Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-23-611

Reviewer A

Comment: In this narrative review the Authors provide a through overview of genetic factors involved in the development of malignant pleural mesothelioma, focusing in particular on BAP-1-related tumors, discussing potential future therapeutic approaches. The manuscript may be of interest.
Reply: None.

Reviewer B

General comments
Congedo MT, et al. presents a narrative review of malignant pleural mesothelioma and genomic variants. The reviewer thinks this is a valuable review for reader easy to understand the relationship between genetic variants and clinicopathological features in patients with malignant pleural mesothelioma.

Minor comments.
Comment 1: Page 2: References 7 and 8 are too old. The latest references should be cited if the authors refer to current situation of prognosis in patients with malignant pleural mesothelioma.
e.g.: Baas P, et al. Treatment patterns and outcomes for patients with malignant pleural mesothelioma in England in 2013–2017: A nationwide CAS registry analysis from the I-O Optimise initiative. Lung Cancer 2021.
Reply: We thank the reviewer. We add the reference as you suggest.

Comment 2: Page 5: The authors describe that malignant pleural mesothelioma patients with BAP1 mutation show longer survival compared to ones without BAP1 mutation, while the mouse model with BAP1 variant shows decreased overall survival compared to the mouse with wild type BAP1. The authors should be comment in why the contrasting findings were seen between human and mouse. Another question is that what kind of histological subtype was seen in mouse malignant pleural mesothelioma model with BAP1 mutation.

Reply 2: We thank the reviewer for this poignant comment. We erroneously elected to avoid discussing in depth the molecular mechanisms underlying *in vitro* observations due to the clinical orientation of the journal, but we are happy to add a paragraph in page 6 to address this comment: *This difference in overall survival of BAP1 carriers can be attributed to the mouse model presenting almost completely with sarcomatoid MM features, which are more aggressive, while the human carriers present with predominantly, around 70%, epithelioid MM features. The different presentations of MM are possibly due to interspecies differences since other independent mouse models for MM present with sarcomatoid features. [41]*

Reviewer C

In this study, the researchers concentrate on exploring the genetic determinants of malignant pleural mesothelioma (MPM), offering a comprehensive understanding of its pathophysiology and clinical features. Specifically, they present detailed insights into the characteristics and treatment modalities for patients harboring germline BAP1 mutations, underscoring the significance of tailored medical interventions for this subgroup. It would be desirable to add a discussion of the following points.

Comment 1: Please provide a discussion on why the Germline BAP1 mutation confers a favorable prognosis in humans with MPM, while the opposite effect is observed in mice in section 4.

Reply: We thank the reviewer for this comment, just as we did for Reviewer B, who made the same observation. Please see above for our answer to the Reviewer B's comment.

Comment 2: It seems that there is a lack of mention regarding somatic variants of BAP1. Please add this information to the introduction section.

Reply: We add the following paragraph in the Introduction (page 3) to address this comment: *It is difficult to distinguish somatic versus germline variants of BAP1 due to tumor sample heterozygosity. Somatic variants may result in worse overall survival due to their late detection: they are usually not identified until a patient is diagnosed with MPM and the concurrence of other oncogenic variants within the tumor. Moreover, while the detection of a germline BAP1 variant elicits genetic counseling and eventually tests involving family members who may carry the same genetic alteration and the related carcinogenic risk, a somatic BAP1 variant does not require genetic counseling because it is not shared by relatives.*

Comment 3: In section 7, Please also add the information of new therapeutic approaches to BAP1 somatic mutant MPM, such as PARP inhibitors that target BAP1 somatic mutations.

Reply: We add the following paragraph in section 7 to address this comment:
As already said, BAP1 modulates DNA damage repair mechanism. It has been suggested that BAP1-altered MPM might be susceptible to poly (ADP-ribose) polymerase inhibitors (PARPi). PARP enzymes play a major role in DNA single-strand break repair and base excision repair pathways and PARPi are approved across many cancer types. In a single-center, non-randomized, phase 2 trial, in which patients with previously treated mesothelioma were given Olaparib, the rationale for the study was that patients with somatic BAP1 mutations or deficiencies of others DNA repair genes could benefit from Olaparib monotherapy. This study reported that Olaparib monotherapy has a limited activity in MPM (ORR of 4%, median PFS 3.6 months, median OS 8.7 months); the median PFS of germline BAP1 mutants (n = 4) was 2.3 months (95% CI: 1.3-3.6 mo) and the median OS was 4.6 months (95% CI: 3.1-4.9 mo). In this study, the analysis of BAP1 mutation status gives an antithetic result: patients with BAP1 mutations had a shorter OS and PFS if they received Olaparib in monotherapy.

Comment 4: Please add the information of a summary of the overview and results of clinical trials involving EZH2 inhibitors against MPM.

Reply: We add the following paragraph to address this comment:
In June 2022, a clinical trial published in THE LANCET ONCOLOGY examined the effectiveness of Tazemetostat, an EZH2 inhibitor, for treating malignant mesothelioma. The study, found as the only one on clinicaltrial.gov, involved 74 adult patients with relapsed or refractory malignant mesothelioma from multiple clinical sites. Divided into two parts, the study focused on pharmacokinetics in Part 1, analyzing plasma samples for Tazemetostat's concentration, and efficacy and disease control rate in BAP1-deficient malignant mesothelioma in Part 2. In Part 1, patients received a single dose of 800 mg Tazemetostat on Day 1, followed by twice-daily doses on Day 15. Pharmacokinetic measurements were taken from plasma samples on Day 15, including Cmax, Tmax, AUC0–t, AUC0–∞, and t1/2. In Part 2, the primary endpoint was determining the disease control rate at week 12, while secondary endpoints assessed response rates, survival, pharmacokinetics, and pharmacodynamics. In patients with BAP1-inactivated MPM, the disease control rate was 54% (95% CI 42-67; 33 of 61 patients) at week 12 after a median follow-up of 35.9 week; no patients had a confirmed complete response and two patients had a confirmed partial response. Serious adverse events were reported in 34% of patients.

Comment 5: Please correct following numbering and spelling.
Line 220: 4.2
Line 265: 4.3
Line 243: hemothorax ---hemithorax?
Reply: We thank the reviewer for this comment. We correct the typos.

Reviewer D

Comment: This manuscript seems well-written and could contribute to readers who related to malignant pleural mesothelioma. I could not detect to correct context of the manuscript.
Reply: None.