Peer Review File

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Reviewer A

The authors present a very informative and comprehensive overview over the passivity and meaningfulness of a tripplet therapy in patients mit mCSPC. I just have one minor comment:

p 2 line 54-62 for the sake of completeness, maybe want to add STAMPEDE Data for Abiraterone

Reply: Thank you for this suggestion. We fully agree and have amended the sentence to include abiraterone and STAMPEDE as suggested. More details regarding the findings of STAMPEDE using abiraterone is shown in Table 1.

Change in text, page 2 lines 60-63:
"Following this, several large phase III trials demonstrated similar benefits of using ARPI doublets (abiraterone, enzalutamide, apalutamide, and rezvilutamide in STAMPEDE, ARCHES/ENZAMET, TITAN, and CHART respectively) for both high and low volume mHSPC."

Reviewer B

General comments:
This is a good editorial comment/narrative on analyses of triplet therapy for mCSPC

Specific comments:
1. This Reviewer agrees with the authors regarding the notion that volume of disease alone would of course not be the sole factor for deciding triplet therapy. However, for lack of a counter argument, this remains our best available evidence since this is how the patient population enrolled in the two major triplet therapy trials were studied. In addition, it may be worthwhile to note (for sake of completion), the recently updated ASCO guidelines as well that emphasizes on volume of disease but also chemo-fit or chemo-eligibility (Virgo et al., JCO: DOI: 10.1200/JCO.23.00155.) such that " For patients with metastatic noncastrate prostate cancer with high-volume disease (HVD) as defined per CHAARTED8 (four or more bone metastases, one or more of which is outside of the spine or pelvis, and/or the presence of any visceral disease) who are candidates for treatment with chemotherapy but are unwilling or unable to receive triplet therapy (eg, due to insurance constraints), docetaxel plus ADT should be offered"
2. Understanding that there has not been (nor likely will be) a triplet vs doublet comparison other than in the form of meta-analyses, ARASEC is a recently concluded trial that seeks to at least answer the safety and feasibility of the ADT + doublet of darolutamide compared to a historical arm and may be worthwhile to mention
3. Curious to see what the authors think to mention data on rezvilutamide in the CHART trial since it was studied in the high-volume population as well and compared to bicalutamide (both with ADT of course) https://doi.org/10.1016/S1470-2045(22)00507-1 since the authors did make mention of ADT doublets with ARPI

Reply: Thank you for the thoughtful and important comments.

1. **We completely agree and have added the recommendation from ASCO guidelines as suggested by the reviewer in special circumstances where ARPIs are not available. In Canada, ARPI and triplet therapies are available and most patients with mCSPC will receive treatment intensification with at least an ARPI, however this may not be the case for other regions.**

Changes in text page 4 line 224:
"As outlined by recent ASCO guidelines, for chemo-eligible patients with high volume mCSPC who decline or cannot access an ARPI (e.g. due to insurance constraints), ADT plus docetaxel may be offered instead of triplet therapy. Docetaxel can overcome some of the financial toxicities associated with ARPIs due to the low drug cost and fixed treatment duration. While docetaxel is associated with notable adverse events, quality of life data from CHAARTED show most patients recover by 6 months, representing an acceptable treatment

option. However, these patients should be made aware that ADT plus docetaxel confers inferior OS compared to triplet therapy."

2. **We agree data from ARASEC (and ARANOTE) will be interesting in the context of the triplet data presented in ARASENS and have mentioned them in this manuscript. We also note the results from LATITUDE and PEACE-1 evluating de novo mCSPC, median OS with ADT + AAP (LATITUDE) was 53.3 months, and ADT + docetaxel + AAP (PEACE-1) was not reached and was 61 months in the high volume subgroup. In the absence of definitive comparative data, this suggests potentially advantage of the triplet therapy over doublet.**

   Changes in text page 4 line 207: "Although there is no definitive evidence comparing survival benefits of triplet versus doublet therapy with ADT & ARPI, ARASEC (NCT05059236) and ARANOTE (NCT04736199) are both evaluating ADT & darolutamide in mHSPC, which will offer interesting data in this context. We also note that in PEACE-1 and LATITUDE, median OS was longer with ADT, docetaxel, and abiraterone in de novo high volume patients (61 months) than ADT & abiraterone (53.3 months). In the absence of definitive comparative data, this suggests there may be a role for docetaxel in selected patients presenting with aggressive mHSPC.

3. **We agree that the CHART data was an important trial which further adds to the evidence of ADT + ARPI with more representation from patients with de novo high volume disease from Asia. While Rezvilutamide is not available for our clinical practice in Canada, this data adds options for access in other countries (received approval in China), and therefore we have added this study in the text and Table 1.**

   Changes in text page 2 lines 60-63: "Following this, several large phase III trials demonstrated similar benefits of using ARPI doublets (abiraterone, enzalutamide, apalutamide and Rezvilutamide in STAMPEDE, ARCHES, TITAN and CHART respectively) for both high and low volume mCSPC". We have also added this trial in Table 1.

Reviewer C

Thank you for the opportunity to review this manuscript. It is a brief narrative review and commentary of the field. It will provide a useful summary for the reader, with correction of some points.

Main comments:
• Line 83-84: suggest change "...and PEACE-1), representing a small subset of real world mCSPC cases with aggressive biologic features" to "...and PEACE-1). The ARASENS population therefore represented a subset of patients with high risk mHSPC where by definition a decision had been made that inclusion of docetaxel was appropriate, and was not necessarily representative of the wider population of patients with mHSPC. This needs to be considered when translating the results into practice."
• Lines 47 and 96: "trend" is a meaningless and in fact misleading term that should be avoided. You should state if there is statistical confidence or not that a true difference existed.
• Lines 131-136: emphasize that all previous evidence was based on conventional imaging with CT and isotope bone scan. PSMA PET may define different biologic subsets and currently there is no high level evidence to guide decision-making in that setting where PET and conventional imaging give conflicting results (note that bone scan can also overestimate metastatic burden).
• There are several errors in reference to ENZAMET, and missing data from STAMPEDE – see below.
• Discussion of radiation to the primary as per STAMPEDE is relegated to a throwaway comment in line 175. This treatment is in very common use, often with an ARPI and so is arguably a different form of doublet or triplet therapy.

Reply: Thank you for the insightful comments.

- **Line 83-84: We agree with the reviewer and have made the following changes in text.**
  - **Page 3 lines 129: "and PEACE-1). In other words, the ARASENS population represents a small subset of mHSPC patients with high risk disease, for which docetaxel is planned.".**
  - **Page 4 lines 219: "In our perspective, the supporting data for triplet therapy is mainly for patients with de novo high volume mHSPC, and one should acknowledge that the ARASENS population reflects an overall small proportion of biologically aggressive mHSPC when translating results into practice."**

- **Line 47 and 96: We have made the following changes in text to better reflect the interpretations of these results.**
  - **Page 2 line 50: "the STAMPEDE trial suggested potential OS benefits with the addition of docetaxel in low volume disease, however, this difference was not statistically significant"**

- **Page 3 line 143: "Although not statistically significant, the results from ARASENS suggest potential OS benefit in patients with low volume disease".**

- **Line 131 to 136, we completely agree with the reviewer and have made the following changes in text**
  - **Page 4 line 244 "It is also important to recognize disease volume defined on conventional imaging is somewhat arbitrary and is subject to significant interobserver variation.[24] Novel functional imaging such as PSMA PET has much higher sensitivity and is increasing utilized. Currently there is no high level evidence on using PSMA PET to guide decision making. Frequently, PSMA PET will upstage low volume disease defined by conventional imaging to high volume disease, conferring risks of over-treatement (adding docetaxel) and under-treatment (omitting radiation to the primary). In select cases where bone scans demonstrate nonspecific lesions in the bone, PSMA PET may play a role in confirming the presence of bone metastases for these lesions. However, the overall extent of disease volume demonstrated on PSMA PET should not be routinely used to define disease volume for the purpose of treatment selection."**

- **Errors in reference to ENZAMET and missing data from STAMPEDE (see below): Thank you for this feedback. Please see our detailed responses below for the specific change in text. We have amended our discussion of ENZAMET to indicate the control arm was NSAA + ADT rather than ADT alone. We also included abiraterone as the doublet regimen being referenced by reference #12.**

- **Radiation to the primary: we have made the following changes in text to expand on the discussion, hopefully without taking away the main focus of addressing the ARASENS volume data. Please let us know if we should go into further details on this important topic.**

Change in text Page 5 line 327:
"Recently, Bossi et al. showed that among the PEACE-1 low-volume mHSPC cohort, while radiation improved radiographic progression free survival (rPFS) and time to serious genitourinary events for patients who received the triplet regimen of ADT, docetaxel, and abiraterone compared to SOC (ADT plus docetaxel), it did not improve OS.[20] In practice, the addition of radiation to the prostate primary for low volume mCSPC (often on the backbone of ADT & ARPI) is a well-adopted paradigm due to the positive OS data shown by STAMPEDE, and potential OS benefit in the HORRAD trial. The seemingly conflicting data between PEACE-1 and STAMPEDE may be due to differences in the study population, as reflected by the median baseline PSA, proportion

of T3/T4 disease, and the use of systemic therapy which could also improve local control (only 18% of patients were planned for docetaxel in STAMPEDE). Currently, we still offer prostate primary radiation for patients with low volume disease and those with bulky primaries, given the treatment is well tolerated and can delay serious pelvic complications from disease progression. In the future, the OS benefit of radiation to the primary in patients with low volume mHSPC in an era of more effective systemic therapies warrants further evaluation, and it would be interesting to explore this question in other triplet therapy trials such as ARASENS.

Minor points:

• Throughout: perhaps acknowledge that "de novo" is sometimes referred to as "synchronous" in the literature.

Reply: Thank you for pointing this out.

Change in text: Page 1 line 36-37 amended to "de novo or synchronous" to highlight both terminology, and used "de novo" throughout the review to ensure consistency.

• Throughout: feedback from consumer/community representatives is that "castrate" should be avoided. Preferable terminology is still unclear but "metastatic hormone-sensitive prostate cancer (mHSPC)" is probably better

Reply: We have amended to use "metastatic hormone- sensitive prostate cancer (mHSPC) throughout the text.

• Line 43 (twice) and lines 55, 56: "=>" should be "≥"

Reply: We have made this change of "≥" in page 2 lines 45, 58, and 59.

• Line 46 (twice): suggest adding confidence intervals.

Reply: We have added confidence interval, page 2 line 48-49.

• Line 56: "criteria" should be "criterion"

Reply: We have changed to "criterion" in page 2 line 59.

• Line 57: STAMPEDE also demonstrated the benefit of abiraterone; this is ref 12, incorrectly placed in line 59.

Reply: Thank you for pointing this out. We have added abiraterone and STAMPEDE to the sentence for reference 12.

Change in text page 2 line 60

"Following this, several large phase III trials demonstrated similar benefits of using ARPI doublets (abiraterone, enzalutamide, apalutamide, and rezvilutamide

in STAMPEDE, ARCHES/ENZAMET, TITAN, and CHART respectively) for both high and low volume mHSPC."

• Line 59: ENZAMET was the first to demonstrate a survival benefit for enzalutamide (ARCHES initial report was for rPFS as primary endpoint).
Reply: Thank you we agree with the reviewer. We have added ENZAMET.

Change in text page 2 line 62
"…enzalutamide and apalutamide in ARCHES/ENZAMET and TITAN respectively"

• Lines 69-70 and 72: initially talks about ENZAMET and PEACE-1, but then talks about abiraterone or enzalutamide, ie the reverse order; the order should be the same in order to avoid confusion.

• Line 72 is incorrect (also line 115 and 171): ENZAMET control arm included an NSAA; it was not ADT alone. This whole paragraph probably needs rewriting for better accuracy and clarity.

Reply to above two suggestions: Thank you for catching this oversight. We have changed the order to discuss enzalutamide first then abiraterone per ENZAMET and PEACE-1. We also amended the text to correctly illustrate the control arm in ENZAMET per the reviewer's feedback.

Change in text, page 2 line 72
"The benefit of triplet therapy was first suggested by ENZAMET (ADT, docetaxel, enzalutamide) then PEACE-1 (ADT, docetaxel, abiraterone), summarized in Table 1. These two trials were not primarily designed to evaluate a triplet therapy approach: ENZAMET compared enzalutamide to a nonsteroidal antiandrogen with both arms receiving ADT, while PEACE-1 added abiraterone to a SOC arm of ADT. Unlike ARASENS, many patients did not receive upfront docetaxel, as chemotherapy was administered per physician's discretion in ENZAMET and was added to ADT in the amended protocol of PEACE-1 after the CHAARTED results were published."

• Line 82: suggest change "Majority of" to "Most" – again in lines 88 and 90 (alternatively use "the majority" not "majority" but I prefer the simpler language).
Reply: We have amended to "most" throughout the manuscript as per reviewer suggestions

• Line 83: suggest change "in" to "in each of"
Reply: We have amended to "in each of" as per reviewer suggestions

Change in text, page 3 line 128:

"Most patients had high volume disease (77%), de novo presentation (86%), and a higher proportion of visceral metastases (17% in ARASENS vs. 11% in each of ENZAMET and PEACE-1)."

• Line 88: suggest change "significant" to "clinically significant"
Reply: We have amended to "clinically significant" as per reviewer suggestions.

Change in text, page 3 line 135:
"The OS benefit was clinically significant, despite most patients (75.6%) in the control arm had received a life-prolonging therapy upon subsequent progression…"

• Lines 78-108: suggest strengthening the point that ARASENS was based on the ADT+docetaxel backbone; and that if a decision is made that docetaxel is not necessary (eg low volume and/or metachronous mHSPC) then the ARASENS data cannot be used to inform decision-making.
Reply: Thank you for this comment. We have added on page 3 line 130 " In other words, the ARASENS population represents a small subset of mHSPC patients with high risk disease, for which docetaxel is planned."

• Lines 78-108: similarly, the ENZAMET 470 event analysis included an exploratory subgroup analysis (post hoc, underpowered) that did not identify any prognostic subgroup that clearly benefited from docetaxel, in a trial population with a much larger spread of risk than was the case for ARASENS.
Reply: Thank you. We have added this important point on page 4 line 241. "In ENZAMET, which included a relative heterogenous patient population, explorative post hoc analysis did not identify any prognostic subgroup which clearly benefited from the addition of docetaxel."

• P107-108: the final sentence is not very helpful without some guidance as to a situation where intensification to a docetaxel triplet might be indicated. Are you suggesting specific clinical features, or biomarkers, or something else? Similarly line 188
Reply: We have deleted the last sentence in line 108 as this will be addressed in the subsequent section.

Change in text page 3 line 154, "However, there are select cases of de novo, low volume mHSPC with additional high risk features that should be considered for triplet therapy, outlined below."

• Line 121: for balance, perhaps include consideration of situations where ADT alone might be reasonable, eg certain comorbidities, patient wishes, financial constraints, access, low-resource countries.

Reply: Thank you.

Change in text: page 4 line 235:
"At present, in an era of treatment intensification with doublet (commonly ADT & ARPI) and triplet (ADT, docetaxel, & ARPI) regimens, ADT alone should not be routinely offered. Very rarely, there are special situations where patients are not fit to receive chemotherapy and/or an ARPI due to serious comorbidities conferring safety concerns or limiting overall prognosis, in which case ADT alone may be reasonable.

• Line 122: specifically darolutamide or abiraterone, because that is where the level 1 evidence currently sits.
Reply: Thank you we agree, and have added "darolutamide or abiraterone" in page 4 line 227.

• Line 145: define HRD.
Reply: Thank you, we have defined HRD as homologous recombination deficiency in page 5 line 303

• Lines 153-155: balance the docetaxel text by its advantages: low cost, short treatment course, most toxicities are transient. The sentence starting in line 155 could also be applied to oral therapies, for balance.
Reply: thank you for this comment.

Change in text, for better flow in the article, we have added this discussion in page 4 line 230:
"Docetaxel can overcome some of the financial toxicities associated with ARPIs due to the low drug cost and fixed treatment duration. While docetaxel is associated with notable adverse events in some, quality of life data from CHAARTED show most patients recover by 6 months, representing an acceptable treatment option."

• Ref 13 is not the correct reference for ARCHES, and ref 14 is not correct for ENZAMET. Both have had primary and follow-up publications that should be cited instead. TITAN ref 15 has also been updated.
Reply: thank you for the feedback. We have amended reference 13 and 14 to the original articles. Reference 15 already includes the updated publication for TITAN.

• Table 1: ENZAMET should also be listed in the doublet section. The triplet component of ENZAMET was not its main aim.
Reply: Thank you, we have added ENZAMET as both a doublet study and a triplet study (with the docetaxel cohort) in Table 1.

• I have not checked the figures in Table 1.
Reply: We have not included any figures.