Author’s response to reviews

Title: Abiraterone Acetate in Patients with Metastatic Castration-Resistant Prostate Cancer: Long term outcome of the Temporary Authorization for Use programme in France.

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Author’s response to reviews: see over
Dear Dr McKeage

We would like to thank you for the opportunity to submit a revised version of our manuscript entitled “Abiraterone Acetate in Patients with Metastatic Castration-Resistant Prostate Cancer: Long term outcome of the Temporary Authorization for Use programme in France” for publication in \textit{BMC Cancer}

We also would like to thank the Reviewers for their insightful comments and/or suggestions. We have addressed all the points raised by each Reviewer and have modified the manuscript accordingly. Our answers to the Reviewers’ comments are detailed below.

We feel that the revised version of our manuscript is now suitable for publication in \textit{BMC Cancer} and are looking forward for your positive answer.

Sincerely Yours,

Nadine Houédé
Answers to the Reviewers’ comments

Referee n°1:

We would like to thank this Reviewer for his interest in our study and his insightful comments and suggestions.

Comment #1.

The authors described that they used univariate and multivariate logistic regression model to identify predictive factor of abiraterone acetate treatment duration. Usually, logistic regression examines the relationship between the categorical variable (for example, patients underwent 6 months and more abiraterone acetate treatment, or not) and one or more independent variables. I could not understand how the authors used logistic regression model. Or, was linear regression model performed ? Provide a table including the detailed results.

Response to Comment #1:

We agree with the Reviewer’s comment on the use of logistic regression for categorical variables. Because Abiraterone Acetate (AA) treatment duration was assessed only every three months according to the biological and radiological assessments planned in the TAU program (as described in the “Outcomes measures” section p.6), it was classified in three categories (≤ 3 month, 3-6 months, and > 6 months). This explains why a logistic regression model rather than a linear regression model was used to identify the predictive factors of AA treatment duration.

The new Table 3 is presenting the detailed results of prognostic factors of AA treatment duration for univariate and multivariate analyses.

Comment #2:

Table 3. The authors should describe the detailed results of univariate analyses, including non-significant factors. Regarding treatment duration, did it remain significant when it was treated as continuous variables in Cox hazard model ?

Response to Comment #2:

Former Table 3 has been replaced by new Table 4 which now includes the modifications that were suggested by the Reviewer. New Table 4 also includes the univariate analysis for non-significant variables included in the multivariate model (Gleason score, number of CT lines).

Regarding treatment duration, it was not possible to include it as a continuous variable in the Cox hazard model because, similarly to overall survival, it is also a time-dependent variable. This is the reason why we performed a Landmark method analysis at 3 months in order to identify prognostic factors known at 3 months as potential prognostic factors of Overall Survival.
Minor:

1. Table 1. Scales (ng/ml for PSA, and months for treatment duration) should be described.

   **Response:** As suggested, scales (ng/ml for PSA, and months for treatment duration) have been added to the revised Table 1


   **Response:** The published reference from Sternberg et al. has been updated in the references of the revised manuscript.

**Referee n°2:**

*We thank the Reviewer for finding our study “of outstanding merit and interest in its field”*

Minor points:

1. In the text of line 258-261, this part is explaining Fig. 2. Have difficulties deciphering the graph from the words. In Fig. 2, what do the dots represent? Need more clever explanations.

   **Response:** The legend of Figure 2 and the corresponding text have been modified for a better understanding of the data that this figure is describing. The dots correspond to the extreme values of PSA levels.

2. When treatment is discontinued with appropriate reasons, in general, further therapy might be applied except BSC. OS usually contains this bias. Furthermore, higher PS can accept longer adherence of medication or therapy, causing better survival benefit. Variables above should be involved and analyzed in the text and Table 1.

   Unfortunately, the performance status (PS) was not collected in this TAU program and therefore cannot be tested as a potential prognostic factor of OS in the present study. As indicated by the Reviewer, it is indeed well-known that patients with good PS receive additional lines of treatment that impact OS. As suggested the different lines of treatment have been added in Table 1 of the revised manuscript.