December
Nameofjournal: World Journal of Clinical Oncology *(WJCO)*
ManuscriptID:89466

Dear Editor-in-Chief of the World Journalof Methodology,

On behalf of the other authors and myself, I would like to extend my gratitude fortheeffortsandtimespentreviewingoursubmission.TheReviewersmakeexcellentpointsand offervaluablesuggestionstoimprovethemanuscript.**Pleasefindthepoint-by-point responses in bold font under each of the comments made by the reviewer below, whichcanalso be foundwith yellow color inthe revised manuscript:**

ScienceEditorandCompanyEditor-in-Chief:

The manuscript has been peer-reviewed, and it is ready for the first decision.I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the author(s) must add a table/figure to the manuscript. There are no restrictions on the figures (color, B/W) and tables. When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

As requested by the Editor, we have added a Table summarizing the immunotherapy strategies for UM in the revised manuscript.

To this end, authors are advised to apply PubMed, or a new tool, the RCA, of which data source is PubMed. RCA is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/, or visit PubMed at: https://pubmed.ncbi.nlm.nih.gov/.

WehavefoundtheRCAtooltobequiteusefulinpreparingthemodifiedmanuscript.
The following has been added:
"Before undertaking this study, we searched PubMed (https://pubmed.ncbi.nlm.nih.gov) and Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com) for the terms "metastatic uveal melanoma"

Reviewer1(numberID:06272301)

In this manuscript, the authors discussed new immunotherapy strategies for uveal melanoma. I suggest accepting this manuscript after they address the following concerns. 1. As a review, there should be a figure or table that allows the reader to better understand the core ideas of the paper. I suggest that the authors add a figure or table summarizing the immunotherapy strategies for UM.

As suggested, we have added a Table summarizing the immunotherapy strategies for UM in the revised manuscript, entitled "Table 1. Drug therapies for metastatic uveal melanoma disease".

2. Generally, narrative reviews will not have a "materials and methods" section. If the author writes this, please add a "discussion and results" title. At the same time, pay attention to the logical relationship between the titles at all levels. I think a lot of the "conclusion" is more about discussion or results.

In accordance with the suggestions made by the Reviewer, we have deleted the heading "materials and methods". The "conclusions" has been modified to include only one paragraph, while the remaining text was left in the section prior.

3. Abbreviations such as "OS" in the article only need to give the full name where they first appear, and only

abbreviations are used elsewhere.

The abbreviation has been defined to read "overall survival (OS)".

4. Authors can discuss in detail whether the unique genetic mutations and genetic changes of UM mentioned in the paper are specifically related to the selection of immunotherapy for UM.

To address the issue, the following has been added:
"Tebentafusp has undoubtedly marked a significant advancement in the treatment of metastatic uveal melanoma, offering a survival benefit over conventional therapies. Its preferential binding to HLA-A0201 has limited its applicability to patients with this specific subtype, prompting a need for the development of alternative treatments for individuals with other HLA subtypes. Although subgroup analyses in the phase III trial raised questions regarding its potential efficacy in certain patient groups, including those with high tumor burden and poorer performance status, its overall benefit still positions it as a preferred therapeutic option for most HLA-A0201-positive patients. Regarding the optimal duration of treatment, current data suggest that continuing tebentafusp until confirmed radiological progression might be a reasonable approach, given its manageable and predictable toxicities. However, more extensive studies are required to establish the most suitable duration for treatment. Additionally, the challenge of evaluating treatment response necessitates the exploration of alternative markers beyond traditional response measures. The correlation between rash appearance and improved survival warrants further investigation, while circulating tumor DNA (ctDNA) reduction holds promise as a potential indicator of treatment benefit.
The investigation of tebentafusp in conjunction with liver-directed therapies is also a significant area of interest, considering the potential benefit for patients with bulky disease. Furthermore, the exploration of other therapeutic targets, such as PRAME, through alternative treatments like IMC-F106C, presents a promising direction for future research efforts**".**

5. This article has devoted a large part to the introduction of ICIs in the treatment of UM. However, the authors hardly mentioned other types of immunotherapies such as tumor vaccine and cell therapy, which is not in line with what the abstract said. It is hoped that the authors could add these contents.

In accordance with the suggestion made by the Reviewer, the following has been added:
"ImmTAC, short for immune-mobilizing monoclonal T-cell receptors against cancer, represents a novel category of T-cell–redirecting bispecific fusion proteins. These innovative molecules utilize an engineered high-affinity T-cell receptor to effectively target any protein, including intracellular antigens, displayed as a peptide–HLA complex on the surface of the target cell.[1,2]Tebentafusp, previously known as IMCgp100, is an example of such a molecule, featuring a soluble, enhanced HLA-A*02:01–restricted T-cell receptor specifically recognizing the glycoprotein 100 (gp100) peptide YLEPGPVTA, that is highly express on uveal melanoma cells. This receptor is fused with an anti-CD3 single-chain variable fragment. When the ImmTAC binds to its designated peptide–HLA complexes on the surface of the target cell, it enlists and stimulates polyclonal T cells via CD3, to kill these cells. In addition to its T cell cytotoxic effects, IMCgp100 stimulates T cells to secrete a diverse array of

cytokines and chemokines, such as IL-6, IL-2, and TNF-a, thereby amplifying its potential as an anti-cancer immune agent.[1, 3-5]The activation of T-cells by IMCgp100 occurs at a concentration of 1pM, with the most significant reaction observed at 1nM. Off-target effects are observable solely at concentrations significantly exceeding 1nM, highlighting the high specificity of the tumor antigen and a broad therapeutic range, and IMCgp100 activity in vitro correlates with the cellular expression levels of gp100-HLA-A*01[6]**".**

6. Although the authors list the results of many studies on UM immunotherapy, they do not give a specific summative strategy, which is they should add.

Based on the suggestion made by the Reviewer, the following has been added:
"In this scenario, while certain limitations exist, tebentafusp represents a groundbreaking development in the field of metastatic uveal melanoma treatment. Unanswered questions regarding response monitoring and application in diverse treatment settings warrant further exploration to optimize its therapeutic potential and expand its applicability to a broader patient population. Future research objectives should include the determination of theoptimal treatment sequence between tebentafusp and checkpoint blockade, as well as the potential benefits of combining these therapies. Ongoing studies focusing on the combination of tebentafusp with other immunotherapies and the assessment of its role in the adjuvant setting after primary disease therapy are critical in further delineating its therapeutic scope. Further research and a comprehensive understanding of tebentafusp's mechanisms will undoubtedly pave the way for improved treatment strategies and outcomes in the management of metastatic uveal melanoma**".**

Many thanks to the Reviewer for the thorough review of our paper. We hope all issues have been addressed in an appropriate manner.

The valuable comments and assistance with our paper are greatly appreciated. We lookforward to your final decision regarding our modifications, with the hopes that all concernshavebeen addressed appropriately.

Kindregards,

Marco Zeppieri *(on behalf of the Grando Martina, De Pauli Silvia, Giovanni Miotti, and Balbi Massimiliano)*