Peer Review File

Article information: http://dx.doi.org/10.21037/tau-20-1118

Reviewer #1

The authors should be applauded for conducting a comprehensive review regarding the current treatment options for mHSPC, a disease stage that has undergone a plethora of management changes during the past decade. The strengths of the review encompass the implementation not only of currently available evidence but also cost and nursing considerations, two aspects that are frequently ignored in current debates.

General comments:

Comment 1: The references in the manuscript start with #3

Response 1: Thank you picking up this error. References now start from #1.

Comment 2: The "LHRH antagonists" section should implement data from the HERO trial, especially with regards to adverse effects

Response 2: Thank you for this comment. We agree that the HERO trial should be included in this section and have made the necessary additions.

"Most recently, an oral third generation LHRH antagonist relugolix was proven to be superior to leuprolide in achieving rapid and sustained testosterone suppression.(14) Over 96% of men who received relugolix maintained castration through to 48 weeks as compared to 88% in the leuprolide group. Moreover, 56% of men reached castration levels at day 4 with relugolix. (14). Of particular note, relugolix was also associated with a 54% relative risk reduction in major adverse cardiovascular events as compared to leuprolide."

Comment 3: Page 5: the authors write: "They have a low affinity for the AR(16) but perhaps most concerning was their agonist effect when castration resistance ensued." Please give a reference for the second part of the sentence.

Response 3: We have added these two references to support our statement

1) Bohl CE, Gao W, Miller DD, Bell CE, Dalton JT. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. Proceedings of the National Academy of Sciences. 2005 Apr 26;102(17):6201-6.
2) Culig Z, Hoffmann J, Erdel M, Eder IE, Hobisch A, Hittmair A, Bartsch G, Utermann G, Schneider MR, Parczyk K, Klocker H. Switch from antagonist to agonist of the androgen receptor blocker bicalutamide is associated with prostate tumour progression in a new model system. British journal of cancer. 1999 Sep;81(2):242-51.

Comment 4: Page 6: There is data for Apalutamide suggesting that Apalutamide might induce lower rates of AR mutations and/or leads to lesser induction of splice variants such as

ARV7 which might be contributors to development of hormone-resistance. This might be added to the respective section.

Response 4: We have now added this sentence with this reference.

"In addition to this, early evidence suggests that apalutamide may not increase the frequency of AR anomalies that contribute to castrate resistance."

1) Smith MR, Thomas S, Chowdhury S, Olmos D, Li J, Mainwaring PN, Oudard S, Feng FY, Gormley M, Ricci DS, Rooney B. Androgen receptor (AR) anomalies and efficacy of apalutamide (APA) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) from the phase 3 SPARTAN study.

Comment 5: Page 6: Regarding Darolutamide, the authors write: "This accounts for its negligible blood brain barrier penetration". Even though it's correctly referenced, the authors might include "…in preclinical models" to highlight this fact.

Response 5: Thank you, we have added this wording to the manuscript.

Comment 6: The information regarding the TROPIC study might be deleted, since it does not apply to the mHSPC setting.

Response 6: Yes thank you, we have taken your advice and deleted this sentence

Comment 7: At some point, the authors should put emphasis on the description of the CHAARTED and LATITUDE high-volume/-risk criteria

Response 7: We have now included the following sentence before introducing the trials and the table below.

"Of note, the definition of high volume/high risk metastatic prostate cancer has not yet been universally defined. The two main criteria derived from the CHAARTED trial and LATITUDE trial is shown in Table 2."

CHAARTED high volume criteria	**LATITUDE high risk criteria**
>4 bone metastases (at least one outside the spine or pelvis **AND/OR** Visceral metastases	Two or more of the following criteria: • >3 bone metastases • Gleason score >8 • Visceral metastases

Comment 8: In the "Treatment choice" section the authors should also discuss "Treatment sequence" considerations. For instance, PFS2 data for Apalutamide or the data from the BCCA cross-over trial (Khalaf et al.) can be implemented

Response 8: Thank you, we have now included the paragraph below.

"Another key consideration centres around the impact of choice of initial therapy for mHSPC on subsequent treatment selection in mCRPC. A logical approach would be to use docetaxel following prior ARPI therapy, and vice versa. Whether any mHSPC patients would benefit from switching to a second-line ARPI at time of progression to mCRPC is unknown, although currently available data suggests this would be of limited value.(43, 44) With additional systemic agents likely to enter the treatment paradigm for mCRPC and mHSPC in coming years, carefully designed prospective clinical trials and high-quality real-world databases will be needed to help address questions around treatment sequencing."

Minor comment:

Comment 9: Being a first-time reviewer for this journal and not 100% aware of the targeted readership of the journal, I feel like the epidemiology part of the introduction is a little "Australia-focused". While this if of course not a criticism per se, I would suggest to implement an additional sentence with more global rates, in order to put it also into perspective for the global readership.

Response 9: We wrote this article under the assumption that the audience is predominantly from Asia/Australasia. We have added a sentence about worldwide mortality rates and it now read as below.

"Despite being extremely treatable in its early stages, prostate cancer still remains a leading cause of cancer related death worldwide, (3) and in Australia, is the second leading cause of male cancer-related deaths.(4)"

Reviewer #2

Well written and well thought out manuscript pointing out the treatment landscape of mHSPC. All relevant studies on this topic have been mentioned, the literature is up-to- date and the tables are complete.

However, a few comments which should be easily to implement.

Introduction:

Comment 1: "Unfortunately, although effective at first, all patients inevitably develop a rising PSA or new metastases during their ADT course thus progressing to a castrate resistant form of prostate cancer known as castration-resistant prostate cancer (CRPC)."

- ➔ Difficult to read; much easier in two sentences.
- ➔ E.g. although effective at first, all patients inevitably develop a rising PSA or new metastases during their ADT course. This progress marks the transition to a castrate resistant form of prostate cancer known as castration-resistant prostate cancer (CRPC).

Response 1: Thank you for your comments. We have amended the sentence to the sentence below.

"Unfortunately, although effective at first, all patients inevitably develop a rising PSA or new metastases despite castrate levels of testosterone. This marks the transition to a lethal form of prostate cancer known as castration-resistant prostate cancer (CRPC)."

Traditional androgen deprivation therapy agents /LHRH agonist:

Comment 2: "This can have a clinical effect causing urinary obstruction, bony pain and even spinal cord compression.(10)"

➔ Bone pain instead of bony pain

Response 2: We have changed this to bone pain.

Combination trials / Enzalutamide plus ADT/ENZAMET Trail:

Comment 3: Even if the statistical design of ENZAMET was not powered to analyze the outcome of patients under triple therapy, the results indicates that patients with high volume disease have less OS-Benefit (was mentioned). It should also be emphasized that the rate of side effects, e.g. neuropathy was much higher under triple therapy compared to ADT + Docetaxel and therefore, a triple therapy cannot be recommended so far. To my point of view, it is appropriate in this context to refer to ongoing clinical trials (e.g. ARASENS) evaluating efficacy of triple therapy in mHSPC.

Response 3: We have emphasised this point in our treatment considerations section as below.

"Similarly, the role of combination chemotherapy and ARPIs requires further investigation. Currently, there is no data to support concurrent treatment with docetaxel and an ARPI. In fact, in ENZAMET triplet therapy (ADT + Docetaxel + Enzalutamide) appeared to be associated with higher rates of adverse events including neuropathy.(38) It must be said however that ENZAMET was not designed to formally assess the combination of Docetaxel and Enzalutamide. Two ongoing trials are assessing the combination of Docetaxel and an ARPI, namely ARASENS (Docetaxel +/- Darolutamide – NCT02799602)(45) and PEACE-1 (Docetaxel +/- Abiraterone – NCT01957436). The results of these trials are eagerly awaited and will help to define the benefit, if any, of concurrent treatment with Docetaxel and an ARPI in mHSPC."