Reviewer’s report

Title: Impact of clinical trial participation on survival in patients with castration-resistant prostate cancer: A multi-center analysis

Version: 0 Date: 12 Feb 2018

Reviewer: Takao Kamai

Reviewer’s report:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

1) General comments

The authors retrospectively investigated the impact of clinical trial participation on survival in 299 M0/I CRPC pts living in east Asia. They found clinical trial participants exhibited significantly higher cancer-specific survival rates than non-participants and discussed the several mechanisms underlying the results. Finally, they stated the important message derived from the results that participation in clinical trials should be offered whenever indicated, as such participation confers as inherent survival advantage.

2) Specific comments for revision including major and minor issues are listed below:

1. Regarding the survival analysis (Table 5 and text)

The authors should include factors as category items in the survival analysis to offset the confounding effect, such as below

1) number of docetaxel courses

2) primary treatment (RP or RT)

3) post-chemotherapy ARAT (Enzalutamide or Abiraterone) use

4) Ra223 use

because baseline character of these factors (all therapies and agents indicated above hold effect to prolong pts survival) showed significantly different in this study population and potentially
affected the survival analysis. If the factor "Clinical trial participation" remained statistically significant or trend, the scientific nature of the author 's argument would become stronger.

2. Regarding the results of difference in metastatic status

The authors include both M0 and M1 pts in the study and simply stated "Our observation remained consistent according to metastatic status at CRPC diagnosis" in the abstract and text. Considering the small number of M0 participants (only 15), I feel it is hard to draw conclusion at this stage as no difference regardless of metastatic status. The authors should alter the expression or also present data as additional files.

3. Regarding the study population and data collection of Non-participants

Follow-up periods indicated in the Method (i.e. Serum PSA measurements every 1 to 3 months, CT/bone scans every 2 to 4 months). Are they the same way for participants and non-participants? Please specify. At least, the bone scans every 2 months is impossible as an inspection using medical insurance in my institute. As the authors also described in the Discussion, a "participation effect" or "trial effect" that positively affects to oncological outcome may firmly exists.

4. Regarding potential mechanisms underlying the results

The authors described inherent differences in baseline patient and tumor features as third mechanism underlying the improved survival outcome. However, age, PSA level, Gleason score, ALP level, ECOG PS, and participation to clinical trial were identified to be independent predictors in this study. Accordingly, comments in page7 line7-9 "In our study, the performance status of patients who participated in CTs was better than that of non-participants; this might have affected the results" seems inappropriate.

Again, I would recommend to include factors classified by category of therapies (RP or RT) and agents (DTX, ARAT, Ra223) to minimize or to offset the confounding effect for survival analysis.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests` below.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons
CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal