Dr Pedro Romero

Editor-in-chief, *Journal for ImmunoTherapy of Cancer*

Dear Dr Romero,

On behalf of my co-authors, we would like to thank you, the editors, and reviewers for the evaluation of our manuscript (jitc-2021-002757). Please find below our responses (in blue text) to the peer review comments.

Please note, based on previous discussions with the *Journal for ImmunoTherapy of Cancer* editorial office, we also submit a graphical abstract and script for a video abstract alongside the revised manuscript.

We hope that the changes we have made make the manuscript suitable for publication in the *Journal for ImmunoTherapy of Cancer*.

We look forward to hearing back from you soon.

Best regards,

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Response to Reviewers' comments

Reviewer: 1

Major:

1. Novelty of this study is limited. Although QoL info was provided, no substantial update info on survival is gained with a one-year longer follow-up time, e.g., median DOR, median OS has not been reached.

- **Response:** We thank the reviewer from this comment. As the reviewer notes, the most important new information in this report is the QoL data. Cemiplimab provided meaningful improvement/stability in global health status/quality of life and maintained a low symptom burden, including a durable reduction in pain. Additionally, the longer follow-up provides clinically meaningful efficacy data, particularly as regards emerging durability of ongoing responses in a patient population that faced a very grim prognosis prior to the availability of immune checkpoint blockade.

2. QoL was measured in different time intervals (groups 1/2 at 8 weeks, group 3 at 9 weeks), is there any statistical effort trying to address this issue? Also should mention some details of the mixed effects model, e.g., if intercept and slope are both allowed to be random, etc. What software was adopted for the statistical analysis, SAS, R, etc.?

- **Response:**
  - In response to the first part of this comment, no statistical methods were used to address the issue regarding the different time intervals. However, we were transparent in the reporting of our results by showing both cycles and equivalent months (per figure 3) as well as indicating the different cycle lengths in the footnotes. We have added further clarification in the Figure 3 footnote. Despite the difference in cycle duration, no differences were observed between Groups 1+2 and Group 3 when analysed as individual cohorts. Therefore, these data have been combined collectively and reported per cycle.
  - For the second part, the mixed models repeated measures models (MMRMs) used an AR(1) covariance structure. Covariates controlled in the model included dose group and baseline pain score. The study visit was considered as a random effect. The analysis was conducted using SAS version 9.4. We have now inserted these details in the Methods section on p. 10.

3. The definition of "responder" on Page 10 is confusing. Readers may misinterpret the "responders" as the more generally defined as patients who achieved PR/CR radiologically.

- **Response:** Since the important point here is the criterion used for a clinically meaningful change (and not the definition of "responder"), the responder language has now been removed and replaced with a sentence reading, "Using this criterion, the number of patients experiencing a clinically meaningful change in symptom score was evaluated at cycle 6 and cycle 12"

Minor:

1. The abstract is confusing. Please provide 95% CI for CR rates. "Estimated proportion of patients with ongoing response at 12 months was 87.8%", taking into account that the "median time to CR was 11.2 months", does this mean within 0.2 months there are around 12% pts progressed? Please specify what the index date of the "12 months" statement is, the initiation of cemiplimab or the date that the patient reached the first objective response.

- **Response:**
  - In the tumor response table (Table 2), in the interest of readability, we have provided the 95% CI for the combined CR rate, because doing so for the individual Group may provide no meaningful interpretation as the numbers are small**.**
  - The statement about estimated proportion of patients with ongoing response includes those with PRs or CRs. As the prior sentence is on CR, we think the reviewer may have misunderstood this statement. As such, we have added "Among patients with PRs or CRs", to clarify the statement [Please see next bullet].
  - The index date is the time of first objective response. The new statement now reads: "Among patients with partial response or CR, the estimated proportion of patients with ongoing response at 12 months from the first objective response was 87.8%..."

2. Please use the same unit across the manuscript, e.g., the time measurement be unified into months or weeks, or cycles, etc.

- **Response:** Please see our response to Major comment #2

3. Background: please check the statement that "CSCC is the second most common cancer in the US", do the authors mean "the second most common skin cancer"?

- **Response:** CSCC is the second most common cancer, as well as the second most common skin cancer. To address the reviewer comment, we have replaced "most common cancer" with "most common skin cancer".

4. What is "rwlc" short for?

- **Response:** In the US, the generic name designated by the FDA uses this suffix ("cemiplimab-rwlc"), so when we are referring to the FDA approval, we use the term "cemiplimab-rwlc".

5. Please provide rationale/reference of using 105 days as the threshold of durable DCR.

- **Response:** As stated in Table 2 footnote, the use of at least 105 days to measure durable DCR was to account for scheduling windows in the protocol. Given the aggressive nature of advanced CSCC and the low efficacy of conventional chemotherapy, a disease control for 105 days or longer is evidence that treatment may have altered the natural history of disease (Coewy 2019).

Reviewer: 2

In detail:
If the authors wish to make a deal out of the comparison of their study to others in the discussion, they need to provide better context by indicating the length of follow up for each study and providing response data at equivalent follow up times since one of the central ideas expressed in this current work is that responses in SCCa may occur quite slowly over time.

- **Response:** We thank the reviewer for this comment. We specified in the paragraph the differences between the studies, particularly the duration of follow-up. However, to avoid misinterpretation that the paragraph is presenting a head-to-head comparison, we have revised the text.

Given the longer follow up, I saw that the authors stated that no new toxicities emerged that had not previously been seen, but did they mean types of toxicities or cases of toxicities?

- **Response:** The intended meaning is that there were no new types of toxicities and no change in frequencies of known toxicities. To clarify, we have updated the statement to "There were no new safety signals or types of toxicities compared to previous analyses".

In the discussion, what does the following statement mean: "Furthermore, DOR and OS are longer than what has been previously described with other agents."

- **Response:** The cited source analyzes clinical response for the common therapies used to treat patients with mCSCC or laCSCC prior to the approval of cemiplimab. We have clarified the statement so that it is not misinterpreted as if we were comparing cemiplimab with another immunotherapy here.

At the end of the discussion, how can the following statement make sense: "….impressive and increasing DOR in patients…" since the DOR doesn't change, the follow up to detect it changes; it should just state that the DOR is impressive.

- **Response:** The duration of response has increased over time (i.e., response is ongoing), as indicated by the Kaplan–Meier 12-month and 24-month estimates of DOR in Table 2. The sentence has been changed to reflect this.

The authors have the third from last line in the discussion flipped; it should read "Further, clinical response to cemiplimab was associated with reduction in pain."

- **Response:** The sentence at the end of Discussion has been changed as suggested.

The data on achieving a CR belongs in the results section, not the discussion.

- **Response**: The paragraph on CR rate has been moved to the Results section.

Please decide on cemiplimab versus cemiplimab rwlc, and explain the latter if it is preferred

- **Response:** In the US, the generic name designated by the FDA uses this suffix ("cemiplimab-rwlc"), so when we are referring to the FDA approval, we use the term "cemiplimab-rwlc".

In the introduction please add how much more follow up is provided

- **Response:** The last paragraph in the introduction now indicates how much follow-up is provided in this manuscript.

Simply point out that in the results section where it is stated that "By cycle 6, among all patients reporting clinically meaningful change…." by definition there are likely benefiting patients since they had made it past 6 cycles

- We have added language indicating that a substantial fraction of patients benefitted from the treatment.

Associate editor:
Please address all of the specific concerns and stipulations of the two reviewers, and ensure that the value added of the work is emphasized above and beyond previous reports.

Response: We have now provided responses to the reviewer comments, made changes to the manuscript as appropriate, and emphasized the added value of the present work vs prior reports.