

June 26, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10984-deited.doc).

Title: Perspective of novel therapeutic medicines targeting androgen signaling pathway in castration resistance prostate cancer

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer #02616017

1. *Add a little more details for clinical trial results on MDV3000 would be benefit for the readers.*

According to the comment, we have added details for the results of clinical trial on MDV3000 and put one more reference about this (p11, line 14-17, and line 19-21, and ref No.53).

2. *Reference could be shorter, focusing on the most recent publications.*

We agree with his/her comment. In this revision, some old references were deleted to focus on the most recent publications.

Reviewer #00579805

1. *As androgen-dependent and androgen-independent are well defined in the literature, it is not clear what castration resistance represents. It seems that the author is indicating a state of androgen-independent or less androgen-independent, the author should use a little ink to describe how this term is coined and why.*

We appreciate the reviewer's constructive comments. We have revised Introduction to describe characteristics of CRPC (p4, line 25 to p5, line 9).

2. *The author used a term androgen ablation, but how it was done is not mentioned.*

We apologize for our ambiguous description. According to the comment, we have changed the term "androgen ablation" to "androgen deprivation therapy (ADT)" (p20, line 20, 21, 23, p5 line 3, 6, p7 line1, p14, line 16, 17).

3. *The first paragraph of the introduction is not flowing well. This reviewer suggests revision for the second sentence: In Japan, partially because the diet are being westernized, the incidence of prostate cancer has been increasing. It would be better if there is reference. If not, use "seems, looks like, etc".The population of older males is becoming larger may also be a contributor.*

We appreciate his/her comment, we revised Introduction as the reviewer suggested (p4, line 10-12).

4. *The word “development and progression” in the second paragraph of introduction is OK, but development is conveying a neutral of positive sense. Onset or formation is probably providing a more negative sense properly.*

According to the comment, we have changed development to onset (p3, line 2, p4, line 2, 13).

5. *The author used a term of functional ARs. Are there some ARs that do not function? Through the text, ARs and AR are both used. Should be consistent.*

Functional AR means activated AR by androgen binding. The ligand-unbound AR does not have transcriptional activity (not function). According to the comment, we have changed all ARs in the manuscript to AR.

6. *At the initial diagnosis. Is there a diagnosis subsequent? Probably it is better by saying at the time of diagnosis.*

Thank you for the suggestion. According to the comment, we have changed the word ‘initial’ to ‘at the time of’ (p4 line 17).

7. *Does the word “Castration” in the third paragraph means removal of testis? If so, castration-resistance is not a good phrase because there is not by prostate cancer can become resistant to surgical removal.*

We appreciate his/her comment, according to comment #1, we described about the characteristics of CRPC in detail. (P4, line 25 to p5 line9). We believe that additional description could be a proper answer to this comment.

8. *The 1sr sentence, 1 paragraph of AR structure: Do the author mean “.....receptor gene family that express estrogen,*

We apologize for uncertain description. In this sentence, we tried to explain about the member of receptor gene family. We revised the sentence (p5, line 16, 17).

9. *In the DBD paragraph, “by atypical AREs” is not clear in meaning. Half site and classical ARE are not well known and the original definitions are better included. The whole last sentence is unreadable.*

We revised the description, adding the definition of canonical ARE (p6, line 10 to 13, and Ref 30) and deleted last sentences.

10. *In the LBD paragraph, how androgen ablation is related to castration is not described. Definition for point mutation is better included.*

According to the comment, we revised in the LBD paragraph by adding the description about the detailed mechanism of how the mutation in LBD cause the castration resistance. (p7, line 1 to 6).

11. *The 1st paragraph of AR signal pathway, last sentence. PSA is a protein not a gene. The expression or product of AR-dependent gene?*

Thank you for pointing out the wrong description. We changed the phrase “AR-dependent gene” to “ product of AR-dependent gene”. (p7, line 21).

12. *The first paragraph of the mechanism of castration resistance section. The first passible mechanisms are important by wording badly. Stable is used to represent that some thing is not changing. Herein, apparently the authors are no emphasizing the activation of then AR can not be done by DHT form intracellularly. Continued, sustained or revived is better than stable. Enhanced should be enhancing. It is uncomfortable to use promiscuous to describe a receptor. Check the literature for the accurate word.*

We appreciate his/her comment. According to the comments, we changed these phrases. (p3, line 6, 7, p8, line 13, 14, p9, line 7).

3 References and typesetting were corrected

Thank you again for considering our manuscript for publication in the *World Journal of Clinical Urology*.

Sincerely yours,

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