Peer Review File

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Reviewer #A:

Authors reviewed the papers and described the current evidence for the efficacy of ICI in thymic epithelial tumors. The manuscript raises several interesting points of view. However, several important issues remain to be mentioned in this manuscript.

First of all, the present manuscript is just a pale sequel of the previous articles. Lack of novel points of view in this field. I recommend the authors should focus on the cutting edge of this field. Please add more figures and explain the molecular pathway of the oncogenesis of TET and its relevance to ICI, such as GTF2I gene mutation, TMB and PD-L1 expression. The authors should also provide easily readable tables rather text narration to enhance the value of this manuscript.

Response: We thank the reviewer for the comments and suggestions in order to improve the manuscript quality. According to reviewer's suggestion we have added the following section: "Molecular features of AIDs and TETs". In addition, we made Figures 1 and 2.

The review is difficult to read and to understand. A lot of information is provided but they seem to be superficial and not logically connected. Extensive proofreading and streamlining are necessary.
There are so many grammatical errors, which make it very difficult to read.

Response: Thank you for those comments. We have corrected some grammatical mistakes and amend some sentences to make it easier to read.

Reviewer #B:

This is a review paper entitled Immunotherapy in malignant thymic malignancies. They performed a nice review for this important topic; however, some points should be corrected before acceptance of this paper.

Major comments:

The article should be improved by providing a clearer structure, e.g.

Response: We thank the reviewer for the comments and suggestions in order to improve the manuscript quality. We have divided the manuscript in 5 sections and we have created the section "*Autoimmunity and tumors of the thymus*" (section 2). In addition, we have included the paragraph "*Ongoing trials*" in "*Immune strategy in Thymic Epithelial* Tumors" section 3 instead of section 4 "*Future challenges*".

The title sounds weird. "Malignant thymic malignancies" should be changed to "thymic malignancies".

Response: We thank the reviewer for this comment. Although "*Immunotherapy in malignant thymic malignancies*" was the title provided by the Journal for this manuscript, we agree with the reviewer and we have amended the title as follows: "*Immunotherapy in thymic malignancies*"

Introduction

Line 74. They should refer to more references to estimate recurrence rates. They should describe recurrence rates according to clinical or pathological stages.

Response: Thank you for this suggestion. We have added some references and information as follows:

"Surgery represents the keystone step for the curative-intent treatment in MK I/II and some stage III tumors, as complete resection represents the most important prognostic factor in terms of survival (12,13), in addition to MK classification (14) and histological features (15) for which a correlation has been found (16). However, between 8% and one third of patients reporting a thymoma or 25 to 59% of thymic carcinomas will present a recurrence depending on MK surgical classification (17–21)."

Line 146 What do they mean by "in addition to it appearance" ? It should be clarified.

Response: Thank you. We have changed the text to clarify the concept: “Importantly, TC are rarely associated with AIDs (43,48). Several series have reported no MG in TC (15,49) with a small representation of AIDs overall (46) maybe due to the presence of non-immature T-cells. The high incidence of AIDs in TETs in addition of the presentation of autoimmune symptoms afterward diagnosis of cancer (45,46) requires an extremely close monitoring during treatment with ICI.”.

Line 168-170 The authors should describe the potential reason(s) why PD-L1 expression rates ranged variously, referring to several papers.

Response: Thank you for this comment. According to the reviewer suggestion we have added an introduction within the paragraph explaining different immune biomarkers and we have reported more references to the text, as follows:
“This upregulated expression of PD-L1 in TETs may be leaded by IFN-γ presence in TETs’ cells (37). Indeed, clinical and pathological elements have been correlated with high PD-L1 expression, such as young age, advanced MK stage, no complete resection and history of neoadjuvant therapy for thymoma (75). By contrast, correlation with histology subgroups remains unclear (71,76,77). Actually, there are no solid results regarding survival outcomes considering that some of the studies have correlated a high PD-L1 expression with better survival (75,76) but others with poor outcomes (71). Furthermore, TILs have been analyzed besides PD-L1 although poor evidence is available. Higuchi and colleagues reached PD-L1 and TILs in surgical samples from 39 patients with thymomas and thymic carcinoma. PD-L1 higher than 1% was reported in 54% of the specimens and with no same distribution among TETs’ subgroups (B2>B3>TC>B1>AB>A). High CD8+ (84%) among CD3+ TILs infiltration was assessed and diffusely distributed in all cases (74). High PD-1 expression in TILs have been found in 23% to 62% of TCs as well with no prognostic nor predictive correlation (77,78). Interestingly, TETs TMB has been demonstrated to be one of the lowest among tumors (25). Whether PD-L1 is the best predictive biomarkers remains controversial due to the impairment of many patients notwithstanding the use of ICI. More beneficial treatment effects seem better for aggressive thymomas such as type B2 or B3 although the high prevalence of AIDs aware the difficulty for the use of ICI.”.

Line 260 “The face have” should be “The fact has”.

Response: We thank you for your detailed revision, nonetheless the written text is "*This fact has*" instead of *"The face have".*

Line 311 There appear to be grammatical errors.

Response: We thank the reviewer for the comment in order to improve the manuscript quality. We have corrected the possible grammatical error within the text.

Line 314-315 Any reference is required to this statement.

Response: This is an important point. The high prevalence of autoimmune disorders in TETs' subgroups justify the comment, we have added references and modified the text: "Immunotherapy is not evoked in type B1/B2 thymoma due to the high rate of AID (13,15,45) and should not be delivered in an off-label setting without full disclosure of risks in the multidisciplinary tumor board.".

Line 339 what do they mean by "becoming more save"?

Response: According to the reviewer's comment we have re-written as follows: "Although the incidence of TRAEs is higher in association with thymoma compared with carcinoma, patients with TC are also at risk of developing immune-related toxicity even during the follow up...".

Line 339-340 What do they compare with in that patients with TC are also at GREATER risk of developing immune-related toxicities?

Response: We have re-written as follows: "Although the incidence of TRAEs is higher in association with thymoma compared to TC, patients with TC are also at risk of developing immune-related toxicity even during the follow up...".