NX-1607, a Small Molecule Inhibitor of the CBL-B E3 Ubiquitin Ligase, Promotes T and NK Cell Activation and Enhances NK-mediated ADCC in a Mouse Lymphoma Tumor Model

Marilena Gallotta, Jennifa Gosling, Austin Tenn-McClellan, Serena Ranucci, Jose Gomez Romo, Frederick Cohen, Gwenn M Hansen, Arthur T Sands, Cristina Guiducci, Ryan Rountree

Nurix Therapeutics, San Francisco, CA, USA

Abstract

The CBL-B E3 ligase (myopathy syndrome B (CBL-B)) is expressed in leukocytes and regulates signaling pathways in T and NK cells, significantly enhancing their antitumor effects. In T cells, CBL-B deletion increases T-cell function, thus setting the threshold for T cell activation in NK cells. CBL-B functions downstream of TCR receptors and negatively regulates cytokine production and cytotoxicity. Here we describe the effects of NX-1607, an orally bioavailable intramolecular glue inhibitor of CBL-B, on primary human T and NK cells and assess NX-1607 in combination with Rituximab in a murine xenograft model of Non-Hodgkin’s Lymphoma (NHL). Previously, we showed that NX-1607 enhances IL-2 and IFN-γ secretion in human T cells following anti-CD3/CD28 stimulation (Regulatory T cells (Tregs) produce regulatory cytokines to dampen the immune response, which is critical for inducing tumor immunosuppression. (TME)) to levels equivalent to that of anti-CD3/CD28 stimulation alone. Therefore, in addition to enhancing T-cell activation, NX-1607 reduces T cell-mediated suppression.

Results

Rituximab significantly enhanced tumor growth inhibition and stable rejections when compared to NX-1607-101 (NCT05107674).

Intervention

NX-1607 strongly potentiates Rituximab-directed NK Cell ADCC against tumor cells in a human NHL animal model.

Conclusions

- The CBL-B inhibitor, NX-1607, acts on multiple immune cells, addressing several antitumor resistance mechanisms
- NX-1607 strongly potentiates Rituximab-directed NK Cell ADCC against tumor cells in a human NHL animal model.

Other NX-1607 posters presented at SITC 2022


These studies also provide support for clinical development of NX-1607 as a monotherapy or in combination with antibody therapeutics to enhance ADCC antitumor effects. We have initiated a clinical trial with NX-1607 in patients with advanced solid tumors (NCT015107674).

Introduction

The CBL-B inhibitor, NX-1607, acts on multiple immune cells, addressing several antitumor resistance mechanisms

- CBL-B E3 ligase: a master orchestrator of the immune response
- CBL-B inhibition increases SCF and NK infiltration and function
- T-cell priming
- NK cell function
- Anti-tumor response
- Antitumor cytokine production/mechanisms: IL-2, GM-CSF, and TGF-β

Figure 1. NX-1607 Limits TGF-β Mediated T-cell Suppression

Human T cell TGF-β assay:

- 3 days stimulation with anti-CD3/CD28
- 1:1 Treg/T cell ratio
- NX-1607 pre-treatment

Figure 2. NX-1607 Limits Treg Mediated T-cell Suppression

Primary human T cell TGF-β assay:

- Donor 1
- Donor 2
- Donor 3
- Donor 4

Figure 3. NX-1607 Increases Secretion of Pro-Inflammatory Cytokines in Human NK Cells

Donor 1
Donor 2
Donor 3
Donor 4

NX-1607-mediated NK activation potentiates Rituximab antitumor activity:

- 60ng/mL IL-2 O.N.
- NK cells isolated and pre-conditioned
- 1-hour pre-treatment prior to addition of K562
- 1-hour compound pre-treatment prior to addition of Ramos

Figure 4. NX-1607 Strongly Potentiates Rituximab-Directed NK Cell ADCC Against Tumor Cells in a Human NHL Animal Model

NX-1607-101 (NCT05107674).

Percentage of Survival

NX-1607-101
Rituximab 10mg/kg
Rituximab 10mg/kg + NX-1607-101
NX-1607-101 + NK depletion

NX-1607-101-mediated NK cell depletion

Percentage of Survival

NX-1607-101
NX-1607-101 + Rituximab

NX-1607-101 with NK cell depletion

NX-1607-101
NX-1607-101 + Rituximab

NX-1607-101 with NK cell depletion

NX-1607-101
NX-1607-101 + Rituximab

NX-1607-101 with NK cell depletion

Percentage of Survival

0 10 20 30 40 50 60 70 80 90 100
0 1 10 100 1000

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