

Dear editor:

I am Dong-Xu Ma, the first-author of the manuscript No.70204, entitled "Combined targeted therapy and immunotherapy in anaplastic thyroid carcinoma with distant metastasis: A case report". Thank you very much for your letter and the referees' reports. We have studied the valuable comments from you and reviewers carefully, and made extensive modification on the original manuscript. A revised manuscript with the correction sections marked yellow was attached as the document . A document answering every question from the referees was also summarized and enclosed. Should you have any questions, please contact us without hesitate.

The point to point responds to the reviewer's comments are listed as following:

Reviewer #1:

Comment : This is an interesting case report about a less common thyroid malignancy. The authors provide sufficient information about the clinical case. They have described in detail the patient's process, as well as the reasons why oncospecific treatments were suspended or maintained. Also, authors presented a good review of the current data of the topic. I consider it a great example of the alternatives offered by the combination of two treatments with different mechanisms of action such as immunotherapy and targeted therapy. I would like to ask a few questions and suggestions: - Did you consider the possibility of Radiosurgery of the cerebellar mass? And if not, why? - It seems contradictory that you named several immune related adverse events suffered by the patient, but you decided to discontinue Cabozantinib. I imagine that it is due to VEGFR-TKI toxicity. I recommend that you name and grade them. - To my knowledge, there is not an standard-of-care approval for combined immunotherapy and TKI in thyroid carcinoma. Why did you selected Cabozantinib and Nivolumab and not other TKI or PD-1 / PD-L1 inhibitor? Maybe there is an early trial in your region, it may be interesting to cite it. - As a suggestion, it could be helpful a graphic including all treatments received with data of start and finish, as the PFS of each therapy

Response: Thank you for your suggestions and questions in our manuscript. According to the comments from you and the editors, we polished the manuscript in writing and checked the entire manuscript for spelling errors, conscientiously. The detailed modification are listed

as bellow.

Modification 1 (page 6,line 22): Radiation therapy for the cerebellar mass has been mentioned in this article, and the original text is as follows:He then received radiotherapy for cerebellar metastases at a prescribed dose of 3.0 Gy/fraction × 14 fractions., However,there is no significant change in metastases.

Modification 2 (page 7,line 13-22): During the treatment, the patient experienced some immune-related adverse events (irAEs) and vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) toxicity, mainly gastrointestinal toxicity and pneumonia, manifested as abdominal pain, diarrhea, cough and dyspnea, However, the patient developed arteriovenous thrombotic events, which were considered to be caused by cabozantinib, so the drug was discontinued.But the patient insisted on anti-programmed death-1(PD-1) therapy for two years, during which time, after symptomatic treatment with glucocorticoids, the grade of irAEs could be controlled below Grade 1[8].

Modification 3 (page 7,line 1-8): The resected tumor tissue was sent for immunohistochemical analysis and targeted next generation sequencing. However, only the RET gene was mutated. Treatment with Immunologicals may not have a significant therapeutic effect. So we used Cabozantinib.At that time, Nivolumab was relatively mature, more experiments were performed in other cancers, the safety was high, and furthermore, the subjective willingness of patients was strong, and the drugs were purchased and used on their own.

Modification 4 (page 16,line 9): Table has been added

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper.We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions! Looking forward to hearing from you. Thank you and best regards.

Yours sincerely!