and supports long-term survival without affecting their ploidy, proliferation, and nuclear speckles formation. In contrast, overexpression of Malat1 leads to metastatic reactivation of dormant breast cancer cells. Moreover, the loss of Malat1 in metastatic cells induces dormancy features and inhibits cancer stemness. Our RNA-seq and ChIRP-seq data indicate that Malat1 KO downregulates several immune evasion and stemness associated genes. Strikingly, Malat1 KO cells exhibit metastatic outgrowth when injected in T cells defective mice. Our single-cell RNA-seq cluster analysis and multi-color flow cytometry data show a greater proportion of T cells and reduce Neutrophils infiltration in KO mice which indicate that the immune microenvironment playing an important role in Malat1-dependent immune evasion. Mechanistically, loss of Malat1 is associated with reduced expression of Serpinb6b, which protects the tumor cells from cytotoxic killing by the T cells. Indeed, overexpression of Serpinb6b rescued the metastatic potential of Malat1 KO cells by protecting against cytotoxic T cells.

Conclusions Collectively, our data indicate that targeting this novel cancer-cell-initiated domino effect within the immune system represents a new strategy to inhibit tumor metastatic reactivation.

Trial Registration N/A

Ethics Approval For all the animal studies in the present study, the study protocols were approved by the Institutional Animal Care and Use Committee(IACUC) of UT MD Anderson Cancer Center.

Consent N/A

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<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0750>

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THE IMPACT OF GRADE OF DIFFERENTIATION AND BRAF MUTATION STATUS ON NEOANTIGEN AND IMMUNE LANDSCAPE IN PAPILLARY THYROID CANCER

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Background The use of immune checkpoint inhibitors (ICIs) in cancer treatment has been approved by the FDA, but its application is experimental in the treatment of papillary thyroid cancer (PTC). Induction of immune response via recognition of neoantigens is considered to be the basis for the treatment mechanism of ICIs.¹ However, the neoantigen landscape has not been explored in PTC. Our aim is to investigate the immune landscape of PTC in relation to neoantigens, taking into account the BRAF mutation status and grade of differentiation as contributing factors.

Methods BRAF V600E mutation status and thyroid differentiation scores (TDSs) were gathered from the PTC cohort of The Cancer Genome Atlas (TCGA). TDS was derived from the mRNA expression levels of 16 thyroid function genes to quantify the grade of differentiation. Tumors with TDSs in the 1st quartile and 4th quartile were defined as poorly differentiated and well differentiated, respectively. The neoantigen burden for each sample was predicted using CloudNeo pipeline. The infiltration of immune cells was calculated through CIBERSORT.

Results Among 400 patients with predicted neoantigen data, 187 (47%) had BRAF mutations. The BRAF mutated tumors showed increased cytolytic activity score (CYT, $p=0.001$), increased infiltration of regulatory T cells (Treg, $p<0.001$), and higher PD-L1 expression ($p<0.001$) compared to BRAF wild-type tumors (figure 1). In regard to grade of differentiation, poorly differentiated tumors showed increased CYT ($p=0.002$), increased infiltration of Treg ($p<0.001$), and higher PD-L1 expression ($p<0.001$) compared to well differentiated tumors (figure 2). However, BRAF mutation status or grade of differentiation did not correlate with the neoantigen burden. Also, the neoantigen burden did not show any correlations with immune landscape features such as infiltration of CD8+ T cells or Treg, CYT, and PD-L1 expression.

Abstract 752 Figure 1 Immune traits according to BRAF mutation status. (a) Cytolytic activity score(CYT). (b) Infiltration of regulatory T cells(Tregs). (c) PD-L1 expression.

Abstract 752 Figure 2 Immune traits according to grade of differentiation. (a) Cytolytic activity score(CYT). (b) Infiltration of regulatory T cells(Tregs). (c) PD-L1 expression.

Conclusions Increased CYT and higher expression of PD-L1 in the BRAF mutated or the poorly differentiated tumors imply the possible role of ICI use in these subgroups of patients. However, the immune response to these subgroups does not seem to be mediated through the increase in neoantigen formation. Further studies are warranted to explore markers for immunotherapy implication.

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