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:

Linda Gummlich, PhD
Editor
BMC Cancer

Dear Dr. Gummlich:

I, along with my coauthors, wish to submit a revised version of our manuscript, “Survival of patients receiving systematic therapy for metachronous or synchronous metastatic renal cell carcinoma: a retrospective analysis”, for publication in BMC Cancer.

We previously submitted this manuscript (submission # BCAN-D-17-01368R3) to your journal and were invited to resubmit after addressing the reviewers’ comments. We have attached a
document providing our point-by-point responses to the reviewers’ comments in the latest round of peer review. These responses include detailed descriptions of the revisions that we have made to address the reviewers’ concerns.

We are grateful to the reviewers, who provided many insightful comments on our work. We hope that our revised manuscript meets their expectations.

As previously noted, this manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. The study design was approved by the appropriate ethics review boards. All of the authors have approved this revised manuscript and are in favor of submitting it to your esteemed journal.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

Jinsoo Chung, MD, PhD

Authors’ Replies

BCAN-D-17-01368R3

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

Replies to Jeanette Eckel-Passow’s comments

We thank Dr. Eckel-Passow for reviewing our manuscript and providing helpful comments.

As noted in all of the previous reviews, there is still concern with the retrospective nature of the design and no propensity adjustment. It is not sufficient to simply state in the Discussion section that a propensity analysis could be done. Without adjusting for the propensity to receive IT or TT, the authors cannot make any conclusions regarding survival differences between the two treatments. Furthermore, since TT is a more recent treatment, as described in the Discussion section, it has short follow up than IT. This further confounds the results.

Response: Thank you for your comment. We concede that the lack of propensity adjustments is a genuine limitation of our study. However, our findings concerning the comparative benefits of TT and IT still provide valuable insights that can be used to optimize treatment strategies for mRCC. Specifically, we found that IT agents such as the cytokines interleukin-gamma and
interleukin-2 compared favorably with TT in terms of remission and survival outcomes. Furthermore, understanding the therapeutic effects of cytokines in mRCC patients may offer clues as to the systemic effects of cytokines.

Comments

* Supplementary Figure 1: More explanation is needed regarding the 45 patients who were excluded due to “without expecting therapeutic effects).

Response: The 45 patients in question had poor clinical statuses involving serious underlying diseases and substantial tumor burdens, including hepatic tumors and brain tumors. These patients were cachectic at the time of their mRCC diagnoses and therefore would have been unable to tolerate systemic therapies, so their treatments were restricted to conservative management. We have added a clause explaining why these patients were not expected to benefit from systemic interventions (page 7, lines 107–108).

* Supplementary Figures 2&3: Still refer to overall survival, which was not evaluated in the paper.

Response: We have changed “overall survival” to “cancer-specific survival” in the Supplementary Figure Legends (pages 23–24, lines 481 and 487) and in the Supplementary Figures.

* Tables 1&2: Survival is added to the table; however, it is not clear what the number represents. Additionally, while the reviewer response describes what follow-up duration represents, the paper does not. Since multiple events are also provided in the table (CSS and PFS), a footnote should be included in the table to describe what follow-up duration is.

Response: We have added cancer-specific survival and progression-free survival data to Table 1. As noted in the main manuscript (page 8, lines 148–149), the follow-up durations “were estimated using the reverse Kaplan-Meier method, in which being alive is treated as the event of interest and deaths are censored.” We have added a brief explanatory note (“Censored/Event”) to the appropriate rows of Table 1.

* Table 2: It is unclear what the pvalue for cancer specific survival denotes? If a chi-square test on the 2x2 was performed, the analysis is inappropriate.
Response: We used a log-rank test to calculate the p-values for the between-group comparisons of survival outcomes shown in Table 2. The event distributions were exploratively confirmed, but we decided not to mention this in the text because it could cause confusion.

Replies to Sophie Gourgou’s comments

We thank Dr. Gourgou for reviewing our manuscript.