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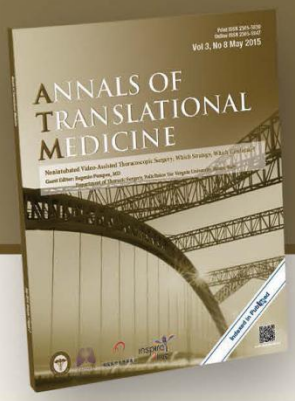

Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-1846

Reviewer A:

In the present study, the authors aimed to investigate in a 35 DM patients' series the incidence of relevant gene alterations in cancer, the PD-L1 expression status and the association with clinicopathological features and melanoma progression. The authors suggest that progressed DMs with deep tumoral infiltration frequently harbor TP53 mutations, PD-L1 expression and present a high inflammatory response, probably related to adaptive immune resistance in this tumor type.

This study expands the knowledge about the possible immune signature of DM microenvironment, especially the expression of the TP53 gene and PD-L1 in DM tumors, which would be relevant for the identification of PD-1 immunotherapeutic targets. However, the manuscript needs to rearrange datas and increase figures to strengths the significantly and reliability of study.

Most critical major issues:

* Language, grammar and scientific writing style require thorough revision. In the current form, it is very difficult to follow the authors' chain of thoughts.

Reply: The manuscript has been carefully reviewed by a native English speaker to improve the grammar and readability.

* This study requires sufficient other scientific figure types to verify the authenticity and reliability of research.

Reply: Thank you for this valuable feedback. We have added new figures within the manuscript as advised below.
Changes in the text: Figures 1-4 have been modified. Two additional figures have been added (survival
curves and associations plots).

* This study requires properly increase the number of patients in our research, instead of having unsuitable specimens in the group.

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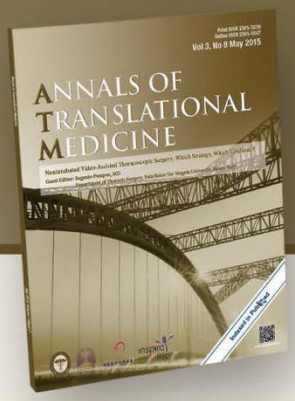


Reply: Desmoplastic melanoma is a rare subtype melanoma (below 4% of primary cutaneous melanoma diagnoses). Its diagnosis is difficult and large cohorts are difficult to accomplished. Over a period of 11 year we have been able to collect a cohort of 35 cases. At the request of the reviewer, we have tried to increase the N of patients and increased the recruitment period for 2 more years (until 2020). Three cases were added in our cohort.
Changes in the text: We have modified the manuscript with the new number of patients included in the study (see changes in the article Page 2-15and in the figures and tables).

Some other major issues:

* Figure 1: The position of Figures c and d are swapped. We want to see the expression PD-L1 of the tumor and tumor side, rather than the enlarged image (100x,200x….). Please make a bar chart of PD-L1 patient expression in 35 patients, whether by yours' score or percentage. In addition, please explain the lot number and concentration of the PD-L1 antibody (PD-L1 22C3 clone pharmDx) in the methodology.

Reply: We have modified Figure 1 as recommended and added information regarding the PD-L1 antibody used. A bar graph of PD-L1 expression is depicted in Figure 3.
Changes in the text: See Figure 1, Figure legend (see Page 20/ line 541-557). We have added the lot number and concentration of the PD-L1 antibody (see Page 6/ line 133).

* Figure 2: The criteria for screening our group of specimens should be improved, rather than all them used (included unqualified specimens cannot be detected) to the group, which causes data mismatch between groups.

Reply: We have updated Figure 2 according with the new N of patients in our cohort.
Changes in the text: We have modified the data in Figure 2.

* Figure 3: If you want to express PD-L1 expression of TILS and TPS, why not take a representative pathological histochemical picture and corresponding bar figure. And the correlation of PD-L1 score expression of TILs and TPS would be a better choice.

Reply: We have modified Figure 3 as advised. Also, as discussed above, we have added a bar graph of PD-L1 expression.
Changes in the text: See Figure 3, Figure legend (see Page 20/ line 595-599 – Page 21/line 600-604).

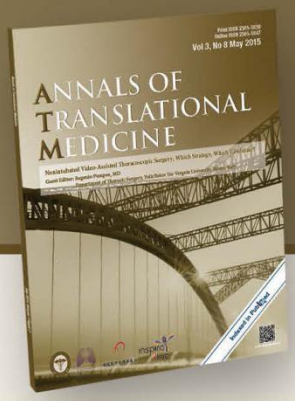


*Figure 4: From the results of the research in this article, I cannot infer the pattern diagram of figure 4.
1.TP53 mutations are associated with elastosis and tumoral infiltration;
2. Correlation between PD-L1 expression with the depth of invasion and TP53 mutations;
3.Association between survival and depth of invasion.
And then: Line 299-304: The results show that OS correlated with depth of tumoral infiltration ($p<0.001$) and sentinel lymph node positivity ($p=0.019$). PD-L1TPS ($p=0.953$), IC-PD-L1 ($p=492$), PD-L1 CPS (0.479), TP53 mutation 304 ($p=0.077$) or BRAF mutation ($p=0.512$). Firstly, please make survival curves separately. Then, TP53 associated with TI (tumoral infiltration), PD-L1 associated TI and TP53, why not PD-L1 or TP53 not associated between OS and TI. Although this phenomenon is well understood, please further study and provide PD-1 antibody treatment cases.

Reply: We have performed and added the survival curves and associations plots as advised. Furthermore, we have performed PD-1 IHC in 34 cases.
Changes in the text: We have added two additional Figures: new Figure 4 (association plots) and Figure 6
(survival curves). PD-1 data is added in the text (see Page 9/ line 257-269) and represented in Figure 3.

Selected minor issues:
* Please review all figures for misplaced axis labels or headlines or missing items.

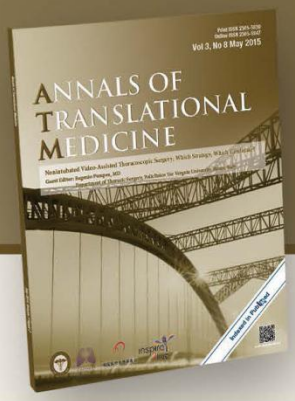
Reply: We have reviewed all figures as advised.
Changes in the text: Figures 1-6.

* Please uniform reference format.

Reply: We have revised the reference format.
Changes in the text: We have revised the reference format (see Page 17-19/ line 491- 568).

Reviewer B:

This manuscript attempted to investigate if TP53 mutations and high-expression of PD-L1 could have a relevant role in tumor aggressiveness and progression, probably related to immune



evasion in DM patients. However, several important issues have not been addressed, the current results were not enough to confirm the conclusion.

1. The authors demonstrated that the expression of PD-L1 was related to TP53 mutation, which hot spot mutations were related should be specified.

Reply: We have specified the *TP53* mutations related to PD-L1 in the text. We have modified the text as follows: Regarding *TP53* alterations, there was a significant correlation with PD-L1 TPS (p=0.016), IC-PD-L1 (p=0.002), and TILS (p=0.044). All *TP53* mutated tumors showed PD-L1 expression in inflammatory cells, and nine out of ten *TP53* mutated cases (90%) showed PD-L1 TPS expression. The *TP53* mutations identified in our cohort of patients and related to PD-L1 expression were: E294*, C242R, G199R, E286D, P98L, F270S, R273C, H179Y, P278L, G279E and V218G.
Changes in the text: Please see Page 11/ Line 286-292.

2. It is recommended to prove the correlation of PD-L1 expression and TILS by performing double immunofluorescent staining, to better reveal their co-localization.

Reply: We have not performed the double immunofluorescent stainings because we do not have fresh tissue samples available of the cases included. Instead, we have performed the association graphs of PD-L1TPS and PD-L1 IC with TILs, p<0.001 and p=0.088, respectively, as well as PD-1 immunohistochemistry in our series.
Changes in the text: See Page 9, line 226-239.The new data generated is represented in Figure 3.