe the sample size estimation procedures, details of the follow up, not the time-points only, the assessment of clinical characteristics, and the ethics approval of this study. The statistical analysis should directly describe that descriptive statistics were performed.

Reply: Thank you for your suggestions. I revised the method part as you suggested.

Changes in text: Page 7-8, line 144-163.

5) Finally, please consider to cite several related papers: 1. Aragon-Ching JB. Rezvilutamide: yet another androgen receptor pathway inhibitor for metastatic hormone-sensitive prostate cancer? Chin Clin Oncol 2023;12(2):12. doi: 10.21037/cco-23-25. 2. Lyou Y, Dorff TB. Hormonal manipulation in androgen signaling: a narrative review on using novel androgen therapy agents to optimize clinical outcomes and minimize side effects for prostate cancer patients. Transl Androl Urol 2021;10(7):3199-3207. doi: 10.21037/tau-20-1053. 3. Vaishampayan U. Global efficacy and clinical application of androgen receptor inhibitors in metastatic prostate cancer. Chin Clin Oncol 2023;12(6):61. doi: 10.21037/cco-23-59.

Reply: Thank you very much for the suggetion. I added these 3 references as in 5, 35, 38.

Changes in text: Page 6 line 101, page 13 line 300, page 14 line 343, Citation 5,35,38.