**Peer Review File**

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**Reviewer A**

Epithelioid tumors of the thymus represent a heterogeneous group of primary thymic neoplasms with a low incidence. While the prognosis of patients treated with radical intent is relatively good, systemic treatment options for patients in the disseminated phase still remain limited. There is a need to seek more detailed information on the molecular profiling of these tumors and to explore new potential therapeutic options.
I, therefore, consider the topic taken up by the authors to be important. The work presented is interesting and well-prepared. However, I have a few comments.

Comment 1: Could the authors consider adding information on the differences in the molecular profile of Caucasian patients in the form of a table? Be tempted to point out the differences and similarities.
Reply 1: As recommended by the reviewer, we have summarized the molecular profiles of Caucasian patients using data from Radovich et. Al (reference 12), in Table 4. The similar points between our study and that of Radovich et al. are as follows: the frequency of *GTF2I* mutation in our patients and Caucasian patients (Radovich et. al.) (38.7% [12/31] and 39.3% [46/117], respectively), frequency of *HRAS* mutations (6.5% [2/31] and 8.5% [10/117], respectively), and frequency of *NRAS* mutations (3.2% [1/31] and 2.6% [3/117], respectively).
The differing points are as follows: types of TETs harboring *HRAS* mutations (*HRAS* mutations were detected only in type AB [100% {2/2}] in our study, but were detected in type A [80% {8/10}], followed by type AB [20% {2/10}] in the study by Radovich et al. in Caucasian patients), types of TETs harboring *NRAS* mutations (*NRAS* mutations were detected in type B1 in our study, but were detected in types AB, B2, and TC in the study by Radovich et al. in Caucasian patients), types of TETs harboring *TP53* mutations (*TP53* mutations were detected in types B2, B3, and TC in the study by Radovich et al. in Caucasian patients, but not detected in our study), and types of TETs harboring *ASXL1* mutations (*ASXL1* mutation was detected in TC in our study, but not detected in the study by Radovich et al. in Caucasian patients.
Changes in the text: We have added relevant data and statements (see Table 4 and page 12, line 21-24 and page 13, line 1-10).

Comment 2: It would be valuable to add some information on the efficacy of molecularly targeted drugs in the treatment of thymic malignancies. I know that the paper was not strictly concerned with the diagnosis of, for example, the KIT gene, but for readers who are clinical oncologists, such information would significantly increase the value of the paper.
Reply 2: We agree with the reviewer. Although this study was not aimed at detecting the gene alterations of receptor tyrosine kinases (RTKs), such as KIT and FGFR, we concur that the information needs to be added to the manuscript because some multi-RTK inhibitors showed promising results in early phase clinical trials. We added the statement that no mutation in RTK genes was detected in our panel.
Changes in the text: We have modified our text as advised, ‘Although some receptor tyrosine

kinase (RTK) inhibitors have been explored in patients with refractory or recurrent TETs in clinical trials (references 3, 4, and 5), we did not detect any gene mutation in RTKs.' (see page 11, lines 12–14).

Comment 3: Based on the literature data, are there any possible directions for research and exploration of therapeutic options in patients with RAS and GTF2I commutation?
Reply 3: Thank you for pointing this out. To the best of our knowledge, no treatment has thus far been reported for TETs harboring *RAS* and *GTF2I* co-mutations. However, a recent preclinical study showed that the activation of cell cycle-related pathways, such as Myc- and E2f-mediated targets, initiate tumorigenesis in the Gtf2i-mutant thymus, which may enable targeted therapies (reference 22). Moreover, compounds targeting *RAS* mutations are being developed for patients with *RAS* mutations.
Future studies are required to clarify whether these treatments show antitumor effects in TETs harboring *RAS* and *GTF2I* co-mutations as monotherapy or combination therapy, which will be valuable for further clinical translational strategies.
Changes in the text: We have modified our text as advised (see page 13, lines 21- 23, page 14, lines 21- 24 and page 15, lines 1-4)

**Reviewer B**

The authors present their study coherently and straightforwardly on the topic of thymic epithelial tumors. There are only a few minor issues that I would like to address.

Comment 1. I would appreciate an explanation of the abbreviations GTF, HRAS and NRAS in the manuscript.
Reply 1: Thank you for pointing this out.
Changes in the text: We have added an explanation of the abbreviations (see page 4, line 16 and lines 18–19, page 6, lines 21-22). We have also included an explanation of *ASXL1* (page 4, line 20, page 11, line 5).

Comment 2: The data deal mainly with somatic mutations of general transcription factor 2i. Did you test for germline mutations, are there data about the incidence of the L424H mutation in the healthy population?
Reply 2: We did not test for any germline mutations but tested for somatic mutations in TETs in this study. Regarding *GTF2I* L424H mutation in the healthy population, we could not find the incidence of *GTF2I* L424H mutation in three databases ([GenomAD; http://www.gnomad-sg.org/], [Human Genetic Variation Database; https://www.hgvd.genome.med.kyoto-u.ac.jp/], and [TOGOVAR; https://grch38.togovar.org/].
Changes in the text: We have included the abovementioned information (see page 8, line 21)

Comment 3: With the Williams-Beuren-Syndrome there is an inherited disease with association to GTF2i. Is there knowledge about an increased susceptibility of this disease to TET?
Reply 3: In our study and in other studies (reference 12, 19), no patient with TETs was associated with Williams-Beuren syndrome. None of the patients in our study had a phenotype

or family history of Williams-Beuren syndrome, and we did not investigate germline mutations. Unfortunately, there is no study that shows the relationship between TETs and Williams-Beuren syndrome.
Changes in the text: Although the germline *GTF2I* mutation was reported to be associated with Williams-Beuren syndrome, no patient in our study had a phenotype or family history of Williams-Beuren syndrome (See page 12, lines 13-14).

Comment 4: In your data overt myasthenia gravis occurred only in GTF2i wildtype patients (though some mutated had Anti Acetylcholin receptor antibodies). Are these observations in concordance with other publications? Is there evidence for a protective effect of the mutation? Some antibodies have been approved by the FDA recently. Are there possibly similarities between these antibodies and GTF2i products?
Reply 4: Yashimizu et al. reported that they could not find any significant somatic mutations associated with myasthenia gravis (MG), whereas missense mutations in *GTF2I* were observed in 49% of patients with thymoma (reference 21).
MG occurred only in *GTF2I* wild-type patients in our study; contrarily, Liang et. al. reported that *GTF2I* mutations were detected in some TET cases with MG (reference 19).
*GTF2I* has been reported to be associated with autoimmune diseases. However, L424H is a somatic mutation variant that exists in TETs, not a germline mutation, and MG-related gene was not observed in either *GTF2I* wild-type or *GTF2I* L424H mutation (reference 21)).
The association between *GTF2I* status and MG has not yet been observed; therefore, several antibodies for MG that have been approved recently do not appear to be a potential treatment for TETs regardless of *GTF2I* status.

Changes in the text: We have added the abovementioned information (see page 13, lines 11-19).

Comment 5: It seems that numbering of patients differ in Fig. 4 and Supplementary table 1 (and probably Suppl. figure 1). I would suggest to align table and figure 1 to the numbering of fig. 4.
Reply 5: Thank you for the pertinent comment. We have revised accordingly.
Changes in the text: We have modified the text as advised (see Supplementary Table 1-v2 and Supplementary Figure 1-v1).

Comment 6: Amongst the study population 33% were males, but only slightly more than 20% of the GTF2i mutated. Is there an explanation for this or do you regard this as a random statistical variation?
Reply 6: We apologize for this confusion. The population of males was 32.3% (10/31), and 30% (3/10) of the male patients had *GTF2I* mutation in TETs, while 42.8% (9/21) of the female patients had *GTF2I* mutation in TETs. The frequency of *GTF2I* mutation tended to be higher in females, but we considered that this might be caused by a random statistical variation because the sample number was too small to be explained statistically.
Changes in the text: Not applicable