Author’s response to reviews

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

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Author’s response to reviews:

August 1, 2018
Alexandros Houssein
Editor
BMC Cancer

Dear Editor:

We wish to re-submit our manuscript titled “Survival of patients with meta/synchronous metastatic renal cell carcinoma receiving systemic immunotherapy vs. targeted therapies: a retrospective analysis.” The manuscript ID is BCAN-D-17-01368.

As before, we thank you and the reviewers for your latest suggestions to improve our paper. In this round of revision, the manuscript has been rechecked and we have made additional changes
to incorporate the reviewers’ suggestions to the text. We have added definitions in the Methods, further explained the exclusion criteria for various analyses, improved the presentation of the data by presenting 95% confidence intervals and actual p-values, and modified Table 1 and Figure 2 to make them clearer. Our responses to the latest comments have been prepared and are attached herewith.

Thank you for your consideration. We forward to hearing back from you.

Sincerely,

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Authors’ Reply

BCAN-D-17-01368R1

Survival of patients with meta/synchronous metastatic renal cell carcinoma receiving systemic immunotherapy vs. targeted therapies: a retrospective analysis

Reply to Jeanette Eckel-Passow’s comments

We thank Jeanette Eckel-Passow for the precious time spent reviewing our manuscript, and for the following valuable comments.

1* While TFI and time zero for the survival analyses (i.e., time from first treatment) are defined in the response letter, they are not defined in the manuscript. Please add these details to the manuscript.
Response: We added definitions of the TFI and time zero for the survival analysis in the Methods section (page 6, lines 103-105). We also added two new references:


2* The response letter states that favorable-risk patients were excluded; however, this was not discussed in the methods section.

Response: We have added a sentence in the Discussion section (page 10, lines 215-218) explaining that the favorable risk group was excluded because the SM included only either intermediate or poor risk patients who had one or more risk factors in the Heng criteria, whereas MM included favorable risk patients. To better compare the survival of SM with that of MM, the favorable risk group should be excluded.

3* The methods section states that patients with incomplete medical records of their survival prognoses were excluded. As stated previously, these patients should be included in analyses and censored at their last known follow-up date. Similarly, using an intent-to-treat design, patients who discontinued therapy before the first-cycle response was evaluated due to disease progression should also be analyzed. Or, at a minimum, an intent-to-treat analysis should also be conducted.

Response: Thank you for the comments. There was a misunderstanding because of the sentences in the original Methods section. We excluded patients who moved to other countries or hospitals without national security numbers, so it was impossible to follow-up their survival in the Korean National Cancer Registry System; those who were younger than 20 years old; those who refused to receive systemic therapies after the adverse events were explained to them; those who stopped medication because of financial expenses; and those with disease progression without expecting therapeutic effects for early withdrawal. Otherwise, the survival prognoses could be checked by the Korean National Cancer Registry system (page 5 line 92-page 10 line 97). We also added a sentence in the limitations section of the paper about the the patients who were lost to follow-up (page 12, lines 270-271).
4* When calculating and comparing follow-up duration, data should only be utilized for patients who have not yet had an event. It is not appropriate to include patients who have had an event when calculating and comparing follow-up.

Response: We added a sentence to the Methods explaining the methodology for defining follow-up and its calculation (page 7, lines 132-135).

5* P-values should be provided in any sentence where the authors compare PFS or CSS across groups.

Response: To make the comparisons more clearly, we have added the actual p-values to the sentences where PFS and CSS were compared between groups (pages 8-10).

6* When p-values are presented, it is not clear what comparison the p-values refer to. For example, please see the 3rd paragraph in the results section. The first sentence provides data comparing SM vs MM in parentheses; however, the p-value at the end of the sentence denotes a comparison of IT to TT. Such sentences need to be revised so that it is clear what comparison each p-values denotes.

Response: We corrected the third and fifth paragraphs to clarify the p-values in each comparison and for the multivariate analysis (page 8, line 166- page 9 line 173 and page 9 line 193-page 10 line 206).

7* Instead of stating p<0.05 or p>0.05, please provide the actual p-value.

Response: We changed the p-values to their actual values in the Results section (pages 8-9).

8* The first paragraph of the discussion section states that the IT group included patients who benefitted from TT. More information regarding prior treatments is necessary and would be informative to include in Table 1.

Response: Among the 126 patients treated with IT, 12 (9.5%) had a subsequent first-line TT history. We added this information to the Discussion section (page 11, line 225).

9* Table 1 would be more reader friendly if a row was utilized for each level of a variable. Also, for any variable that includes censoring, median (min-max) is not appropriate. These should be
presented as median and 95% CI. Please see comment above regarding follow-up duration. Same comments hold for Table 2.

Response: We changed the text to show the median and 95% confidence interval (page 2, lines 31-32 and page 8, line 150-151). We also changed Tables 1 and 2 as the reviewer has suggested.

10* Figure 2 does not appear to be labeled correctly and is confusing. Are panels A and B supposed to denote intermediate risk, and panels C and D high-risk? If so, please label similarly to panels E-H.

Response: We corrected Figure 2 to make it clearer. We also corrected the figure notation in the Results section (pages 8-9).

11* If TFI is one of the variables in the Heng risk model, why is it evaluated again by itself? And if TFI is being evaluated, why not similarly evaluate the other variables that comprise the Heng model?.

Response: The Heng risk criteria comprised six risk factors including the time from diagnosis to systemic treatment < 1 year, and the risk classification depends on the total number of risk factors. For example, the intermediate risk group had one or two risk factors, while the poor risk group had three or more risk factors. As such, TFI might be included in the determination of the risk groups, or it might not. In addition, the metachronous type of metastasis is a tumor recurrence after complete surgical resection of the primary kidney tumor in the nonmetastatic RCC setting, whereas synchronous metastasis has a primary RCC in situ. This study chose TFI < 1 year to compare survival outcomes between SM and MM, because the current risk criteria did not stratify patients by their metastatic type. We therefore used TFI focusing on the intermediate and poor risk patients with different metastatic types to better stratify the patients in the metastatic cohort, and to better to understand the prognostic survival differences.

In addition, we designed this study to apply the determining factor of TFI with a cut-off point of 1 year because we hypothesized that SM and MM were different disease entities with different disease characteristics and prognoses. This TFI cut-off point was chosen as an important factor in conditional survival of mRCC. A recent changing trend in the therapeutic strategy for mRCC is to apply delayed treatment, whereas the opinion in the past decade was to start systemic treatment as early as possible after diagnosis of mRCC, regardless of its metastatic type (J Clin Oncol. 2018 Jun 1;36(16):1588-1593).

Lastly as for the reviewer’s question about the evaluation of other variables comprising the Heng model, we have tried to identify new additional markers to help improve the accuracy of the current Heng and MSKCC risk criteria:


Others

All files, including the manuscript and response letters, were reviewed by a native English speaker from an English editing service company (Editage.co.kr).