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Dr. Ying Dou
Science Editor
World Journal of Clinical Oncology

May 8th, 2019

Dear Dr. Dou,

we would like to thank you very much for accepting our manuscript NO 45554 for publication in "World Journal of Clinical Oncology" pending revision. We would also like to thank the reviewers for their important and helpful comments on our article. All points mentioned by the reviewers have been very carefully considered and the manuscript has been altered respectively. Based on your efforts we think the quality of the present article has been improved significantly. We would be proud if you rate our revised manuscript valuable for the readership of "World Journal of Clinical Oncology".

Please find the remarks of the editorial office and reviewers as well as our comments (*italic*) below in a point-to-point discussion.

With Kind Regards,

Mona Passler

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Department for Gynecology and Obstetrics

Manuscript No. 45554

Requests from the editorial office:

1. This is an interesting review of the use of nivolumab in ovarian cancer. The authors report on a 47 year old lady who experienced both pseudoprogression of the tumor and real progression at an extra-ovarian site. Unfortunately the pseudoprogression was not verified with imaging of the left groin and no histologic data are mentioned. I suggest that the authors describe histological data if available on the affected lymph node.

We feel that this comment is extremely important. It would be intriguing to include histological data or imaging of the lymph node with pseudoprogression into this manuscript. We share the opinion of the reviewer, that further diagnostics would be of uttermost interest for didactic purpose and would show the reader even more vividly how to differentiate between pseudo- and real progression. Sadly, this was not part of the pathological reviews that we analysed, since pseudoprogression is primarily a clinical diagnosis following Wang et al.

The lymph node was affected by ovarian cancer and easily palpable before we started nivolumab treatment. Within a short amount of time, this lymph node doubled in size. Taking all of this into consideration, we interpreted this noticeably fast growth of an already by cancer affected lymph node under checkpoint inhibition therapy as pseudoprogression. We felt confirmed in this assumption when we saw that the lymph node shrunk under subsequent nivolumab treatment.

We took a picture of the patients' groin to visualize the rapid growth of the lymph node, which you can find below. Unfortunately, the picture does not depict the explicit clinical appearance, but we have the consent of the patient to publish this picture if you feel that it improves our manuscript.



We did not perform a CT scan to verify pseudoprogression in this lymph node, because our patient had already received numerous imaging procedures due to her recurrent ovarian cancer. We felt that it was clinically unambiguous to diagnose pseudoprogression and believed that it was ethically not justifiable to perform several CT scans only for didactic purpose. Additionally, the patient did not consent to imaging if no clinical consequences were to follow.

When our patient experienced pseudoprogression, we felt that histology could not confirm pseudoprogression, therefore we did not perform a biopsy of the lymph node affected by pseudoprogression.

After your revision, we engaged into an intensive discussion with our pathology department and they confirmed that to this date to their best knowledge no specific histological signs have been tested or established to prove pseudoprogression and it would be misleading to state otherwise in the manuscript.

Nevertheless, we re-evaluated the pathological slides of the patients' histological slides and are pleased to inform you that we found another lymph node which showed edema, dilated vessels and activated lymph follicles including positive staining for Ki-67 which can be interpreted in the context of pseudoprogression and is most likely caused by nivolumab treatment. You can find the slides below and we have consent of the patient to publish these slides as well.

We recently performed staining on the slides in order to show the changes vividly (including Ki-67) and hope that those new histological findings make our manuscript more valuable.

Reviewer: 1; Comments to the Author

1. Please provide the manuscript documents in word version so that we can edit.

The manuscript was uploaded in word version.

2. Our policy for the Case Report manuscript requires the title to include the disease name, the number of cases, and the phrase "literature review". In addition, the description of the paper as a literature review must be supported by the manuscript's content. Please update the reference list and add references with accompanying textual content that will strengthen the manuscript as a literature review of the appropriate and up-to-date case-related information. Please note that if authors only add the words "literature review" to the title, but do not revise the textual content of the manuscript to provide a literature review, the manuscript will be rejected.

The title was changed.

We added 16 references, one table and another histological slide.

Changes in the manuscript are marked yellow.

3. I'm sorry that the informed consent you submitted does not meet the requirements. Please upload the primary version (PDF) of the Informed Consent Form (Surgical procedures or other) that has been signed by the patients in the study, prepared in the official language of the authors' country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc.

We uploaded the original informed consent form in German and hope that it now meets the requirements. Please inform me (mona.passler@charite.de) if this is not the necessary document, so i can provide the relevant documents as soon as possible.

4. Please check and confirm that there are no repeated references!

We confirm that there are no repeated references.

5. Please provide the decomposable figure of Figures, whose parts are movable and editable. So you can put the original pictures in ppt and submit it in the system.

Has been uploaded.