

Dear Professor Hiten RH Patel

Dear Professor Stephen Safe

Editors-in-Chief, World Journal of Clinical Oncology

Manuscript ID: 62909

Title: **RECIST in the assessment of atypical responses in immunotherapy**

We are going to upload the revised version of the abovementioned manuscript, after accepting the transfer option offered by the editorial board of World Journal of Gastrointestinal Oncology.

In the revised manuscript you will find the underlined changes made in response to the Reviewers.

In this letter, we also indicated how we have dealt with the Reviewer's comments.

We are enclosing a point-by-point reply to the Reviewer's comments and we are submitting a copy of the revised version of our manuscript (named "Manuscript Track Changes"), with all changes underlined or crossed out, as appropriate. A clean copy of the revised manuscript (named "Manuscript Clean"), including the correct number of figure and the suggested table, is uploaded as well.

Finally, on behalf of all the authors, I would like to thank you for your consideration of this paper.

Davide Ippolito, MD

Q: Pseudoprogression gives a few of reference cases, so it is suggested to refer to more cases. The incidence of Pseudoprogression only describes a few tumors, so the data is not enough.

A: Thanks for the comment. As suggested, we edited the specific sentence by adding more cases regarding the pseudoprogression as follows: "Pseudoprogression has been described in different types of tumors, mainly in melanoma patients but also in non-small lung cell carcinoma (NSCLC), renal cancer, urothelial cancer, uveal melanoma, Merkel cell carcinoma, mesothelioma, Hodgkin lymphoma, and head and neck squamous cell carcinoma (HNSCC) and it can also occur in metastatic lesions and some oncologic patients with pleural effusion and ascites."

Q: It is suggested to adjust the order of paragraphs in writing, because the logic is not smooth enough.

A: Thanks for your suggestion. We apologize to be not so clear and we edited the sentence to obtain a more readable text.

Q: Since there is no definition of HPD, how to clarify its incidence and explore relevant predictors? This part of the content is not mature, it is suggested to write down the latest major consensus, more persuasive.

A: We agree with Reviewer's advice. We edited the whole paragraph regarding the hyperprogression as follows "For example, an empiric doubling of tumor volume or by using linear growth in tumor diameter have been purposed to identify the HPD and, as a matter of fact, recently published papers reported different ways to define HPD and different thresholds to stratify patients [32-34]. Moreover, considering that HPD can be shown in different cancer types, a standardized definition is needed."

Q: In pseudoprogression, the probability data of this phenomenon in various tumors were not available; In pseudoprogression, there were less references to the two sections of iRECIST Guidelines.

A: According to the Reviewer's suggestions, we added more data regarding pseudoprogression and the linked references, underlined in the text.

Q: There are few examples of Dissociated Response; Since the standard of Dissociated Response in iRECIST Guidelines is not clear, we can find some guiding literatures for its subsequent research and introduce the possibility of its subsequent development.

A: Thanks for the suggestion. We added details in the text to obtain a more complete and detailed paragraph regarding the dissociated response, as follows “Considering the vary interpretations of DR given by the different authors, a more uniform definition of DR is crucial to better define the prognosis of patients undergoing immunotherapy, in order to assess with further prospective studies the precise prognosis of patients with DR compared to progressive and non-progressive disease. As suggested by Humbert O. et al [56], DR on CT exam should be inspired by RECIST 1.1 criteria, defined as a concomitant decrease in size >30% in some lesions and increase in size >20% in others (and/or presence of new lesions), while on PET/CT, DR should be motivated by PERCIST criteria, defined as a concomitant decrease >30% in some tumor lesions metabolism (Δ SUV) and metabolic increase >30% in others (and/or new hypermetabolic lesions).

Q: The classification of atypical responses in recent introduce and core tips are different.

A: We apologize for the mistake. We edited the specific paragraphs to be more consistent.

Q: Reducing the frequency of using Cosequently (the text appears 6 times), and consider replacing it by using other words

A: Thanks for your comment. We edited the whole text by reducing the use of “consequently”.

Reviewer **2**

Reviewer #2 uploaded the original manuscript along with specific comments regarding the submission.

We really want to thank the reviewer for the precious comments, and we edited the text as suggested including the correction of different mistakes. All changes are underlined in the text.

Reviewer **3**

Q: The images in figures 3 and 4 seem to have mixed up: please correctly assign the images to the text

A: Thanks for the comment. We edited the figure legends as suggested.