Dear Editor,

Thank you very much for your time to review our manuscript entitled “Anti-PD-1 antibody zimberelimab combined with chemotherapy as the first-line treatment of advanced malignant peritoneal mesothelioma: A case report and review of literature” (Manuscript NO: 83925; Reviewer ID: 03397272). Those comments are all valuable and very helpful for improving our paper. We have revised the manuscript accordingly, which we hope meet with approval. These changes will not influence the content and framework of the paper. The changes are currently shown in the revised manuscript in highlighted color, and please find our point-by-point responses along with the corresponding line numbers and our revisions/corrections in the re-submitted files.

It should be noted that the CASE PRESENTATION section of our previously submitted manuscript did not conform to the format requirements of this journal. Therefore, we adjusted the format in this revision to meet these requirements without altering the content of the manuscript itself.

Thanks again!

Response to comments from Editors and Reviewers:

Reviewer ID: 03397272

Comments from Reviewer 1:

1. Rare case report of malignant peritoneal mesothelioma treated with combination of chemotherapy and immunotherapy.

Reply: We would like to thank Reviewer 1 for this acknowledgment. We believe that this case with substantial literature review may provide some experience in clinical practice.

2. It was mentioned that he was treated with zimberelimab as it achieved a higher ORR in relapsed/refractory classical Hodgkin lymphoma, any data for this drug in mesothelioma?

Reply: We thank Reviewer 1 for the comment. To our knowledge, there are no data of zimberelimab for MPeM so far. From our perspective, there are three rationales to choose zimberelimab over other PD-1 inhibitors. First, as discussed in the manuscript, several PD-1/L1 inhibitors showed efficacy in advanced MPM and MPeM as monotherapy or in combination with CTLA-4 inhibitors, which suggested that it was a class effect through inhibiting the PD-1/L1 signaling pathway. Second, in addition to in relapsed/refractory classical Hodgkin lymphoma, zimberelimab also achieved the highest ORR historically in the clinical trials (compared with another PD-1 inhibitor pembrolizumab, not a head-to-head comparison) of recurrent/metastatic PD-L1 positive cervical cancer treated with PD-1 inhibitor monotherapy. Third, the patient cannot afford the PD-1/L1 inhibitors that are used globally and have established efficacy in MPM/MPeM, that is why we chose relatively inexpensive zimberelimab as an alternative option, without any safety comproise.

3. In the discussion - there was not even phase 1 or phase 2 trial discussion of combination of chemotherapy and immunotherapy in mesothelioma - so what was rationale for using the combination apart from he was young. Is there any data to back it up or was it used as a part of clinical trial.

Reply: We appreciate the reviewer's comment. In the Discussion section, we have now referenced two phase 2 studies that provide data on the efficacy and safety of PD-L1 inhibitor combined with chemotherapy in advanced MPeM (lines 214-217). We hope that these data establish sufficient rationale for the application of this combination regimen as first-line therapy.

4. There was no discussion about CheckMate 743 phase 3 clinical trial first-line nivolumab plus ipilimumab significantly improved overall survival (OS) versus chemotherapy in patients with unresectable malignant pleural mesothelioma (MPM). Pts were randomized 1: 1 to nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks) for up to 2 years, or six cycles of platinum plus pemetrexed chemotherapy. Median OS was 18.1 versus 14.1 months [hazard ratio (95% confidence interval), 0.73 (0.61–0.87)], and 3-year OS rates were 23% versus 15%, respectively supporting the combination of immunotherapy. Although the benefit appeared to be greater in the non-epithelioid histology subgroup, median OS was similar with nivolumab plus ipilimumab in the epithelioid [18.2 months (95% CI, 16.9-21.9 months)] and non-epithelioid [18.1 months (95% CI, 12.2-22.8 months)] histology subgroups; 3-year OS rates were 24% and 22%, respectively. In contrast, median (95% CI) OS and 3-year OS rates differed with chemotherapy across histology subgroups; these were 16.7 months (14.9-20.3 months) and 19% in the epithelioid histology subgroup, and 8.8 months (7.4-10.2 months) and 4% in the non-epithelioid histology subgroup.

Reply: We thank Reviewer 1 for the comment. We have further improved the Discussion section of this study by highlighting the superior efficacy of immunotherapy over chemotherapy in both overall and subgroup populations and supplementing data on median OS and 3-year OS rates; we have also discussed these data according to PD-L1 expression and the histological type (lines 195-202).

Comments from Reviewer 2:

We thank Reviewer 2 for acknowledging our paper. Your recognition provides us with great encouragement in our research endeavors.

1. In Abstract, “A significant reduction in the patient’s peritoneal tumors was accompanied by remarkable improvement in the patient’s symptoms. Partial remission was achieved with a progression-free-survival period of 7 months. In

addition, no immune-related adverse events occurred" should be placed in CASE SUMMARY. These sentences are not CONCLUSION.

Reply: We thank Reviewer 2 for the comment. We have placed these sentences into the Case Summary section (lines 46-49) and deleted them from the Conclusion section.

1. In FIGURE 1, the tumor should be pointed out by arrows.

Reply: I truly appreciate the comment. We have changed the original Figure 1 to Figure 2, and the red arrow indicates the primary lesion, whereas the yellow arrow points to a new one (Figure 2).

2. In Outcome and follow-up, it is described that a new irregularly shaped solid mass in the pelvic vesicorectal fossa region was also observed (Figure 1C). This new lesion as well as the primary lesion should be specified by arrows in Figure 1. In addition, the authors say that the tumor enlarged from 4.1 x 4.0 cm to 4.4 x 4.0 cm, which was evaluated as PD in the caption of Figure 1C. However, it must be stable disease by the RECIST guideline.

Reply: We regret this error in the description of tumor response of primary lesion. We have revised the overall response of progressive disease based on new lesion appearance in the revised manuscript (Figure 2D) (lines 148-150).

3. In CASE PRESENTATION, procedure of pathological diagnosis, such as needle biopsy or incisional biopsy, should be presented. Next, microscopic findings of the tumor by hematoxylin and eosin staining should be presented. Immunohistochemistry of at least calretin should be presented to show the origin of mesothelium. Furthermore, presentation of PD-L1 is strongly desirable to increase the value of this case report. I recommend the authors get unstained sections from the pathological department and perform PD-L1 staining.

Reply: Thank you so much for your guidance with improving our paper. In the final diagnosis section, we have presented the procedure of pathological diagnosis. The patient was pathologically diagnosed as stage III MPeM (cT3N0M1) by core needle biopsy (lines 130-131).

Furthermore, we have added pathological images of MPeM, including pathological findings of hematoxylin–eosin staining (Figure 1A and 1B) and positive calretinin immunohistochemistry staining (Figure 1C and 1D), both of which show 200× and 400× magnification under the microscope.

We also acknowledge that PD-L1 expression is a worthwhile test to better understand the mechanisms of combination therapy. However, unfortunately, it is very difficult for us to perform it when patients are lost to follow-up. Based on the present experience, we would like to recommend regular PD-L1 staining for MPeM patients in the future.

Yours sincerely,

Deng

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