Author's response to reviews

Title: Targeting Molecular Resistance in Castration-Resistant Prostate Cancer

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Author's response to reviews: see over
Dr. Alam:

Please find below a complete response to the reviews submitted for our manuscript, as well as answers to additional questions posed in the response email.

First reviewer (specific concerns):

1) "leading" in the abstract does not apply – Agree (edited)

2) The sentence commenting on the prognostic significant of PSA seems both out of place and awkward unless couched in other discussion of prognostic factors – Agree (deleted)

3) The last sentence in paragraph 4 is out of place as the next paragraph discusses intratumoral androgen synthesis as well as the AR and non-AR driven mechanisms of resistance. Consider deleting – Agree (deleted)

4) Consider providing more background regarding AR ligand independent mechanisms of resistance – Disagree. As the focus is more on CRPC, we have decided to focus more on mechanisms specific to CRPC treatment modalities. This topic is briefly addressed in the introduction.

5) Docetaxel is a standard of care but not "the" current standard of care for CRPC. Use of AR targeting agents as the first intervention is significantly more common. This phrasing, which is used in multiple parts of the MS needs to be edited. – Agree, edited.

6) Change enza to enzalutamide at initial use in the manuscript – Agree, deleted.

7) Describe what COU 301 and AFFIRM are and the population treated for this general audience at the first use of the titles of these studies – Agree, edited.

8) Define "non response" – Disagree, did not find this term used.
9) The approach of frontline docetaxel per the CHAARTED study is indicated ONLY, not "primarily" in high risk de novo patients. The acronym for CHAARTED, the study design and the details of what constitutes high risk de novo disease should be delineated.
   – Agree, edited

10) Docetaxel binds the β tubulin subunit, stabilizing total microtubules, not through specific stabilization of β tubulin. – Agree, edited

11) The primary mechanism of resistance mediated by BIII tubulin is through reduced MT stabilization, not altered binding of taxane to this specific isotype – Agree, edited.

12) It is not clear that CBZ has a novel mechanism of action but due to reduced PGP export may simply have higher tissue levels of taxane. – Disagree, this was left unchanged. As yet undetermined in the literature.

13) Consider including a schematic of androgen conversion as the paragraph describing androgen metabolism will be very difficult for the average reader to understand. – Agree, included.

14) The paragraph describing reactivation of steroidogenesis in response to abiraterone needs extensive editing. – Disagree, no edits made.

15) The text does not describe mutation of enzymes of steroidogenesis – Disagree, the above described paragraph does review mutations of enzymes of steroidogenesis.

16) Glucocorticoid receptor upregulation should be discussed as another mechanism of resistance to enzalutamide - Agree, included

17) Most CAP cell lines do not express AR splice variants. This statement should be modified. – Agree, edited

18) The Hornberg study did not establish that ARsv led to CRPC. It defined the presence of ARsv in a subset of CRPC mets and a worse prognosis associated with presence of ARsv. – Agree, edited

19) In the schematic docetaxel is shown inhibiting nuclear transport of AR – I do not find the portion of the MS describing the work of Kyprianou or Giannakakou. – Disagree, we did not feel this was high yield for a review discussion.

Second review (specific concerns):

1) Can be improved by adding discussion on additional AR targeting agents in clinical development like Bayer ODM201, ARN509, the ISIS/AZ AR antisense drug (Yamamoto et al CCR 2015), galaterone, VT-486, and the OGX427 (targeting the AT co-chaperone hsp27), all in Phase II or III development. – Disagree, for a review paper, we focused on approved therapies.

2) While they do mention the recent work on AR-V7 in CTC being prognostic for poor outcome, a more recent study used combination of copy number profiling and AR
sequencing to identify AR amplifications and mutations in the cfDNA of mCRPC patients progressing on novel systemic agents (Azad et al CCR 2015), reporting how AR amplifications or mutations accompanied enzalutamide resistance, and were predictive for adverse outcomes on enzalutamide. This worth mentioning alongside of the AR-V7 work as liquid biopsies that may prove useful as predictive or prognostic markers — Agree, cited.

3) They mention AR and CRPC as abbreviations and define them in parenthesis several times on the first page and throughout the paper – should only be defined once then use the abbreviation thereafter – agree, edited

4) 3rd paragraph first page - Maha Hussain should be Hussain et al – Agree, deleted

5) Several references are either incorrect or suboptimal – Disagree, reviewed.

6) They may want to update to include STAMPEDE presentation and press release for ASCO 2015 in support of CHAARTED data – disagree, decided not to include this press release at this time.

To address other issues in the formal response email:

1) Clarify the permissions for reproduction of the figure. If this was not specifically created for this manuscript, please do ensure you have the appropriate permissions for reproduction in an Open Access journal

   a. Figure 2 previously published in Clinical Cancer Research; authors CPE, ACG and JCY are also authors on the original paper. Diagrams are owned by the author and permission has been granted for publication

   b. Figure 1 has not been previously published in its current form

2) Clarify your Competing Interests statement for all authors

   a. Author CPE: This work is supported in part by Grants DOD PC111467 and Medivation/Astellas to CPE, NIH RO1 CA 165263–13 to H-JK and by a Stand Up To Cancer—Prostate Cancer Foundation—Prostate Dream Team Translational Cancer Research Grant SU2C-AACR-PCF DT0812 to Eric Small, Owen Witte and CPE. This research grant is made possible by the generous support of the Movember Foundation. Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research: The costs of publication of this article were defrayed. Mention of trade name, proprietary product or specific equipment does not constitute a guaranty of warranty by the Department of Defense, nor does it imply approval to the exclusion of other products. The views expressed herein represent those of the authors and do not necessarily represent the position of the Department of Defense.

   b. Author CPE: Research funding for CPE is in part funded by Medivation/Astellas.
c. Authors ACG, JCY, and TC: The author(s) declare that they have no competing interests.

Included in this online submission are:

1) Manuscript (revised)
2) Figure 1
3) Figure 2

If you have questions, please call me at (732) 742-1025 or email me at tchandrasekar@ucdavis.edu.

Sincerely,

Thenappan Chandrasekar, MD