Small molecule inhibition of the ubiquitin ligase CBL-B with NX-1607 results in potent T and NK cell mediated anti-tumor response

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Introduction

- CBL-B is an E3 ligase that regulates the innate and adaptive immune system by ubiquitinating proteins involved in signaling.
- CBL-B attenuates T-cell activation initiated by TCR engagement in part by mediating the requirement for CD28 co-stimulation, thus setting the threshold for T-cell activation.
- CD4+ and CD8+ T cells from mice deficient in Cbl-b have 5 to 10-fold enhanced secretion of IL-2 and IFN-γ when stimulated ex vivo with anti-CD3.
- Cbl-b deficient mice also demonstrate enhanced NK cell function.

Results

- NX-1607 inhibition of CBL-B enhanced IL-2 and IFN-γ secretion in primary human T-cells stimulated with anti-CD3 antibodies, in both the presence and absence of CD28 co-stimulation, although to a lesser degree in the absence of co-stimulation.
- In vivo, once daily oral administration of NX-1607 in mice demonstrated significant anti-tumor activity in two colon carcinoma tumor models, CT26 and MC38, as well as a metastatic triple-negative breast tumor model, 4T1.
- Anti-tumor activity of NX-1607 is associated with infiltration of T cells and innate cells such as DC, macrophage, and NK cells.
- Depletion of CD8+ T cells or NK cells abrogated NX-1607 anti-tumor activity.
- The combination of NX-1607 and anti-PD-1 substantially increased the median overall survival and the frequency of long-term tumor rejections in all three tumor models.

Conclusions

- NX-1607 mediates anti-tumor activity through both T cells and NK cells.
- Preclinical tumor models support clinical development of NX-1607 as monotherapy or in combination with PD-1 blockade.

CBL-B: A Modulator of T Cell Activation and a Novel Target for Immuno- oncology

NX-1607 Promotes Infiltration of CT26 Tumors with Activated T and NK Cells

Effect of NX-1607 on CT26 Tumor Volume

Day 25 Tumors


Effect of NX-1607 on Survival of 4T1 Tumor Bearing Mice


NX-1607 Antitumor Efficacy is Abrogated By CD8+ T or NK Cell Depletion

NX-1607 optimized CBL-B inhibitor for oral delivery.

Developing an oral intracellular checkpoint inhibitor for treating solid tumors.

CBL-B inhibition

- IL-2 production
- IFN-γ production
- Proliferation
- Anti-tumor activity
- Threshold of activation

NX-1607

19 Doses

4 Doses

Conclusions

- NX-1607 was administered at 30 mg/kg, PO QD. Anti-PD-1 antibody (RMP1-14) was administered twice weekly IP at 10 mg/kg. For 4T1, lung tissue was dissociated 28 days after tumor implant and cultured with 6-Thuamine to select and enumerate 4T1 metastatic colonies. Statistical analysis used one- or two-way ANOVA with corrections for multiple groups or Log-rank tests for survival curves. Shaded area: NX-1607 (30 mg/kg, PO QD) vs. NX-1607 + Anti-PD-1 (P < 0.05, ** P < 0.01, **** P < 0.0001).

NX-1607

Vehicle

NX-1607 + Anti-PD-1