810 NX-1607, A SMALL MOLECULE INHIBITOR OF CBL-B, ENHANCES ANTI-PD-1-MEDIATED TUMOR GROWTH INHIBITION BY RESHAPING INTRATUMORAL INNATE AND ADAPTIVE IMMUNE RESPONSE

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Background The E3 ubiquitin ligase Casitas B-lineage lymphoma B (CBL-B) is expressed in leukocytes and regulates signaling pathways in T and NK cells, significantly limiting their antitumor effector function. In T cells, CBL-B attenuates activation initiated by TCR engagement in part by mediating the requirement for CD28 co-stimulation, thus setting the threshold for T cell activation. In NK cells, CBL-B functions downstream of TAM receptors and negatively regulates cytokine production and target cell killing.

Methods We previously reported that oral administration of NX-1607, a potent inhibitor of CBL-B, resulted in significant dose-dependent, single-agent inhibition of tumor growth in the subcutaneous CT26 colon carcinoma model. This inhibition was dependent on NK cells and T cells. When NX-1607 was combined with anti-PD-1, we observed a substantial increase in the median overall survival and the frequency of complete tumor rejections in this preclinical tumor model.

Results To gain a better understanding of how NX-1607 treatment affects different immune cell types and immune pathways within the tumor microenvironment, we conducted gene expression analysis of tumor samples obtained from mice treated with NX-1607 as monotherapy or in combination with anti-PD-1. Our analysis revealed that CT26 tumors from mice treated with NX-1607 exhibited significant changes in the immune cell density score and gene expression pathways related to innate and adaptive immune signaling, including antigen presentation, cytokine and chemokine signaling, and interferon-gamma response genes. When NX-1607 was combined with anti-PD-1 we observed further enhancement of most of the immune cell scores and immune gene signatures induced by NX-1607 monotherapy, consistent with the observed antitumor synergy of these agents.

In addition, we performed TCR repertoire analysis and found that the response to NX-1607 was associated with an expansion of unique T cell clones in the tumor microenvironment. This expansion was evidenced by a significant increase in the number of unique complementary determining region 3 (CDR3) sequences. The increased richness of TCR repertoire following NX-1607 treatment was similar to that observed with anti-PD-1 monotherapy.

Conclusions These results demonstrate that the response to NX-1607 in the CT26 tumor model is associated with increased density and function of innate and adaptive immune cells within the tumor. These effects are further amplified when NX-1607 is combined with anti-PD-1. These findings provide additional support for clinical development of this novel CBL-B inhibitor given as monotherapy or in combination with PD-1 blockade. A Phase 1 clinical trial of NX-1607 in patients with advanced tumors is ongoing (NCT05107674).

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0810