Peer Review File

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Reviewer A

This case report is very interesting because it describes a case of hyperprogression disease in mesothelioma treated with ICI, which has recently become the standard of care.

Thank you for this positive feedback.

ICI is often the first choice for sarcomatoid mesothelioma, but it is important to mention whether or not the incidence of hyperprogression disease differs by histological type.

There is no association between HPD and histological subtype, but it seems to be more frequent in epithelioid subtypes. For this reason, the debate remains open as to whether these patients should be treated with chemotherapy or immunotherapy. We highlight this fact on the discussion section, line 127

The review article on hyperprogression disease in the text is mainly related to lung cancer, but strategies to detect and avoid the specific predictive markers of mesothelioma are needed and it would be desirable to include more specific strategies. It would be desirable to include more specific strategies for detecting and avoiding the specific predictive markers of mesothelioma.
For example, can low TMB level be used as a reference? etc. or if unknown, you should mention the detail is unclear.

As you mentioned, we don't have clear specific predictive biomarkers of mesothelioma to predict hyperprogression. Moreover, TMB is usually low in this tumor. Of note, 8 out of the 11 patients described with HPD in MAPS2 had a PDL1 <1%. In NSCLC, denutrition, ECOS-PS > 2 and age are the most common clinical factors that are associated with poor prognosis. We highlight this point on discussion section, line 122.

You mention the mechanism of hyperprogression of the disease, but I would be glad if you could go into this in more detail, if possible.

We mentioned different hypothesis to explain the mechanism of hyperprogression disease, but none is clearly verified or validated. "We added supplementary information to explain more deeply this mechanism on discussion section line 131"

Reviewer B

This is a case report describing Hyper progressive disease (HPD) condition noted in two patients with unresectable pleural mesothelioma (PM) treated with first-line immune checkpoint inhibitors. The clinical information related to the cases is presented in a reasonably detailed and straightforward manner.

Thanks for this positive feedback

I noticed the type of ICIs infused to patient # 2 is missing. Adding this information will help to better compare and contrast the two cases.

We do it, paragraph results, line 91

While I find the discussion and conclusion statements are reasonably made, I think including a statement providing the author's perspective on the frequency of this condition occurrence from their own experience in treating PM patients with first-line ICIs will be beneficial.

Thanks for this suggestion. We mention that MAPS2 study identified 6.4% of HPD in PM. This rare occurrence of HPD seems to match our clinical practice, as we mention in discussion section line 125.

Accordingly, if it is identified that the frequency of this condition development is low among all patients receiving first-line ICIs, I'd suggest editing the title of the manuscript to indicate this.

Thanks for this suggestion. However, we edited the title according to author recommendations.

In addition, if there is data available to compare, commenting on any contrasting features (e.g. NLR, mutation status) noticed among patients with PM who received first-line ICIs but did not develop HPD condition will be valuable.

Unfortunatly, we don't have specific predictive biomarkers of mesothelioma to predict hyperpogression. It is important to perform ancillary studies to solve this problem. Peters et al showed in the CM743 a four-gene signature predictive of response but it cannot be used in practice as it requires frozen sample and perform transcriptomic analysis.

Please highlight the liver metastases in Fig 2B.

Thank you for this comment, we edited the figure to highlight the liver metastases more clearly.

Reviewer C

The authors have submitted two cases of HyperprogressiveMesotelioma after treatments with IO
The MS needs to be deeply revised prior to being considered for publication
The authors shouold include a broader insight into raising evidences that cast doubts on the efficacy of Ipi/ Nivo and IO for Meso, particularly for non-epithelial subtype

Thank you for this comment. We think the challenge in the coming years will be to correctly identify which patients better benefit from double ICI compare to chemo or chemo-IO. We added this concept in our conclusion section line 142.

Hence the authors should include and comment several papers published from 2022 up to April 2024 that raised serious concerns on the efficacy and the financial sustainabiity of Ipi/Nivo for Meso (RWE inclusive)

"In our opinion, immunotherapy in the broad sense will lead the way in the future years either in monotherapy or in combination. Indeed, since the published results of Checkmate-743 [11], Nivolumab plus Ipilimumab is the new standard of care in non-treated PMand it seems that sarcomatoid types get the most benefit from those ICI whereas epithelioid types respond similarly to chemotherapy. Two real world cohorts published recently by Dumoulin et al (Nivolumab and ipilimumab in the real-world setting in patients with mesothelioma. Lung Cancer. 2024 Jan;187:107440.) and McNamee et al (Brief Report: Real-World Toxicity and Survival of Combination Immunotherapy in Pleural Mesothelioma-RIOMeso. J Thorac Oncol. 2024 Apr;19(4):636-642.) show similar results to Checlmate-743 even though the population was older and with poorer PS. However, recent meta-analysis by Meirson et al. showed that the benefit shown of immunotherapy in Checkmate-743 was similar to the chemotherapy-group in the MAPS trial, bringing out concerns about this approval in this first-line setting. Moreover, Correale et al. are questioning the real

efficiency of immunotherapy in second-line setting with the CONFIRM trial positive for nivolumab but against placebo while the PROMISE trial which is negative for pembrolizumab against second-line chemotherapy (Gemcitabine or Vinorelbine). The future of ICI monotherapy is really to be able to determine which patient will benefit from it. In addition, as for NSCLC, some hyperprogressions under ICI therapy begin to be seen in PM and we don't have any predictive factor for it. Then, combination therapy could be our savior by administering ICI with chemotherapy." We added a paragraph in the revised manuscript in the discussion session lines 135-138 explaining why we think research should continue on ICI in PM.

It is unclear what type of treatment the pat #2 has been on

Thank you for this comment, we precise it on the results section, line 91