KIT mutation with a low MS4A1/CD20 expression is associated with poor prognosis in melanoma

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Abstract Melanoma has high response rate to immune checkpoint inhibitors. KIT, a driver mutation in melanoma seen in ~10% of the patients. However, the role of the KIT mutation in immune microenvironment of melanoma is not well established yet. Here we report a case with KIT mutation and a likely impaired B cell activity with poor response to Immune-checkpoint inhibitor therapy (ICI). We also describe the overall survival of melanoma depending on KIT mutation and MS4A1/CD20 expression, which encodes CD20, B-lymphocyte-specific membrane protein that plays a role in the development, differentiation, and activation of B-lymphocytes.

Methods A case with poor response to ICI with KIT mutation and monoclonal B cell lymphocytosis was identified. Clinical and molecular characteristics of melanoma in TCGA was analyzed using cBioPortal web page. TCGA data were analyzed to determine KIT mutation status and MS4A1/CD20 expression in melanoma cohort. Samples in the upper 33 percentile of MS4A1 expression were identified as high expression, and the lower 33 percentile were identified as low expression. Mantel-Cox method was used for overall survival (OS) comparison between the cohorts.

Results 69-year-old male with initial diagnosis of stage III-B melanoma of the left thumb with local recurrence in the resection site and then lung metastases. Patient was then started on nivolumab/ipilimumab with rapid progression on immunotherapy. He was found to have KIT mutation (exon 13K642EMT), and started on imatinib, but he continued to have progression. He was switched to temozolomide with no response. He also had history of leukopenia, pre-dating the metastatic melanoma and was diagnosed with monoclonal B cell lymphocytosis. With the hypothesis that the patient’s dysfunctional B cells may have impaired ability of ICI and poor prognosis; we analyzed TCGA database for KIT mutation and MS4A1/CD20 expression - which was used as marker for B

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Abstract 525 Figure 1 KIT mutation and MS4A1/CD20 expression - overall survival Low MS4A1/CD20 expression with concurrent KIT mutation is associated with poor overall survival
cell activity. KIT mutation was seen in 10 of 147 patients with high MS4A1/CD20 expression, and 10 of 135 patients with low MS4A1/CD20 expression. Overall survival was 15 months for the patients with KIT mutation and low MS4A1/CD20 expression, and significantly lower when compared with other groups despite low number of patients. (P<0.0001) (figure 1).

Conclusions B cells have significant role in immune response to tumor. Lower expression of MS4A1/CD20 is known to be associated with poor prognosis in melanoma and other solid tumors. We demonstrated that a concurrent KIT mutation in melanoma with lower expression of MS4A1/CD20 contributes to poor prognosis in melanoma. Therefore, this small subset of aggressive tumors may need combination strategies involving targeting driver pathways with a kinase and immune checkpoint inhibitor.

REFERENCES
3. Liu Y, Wang L, Lo KW, Lui VW. Omics-wide quantitative B-cell infiltration analysis of the CD4+ (mean 10.3%; 0.5 - 42%) versus CD8+ (mean 47.5%) were classified as Inhibigens, which were found more

Background Personalized cancer immunotherapies can generate potent antitumor responses yet finding the right targets remains challenging. The ATLAS™ platform employs ex vivo functional screening of tumor mutations using autologous cells to identify patient-specific neoantigens. Stimulatory neoantigens are identified by upregulation of inflammatory cytokine secretion and can be employed in vaccines or cell therapies. Conversely, ATLAS also identifies inhibitory neoantigens (termed Inhibigens) that lead to cytokine downregulation, and in murine models accelerate tumor growth and abrogate the efficacy of otherwise-protective vaccines. Here we further explore Inhibigen mechanism of action in humans and mice including whether checkpoint inhibition (CPI) can ameliorate Inhibigen-accelerated tumor growth.

Methods Human and mouse ATLAS screens were performed as previously described. ATLAS-identified stimulatory or Inhibigen peptide vaccines were evaluated in a therapeutic B16F10 melanoma tumor model + CPI. Immune responses were measured using ELISPOT, flow cytometry, and immunohistochemistry (IHC).

Results In the GEN-009 personalized neoantigen vaccine trial (NCT03633110), Inhibigens were observed in 92% of patients (N=39). Of total mutations screened, 16% (1.8 - 47.5%) were classified as Inhibigens, which were found more often in the CD4+ (mean 10.3%; 0.5 - 42%) versus CD8+ T cell subset (mean 6.1%; 1.2-23%). No relationship between Inhibigen-specific responses and tumor type or mutational burden were observed. To study the functional effects of Inhibigen vaccination in vivo, a B16F10 mouse melanoma model was employed. Inclusion of Inhibigens in an otherwise protective vaccine abrogated efficacy and correlated with decreased T cell responses to vaccine antigens as well as a global depression of T cell cytokine secretion. Early experiments suggest that these decreases are not due to MHC competition. In addition, administration of a therapeutic vaccine containing an Inhibigen led to reduced tumor infiltration of CD8+ T cells and myeloid populations. A corresponding increase of classical Tregs in the tumor or periphery was not observed. Surprisingly, preliminary data show combination therapy with anti-CTLA4 partially ameliorated Inhibigen-accelerated tumor growth but anti-PD1 provided no additional benefit.

Conclusions The nearly ubiquitous presence of Inhibigens in human cancer patients and the demonstrated pro-tumor effects in mice suggest that ATLAS-identified Inhibigens must be considered and omitted in the design of cancer immunotherapies. Furthermore, in mice, CPI co-administration has a modest (anti-CTLA4) or no (anti-PD1) effect on Inhibigen-accelerated tumor growth suggesting that Inhibigen profiling could guide CPI selection or predict clinical outcome. These data confirm the benefits of the ATLAS platform for neoantigen and Inhibigen identification.

Ethics Approval All animal studies were undertaken in conformance with the Cambridge, MA City Ordinance 1086 of the city’s Municipal Code and in accordance with the policies and protocols approved by Genocea’s Institutional Animal Care and Use Committee (IACUC).