Peer Review File

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Reviewer A

The paper is an editorial for on triplet vs doublet therapy.

- The authors would like to thank reviewer #1 for his/her time to evaluate the current manuscript. Please find below detailed response to each point raised.

Comments 1: P4 L83: docetaxel and ADT should not be labelled as placebo but standard of care or comparator

- The authors would like to thank Reviewer A for this pertinent comment. We gladly changed the phrasin according to Reviewer A's suggestion and kindly refer to the updated manuscript which reads as follows:

'It is of note that doublet therapy consisting of docetaxel&ADT, which was used in 49 both ARASENS and PEACE-1 as standard of care […]' (Page 4)

Comments 2: P4 L83 " lost in the meanwhile its importance" -> please rephrase

- The authors would like to thank Reviewer A for this comment. We have rephrased the sentence which reads as follows:

'It is of note that doublet therapy consisting of docetaxel&ADT, which was used in both ARASENS and PEACE-1 as standard of care, was superseded by doublet therapy consisting of ARAT and ADT, demonstrating more favorable survival outcomes with less toxicity' (Page 4)

Comments 3: in today's setting with emerging "modern imaging" it should be mentioned that criteria for high risk / high volume are based on conventional imaging

- The authors would like to thank Reviewer A for this helpful comment. We edited the manuscript accordingly which reads as follows:

'It is of note that differentiation according to disease volume was based on conventional staging (Computerized tomography [CT] or magnetic resonance imaging [MRI] and bone scanning) in ARASENS and PEACE-1. As a consequence, ongoing research is mandatory to answer the question whether current disease stratifications (CHAARTED, LATITUDE) are fully applicable for 'modern' staging relying (positron emission tomography/computed tomography [PSMA PET-CT].' (Page 4/5)

Comments 4: you could consider a sentence about local therapy - radiotherapy (or prostatectomy) in low vol mHSPC

- The authors would like to thank Reviewer A for this helpful comment. We edited the 77

manuscript accordingly which reads as follows: 78

'[…] – while those might benefit from local treatment.' (Page 5)

We hope that the modifications are satisfactory for Reviewer A.

Reviewer B

This is overall a nicely written editorial highlighting the post hoc analysis by Hussain et al. and the authors adopt a stance of caution in dismissing triplet for low-volume disease due to immaturity of current data.

- The authors would like to thank reviewer #B for his/her time to evaluate the current manuscript. Please find below detailed response to each point raised.

Comments 1: Line 80 sentence structure "mHSPC patient (patients) will likely benefit of(from) a treatment intensification in terms of (with) triplet therapy"

- The authors would like to thank Reviewer B for this helpful comment. We edited the 93 manuscript accordingly which reads as follows:

'The current post hoc analysis by Hussain et al. contributes substantially to understand which mHSPC patients will likely benefit from a treatment intensification in terms of triplet therapy.' (Page 4)

Comments 2&3:

2. Line 83 "ARASENS and PEACE-1 as placebo, has lost in the meanwhile its importance..." I think there are certain nuances that need to be considered with this statement. Chemohormonal doublet therapy is still relevant in certain parts of the world where ARAT may not be available or reimbursed. These real-world trends are important. Perhaps a more neutral word to use here will be "relevant" or "superceded by". In making a case for the ARAT, the authors can also mention the body of literature showing in several parts of the world that ARAT+ADT (specifically AAP) has been shown to be more cost-effective as well compared to DOC+ADT.

3. Beyond the lack of direct comparative data between doublet and triplet therapy, to add more perspective to this topic, the authors should highlight briefly the other important and relevant conversation regarding real-world data showing poor adoption of the doublet strategy and a good recent article to cite for this would be Chen et al (https://pubmed.ncbi.nlm.nih.gov/36509970/). If the community at large has not even embarked on doublet as the standard of care, it will be an uphill task to make a case for triplet therapy regardless of the hard evidence.

- The authors would like to thank Reviewer B for this helpful comment. We gladly changed the wording and changed it in more neutral phrasing which reads as follows in the updated manuscript:

'It is of note that doublet therapy consisting of docetaxel&ADT, which was used in both ARASENS and PEACE-1 as standard of care, was superseded by doublet therapy consisting of

ARAT and ADT, demonstrating more favorable survival outcomes with less toxicity [11–13].' (Page 4)

- Moreover, we totally agree with the opinion of Reviewer B that real world treatment patterns are likely to mismatch from most recent treatment recommendation deducted from randomized controlled trials (RCT) due to various reasons, mainly due to lack of financial reimbursement and lack of availability in a real-world setting. Wegladly incorporating these considerations in our updated manuscript which reads as follows:

'Finally, the study by Hussain et al. – together with various landmark trials investigating treatment intensification in mHSPC patients in the past decade – should remind the uro-oncology community to deliver evidence-based care for mHSPC patients. As recently outlined by Chen et al., real world data from around the world demonstrated an alarming dismal adoption of combination therapy for mHSPC patients clearly indicating a need for greater awareness and hence, uptake of treatment intensification for mHSPC patients [15]. Within this context, it must be emphasized that above outlined considerations regarding treatment intensification might not be realizable in everyday practice in some parts of the world due to potential lack of financial reimbursement or availability in some parts of the world [16–18].' (Page 6)

The authors would like to thank reviewer #B for his/her time to evaluate the current manuscript. Please find below detailed response to each point raised.