Reviewer’s report

Title: Survival of patients receiving systematic therapy for metachronous or synchronous metastatic renal cell carcinoma: a retrospective analysis

Version: 2 Date: 04 Oct 2018

Reviewer: Sophie Gourgou

Reviewer's report:

The remarks and requested corrections of the first reviewer have been taken into account.

The main bias of this paper is the comparison of 2 treatments without randomisation in 2 sub-groups of treatment.

So, a sub-group analysis was proposed (Table 2 and figures) due to different medical history of patients and justified by logical different median follow-up between synchronous and metachronous patients.

In table 2 : The median follow-up datas (performed with the reverse KM method) are discordant with respect to the presented CSS data (50% of the patients died at 9 and 21 months in MS and MM respectively, with a median follow-up of 81 and 142 months), this data seems strange.

In the cox model presented in Table 3, univariate and multivariate cox model including sub-groups with different follow-up; so the estimated effect-size of treatment if biased and the subgroups SM/MM is not identified as independent prognosis parameter which would lead to disregard for the rest of the analysis.

However, it is clear the sub-groups are justified to evaluate the impact of treatment in each of them.

This multivariate result is discordant to explain the methodology and need to be explain.

I suggest a multivariate prognosis model for each sub-group of patients (SM ans MM).

In addition, comparison between TT and IT is biased in each sub-group of patients (metachronous or synchronous) because of no randomisation.

To compare the trt TT vs IT, it will be appreciate to know the median follow-up of patient by treatment group to estimate the bias for comparison.

Indeed, if you observe the subjects for a shorter time, you are less likely to observe the event of interest and we can wrongly conclude that there is a difference between TT and IT. The use of the propensity score method will be appreciated as complementary analysis to conclude for the comparison of 2 treatments as discussed by the authors.
These results must be presented in order to be able to interpret and measure the sensitivity between the presented biased analysis and the analyses using the propensity score.

L103: TFi definition is not clear: Heng score defined as from time of diagnosis to systemic therapy. Why is it not the same definition?

In the Statistical analysis section:

L132: please clarify PFS and CSS definitions separately with each event of interest and date of point.

In the figures:

To evaluate the level of evidence of the data described, it is necessary to add in the figures the number of patients at risk in each of the subgroups.

x-axis legend is confused with "first-line TT time": TT for treatment ?? or for Target Therapy ???. It is expected to have "first line treatment time" in order to match the 2 compared treatments. If it is not the case, please clarify.

Minor remarks:

Table 1:

Put capital letters on each title variable

Modify the modalities for cancer specific survival status:

Survival >> Alive and death due to non cancer =32 (I don’t understand survival, is it ALIVE)

Table 2:

Age (years) (add the range)

Table 3:

Justify the reason of sample size decrease N=214 >> 207 (PFS)
Justify the reason of sample size decrease N=214 >> 202 (CSS)/ due to missing data for variables?

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

No

**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:

Not suitable for publication unless extensively edited

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