Inhibitors of the E3 Ubiquitin Ligase CBL-B Promote Potent T and NK Cell Mediated Anti-Tumor Response

Non-Small Cell Lung Cancer Drug Development Summit

Boston, MA

Sept 21st, 2022

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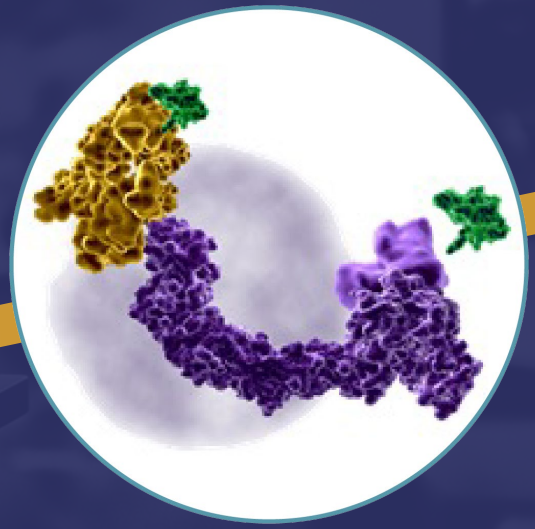
Nurix Drugs Engage Ligases for the Treatment of Cancer

Targeted Protein Modulation: TPM = TPD + TPE

A Powerful Cellular System



Harness ligases to decrease specific protein levels

Targeted Protein Degradation (TPD)

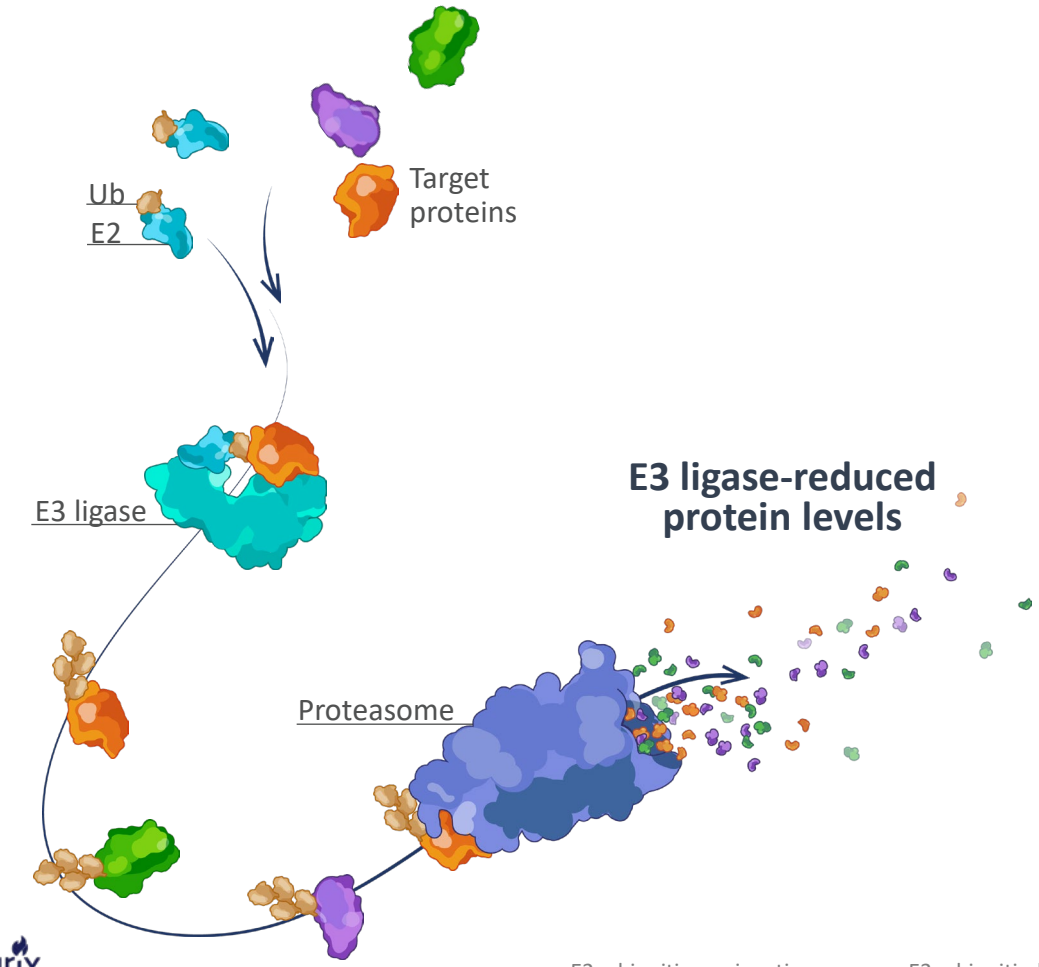
Ubiquitin is ligated to target proteins to tag them for degradation by the proteasome

Targeted Protein Elevation (TPE)

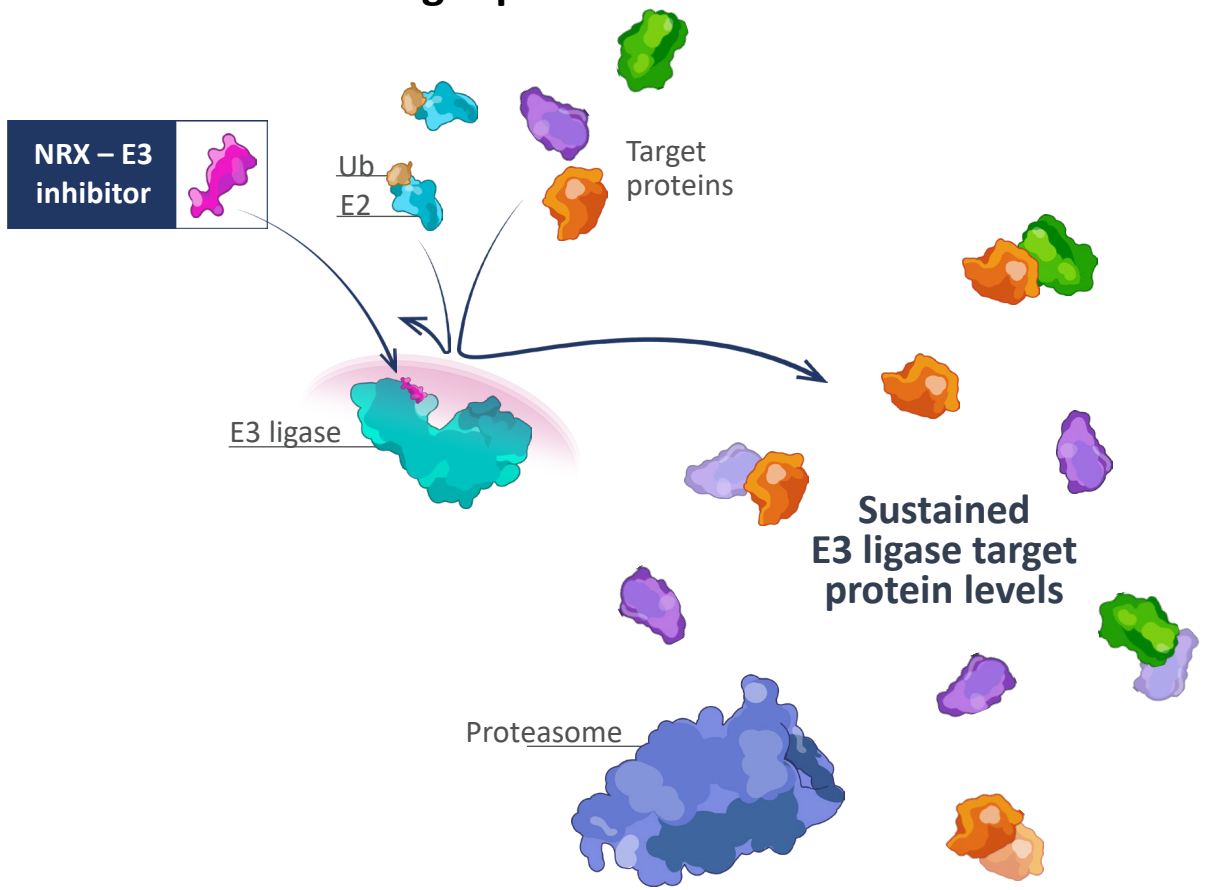
Inhibit ligases to increase specific protein levels

E3 Ligase Inhibition Results in Targeted Protein Elevation (TPE)

Native E3 Ligase activity –
Maintains target proteins at low levels



Inhibited E3 Ligase –
Target proteins elevated



E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; NRX, Nurix; Ub, ubiquitin

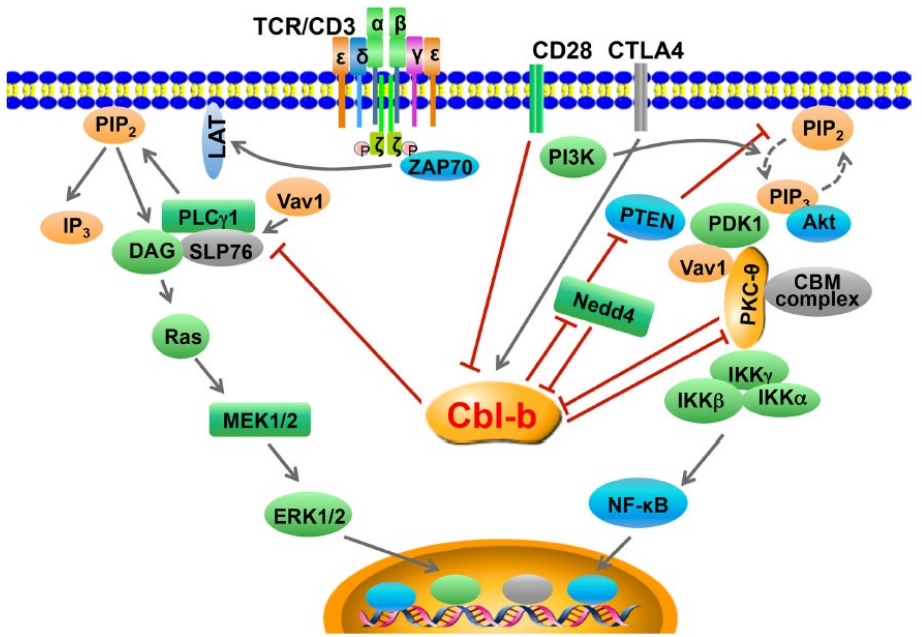
Nurix Is Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

MOA	Drug Program	Target/ Delivery	Therapeutic Area	Pre-Clinical	Phase 1	Phase 2	Phase 3
TPD	**NX-2127** Degrader	BTK-IKZF *Oral*	B-Cell Malignancies				
TPD	**NX-5948** Degrader	BTK *Oral*	B-Cell Malignancies				
TPE	**NX-1607** Inhibitor	CBL-B *Oral*	Immuno-Oncology				
TPE	**DeTIL-0255** Cell Therapy	Adoptive Cell Therapy *Ex vivo CBL-B Inhibition*	Gynecologic Malignancies				
TPM	Wholly owned	5 targets	Multiple				
TPD	Gilead Sciences	5 targets	Multiple				
TPD	Sanofi	5 targets	Multiple				

MOA, Mechanism of action; TPD, Targeted Protein Degradation; TPE, Targeted Protein Elevation; TPM, Targeted Protein Modulation

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

- CBL-B is an E3 ubiquitin ligase that is expressed in and regulates immune cells, including T, B, NK and dendritic cells
- Mice deficient in CBL-B demonstrate enhanced signal-dependent T cell activation and robust T and NK cell dependent anti-tumor activity
- In T cells, CBL-B limits cell activation following TCR engagement, enforcing the need of CD28 co-stimulation
- Inhibition or deletion of CBL-B increases IL-2 production in T cells upon stimulation and enhances the immune response
- Inhibiting CBL-B with a small molecule represents a novel immunotherapy target opportunity to overcome checkpoint resistance and reduce effects of the suppressive tumor microenvironment



Cellular Immunology
Volume 340, June 2019, 103878

CBL-B inhibition

- IL-2 production
- Proliferation
- Central memory phenotype
- Anti-tumor activity
- Threshold of activation
- T cell exhaustion

Synergy with anti-PD-1

NX-1607: Optimized CBL-B inhibitor for oral delivery. Developing as an oral intracellular checkpoint inhibitor for treating solid tumors.

NX-0255: Optimized CBL-B inhibitor for *ex vivo* use. Developing in conjunction with autologous T cell therapies including TIL and CAR T.

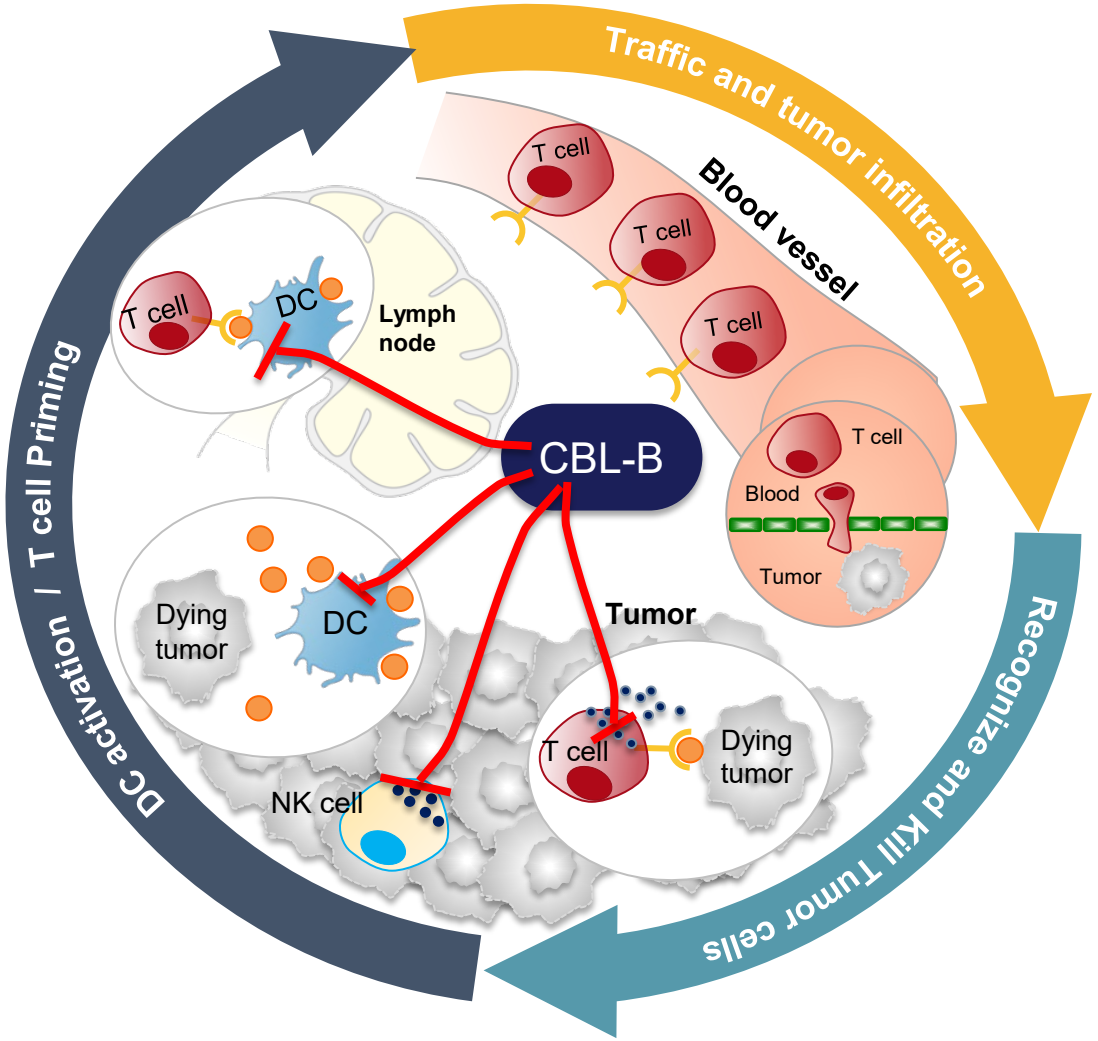
Targeting CBL-B Enhances Antitumor Response

A Master Orchestrator of the Immune System

CBL-B mediated mechanisms strongly restrain a productive anti-tumor response

CBL-B inhibition increases:

- DC and NK infiltration and function
- T cell priming
- Cytotoxic T cells function
- Ability of T cells to resist tumor immunosuppressive mechanisms: Treg, MDSC, and TGF-β



Targeting CBL-B Enhances Antitumor Response

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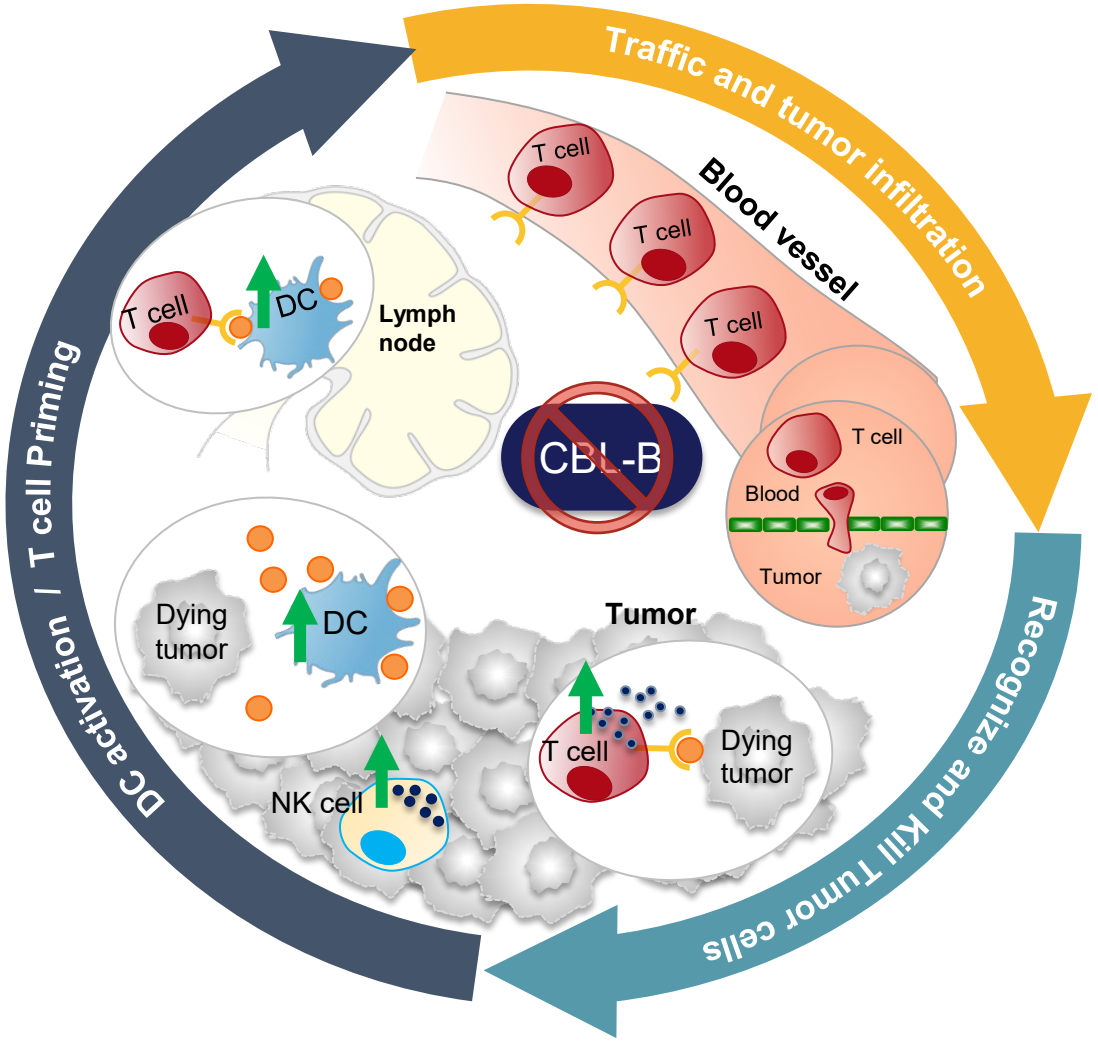
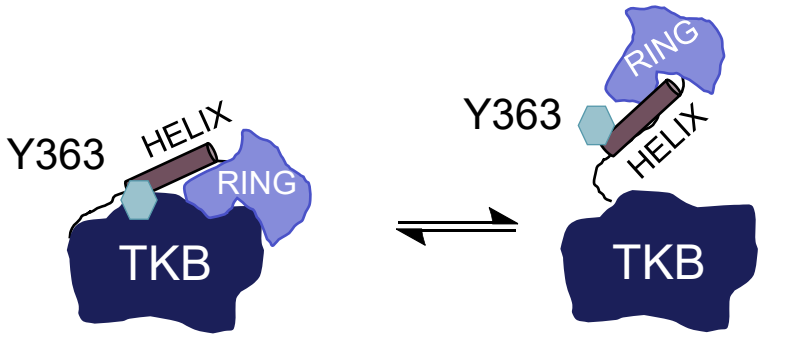


NX-1607 Mechanism of Action: Intramolecular Glue

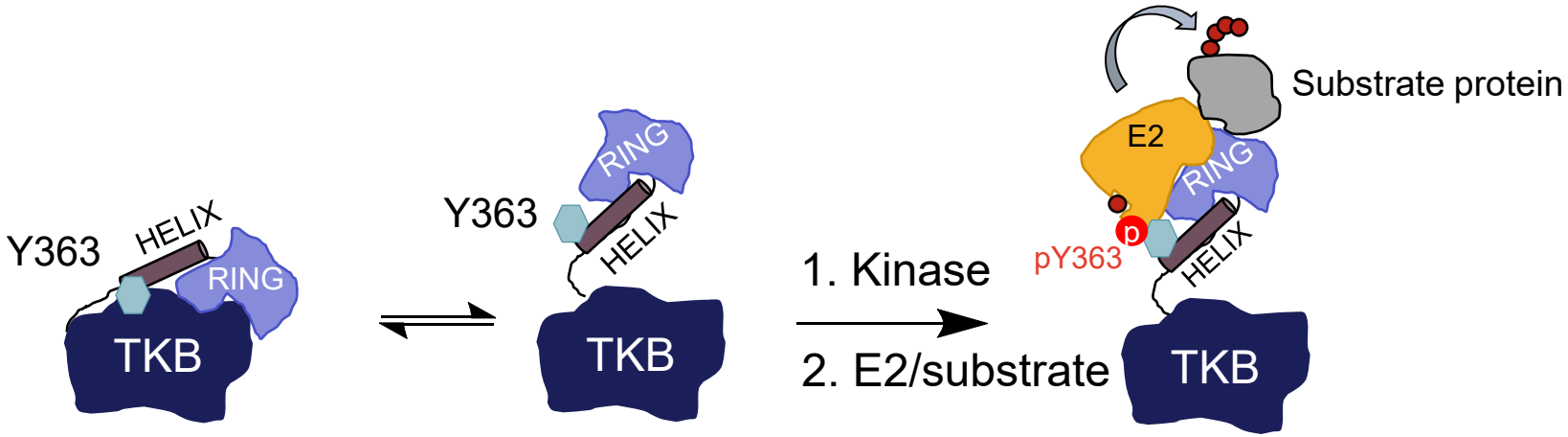
CBL-B is in Equilibrium Between Closed and Opened State



Closed State
INACTIVE

Opened State

NX-1607 Mechanism of Action: Intramolecular Glue



Closed State
INACTIVE

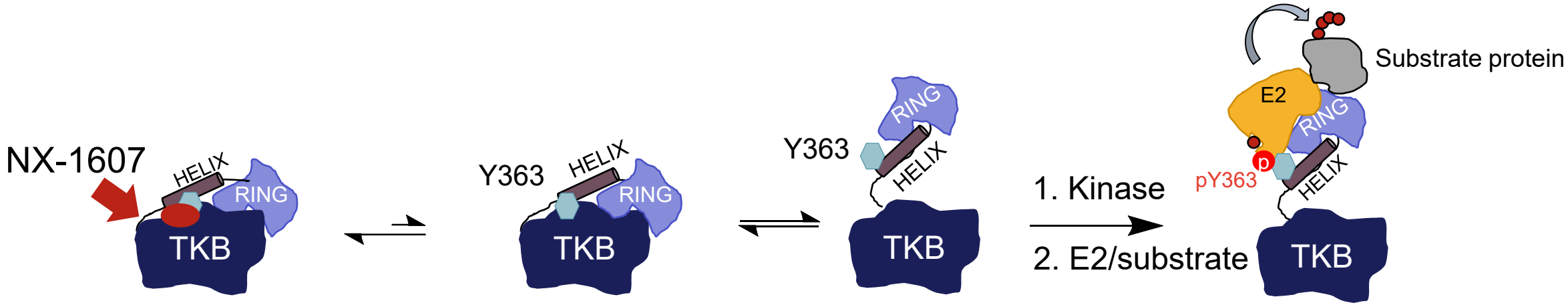
Opened State

Phosphorylation locks CBL-B in the **ACTIVE** Conformation

CBL-B target proteins at low levels

Immune Response

NX-1607 Mechanism of Action: Intramolecular Glue



NX-1607 acts as an intramolecular glue forcing CBL-B in its folded **INACTIVE** state

Closed State **INACTIVE**

Opened State

Phosphorylation locks CBL-B in the **ACTIVE** Conformation

CBL-B target proteins elevated (TPE)

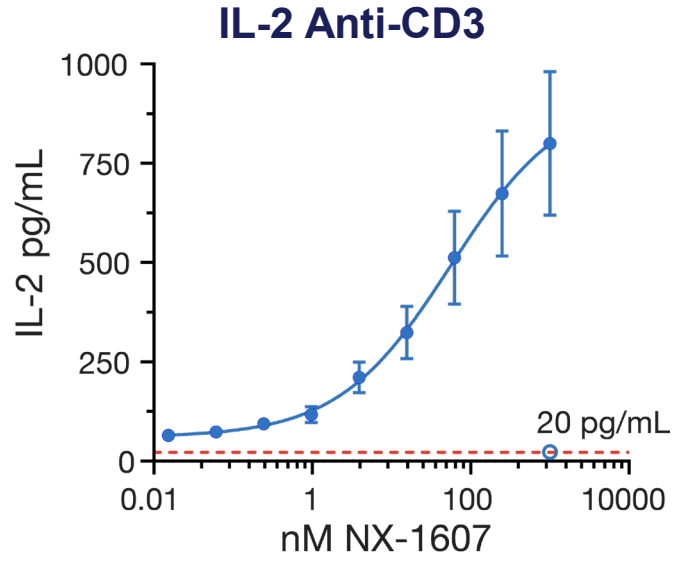
Immune Response

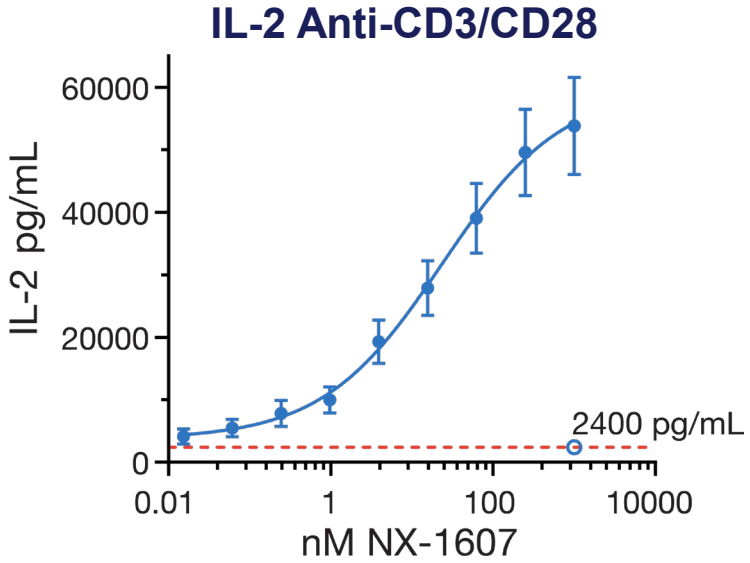
CBL-B target proteins at low levels

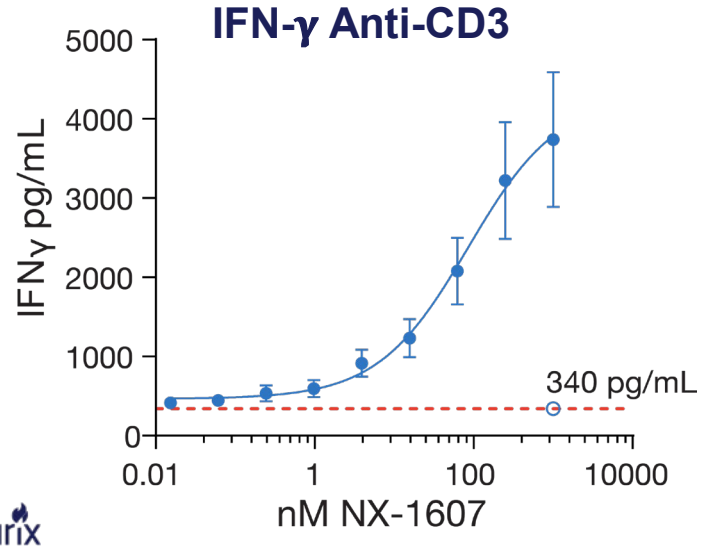
Immune Response

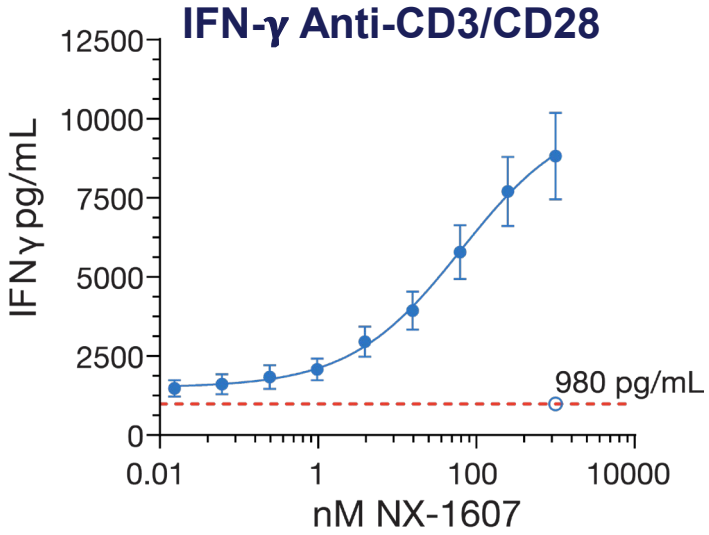
nurix

NX-1607 Increases IL-2 and IFN-γ Secretion in TCR Stimulated Primary Human T cells







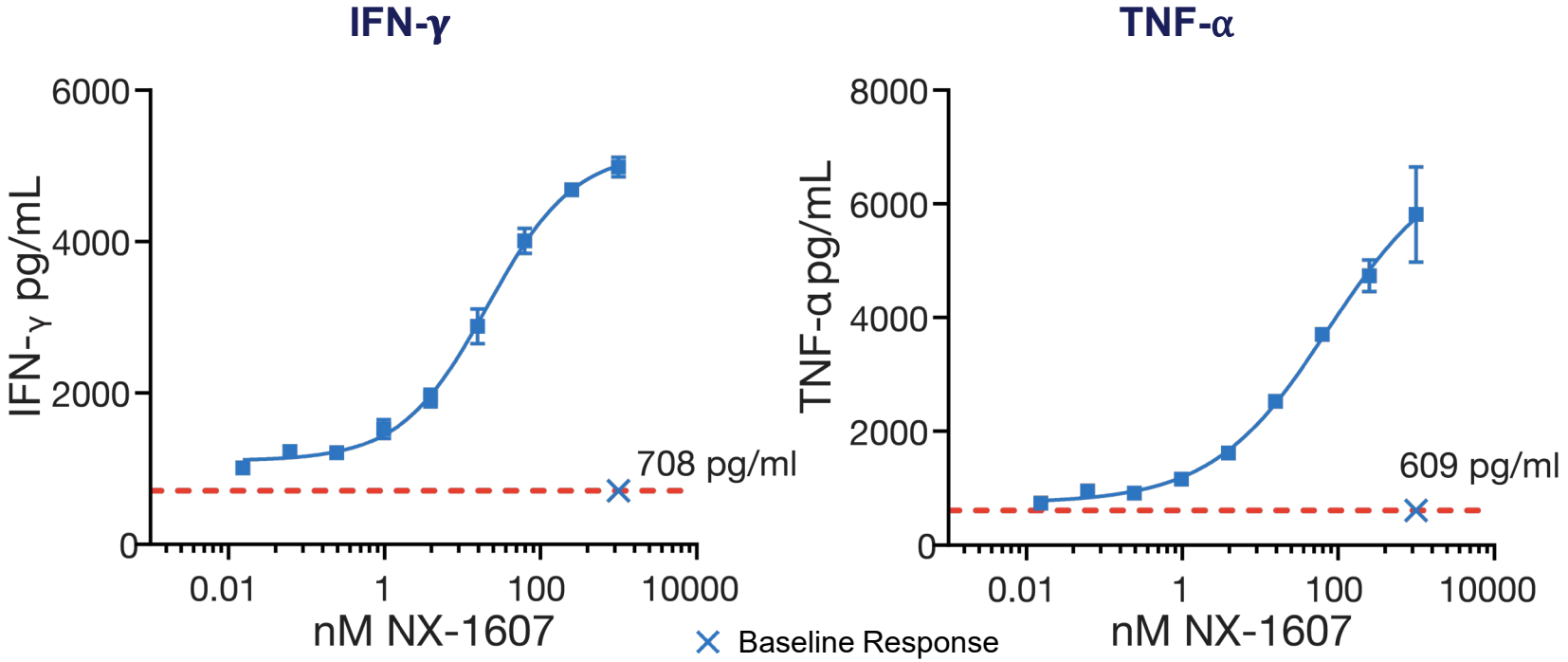


NX-1607 increases TCR stimulation-dependent production of IL-2 and IFN-γ in primary human T cells

NX-1607 has no impact in the absence of T cell stimulation as measured by proliferation, activation, or cytokine release

Cytokine Response
Baseline Response

NX-1607 Increases Secretion of Pro-Inflammatory Cytokines in Human NK cells



NX-1607 increases stimulation-dependent production of IFN-γ and TNF-α in primary human NK cells

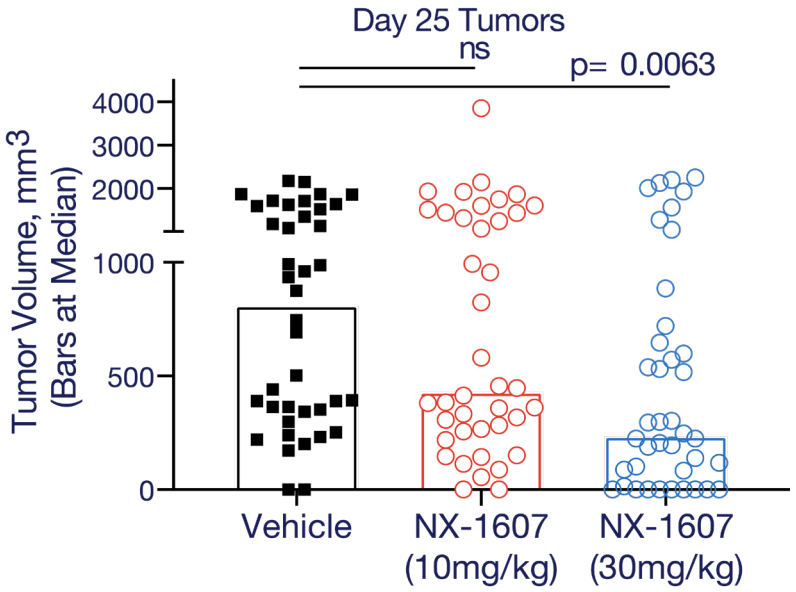
NX-1607 has no impact in the absence of NK cell stimulation, as measured by cytokine release

NK K562 Killing Assay

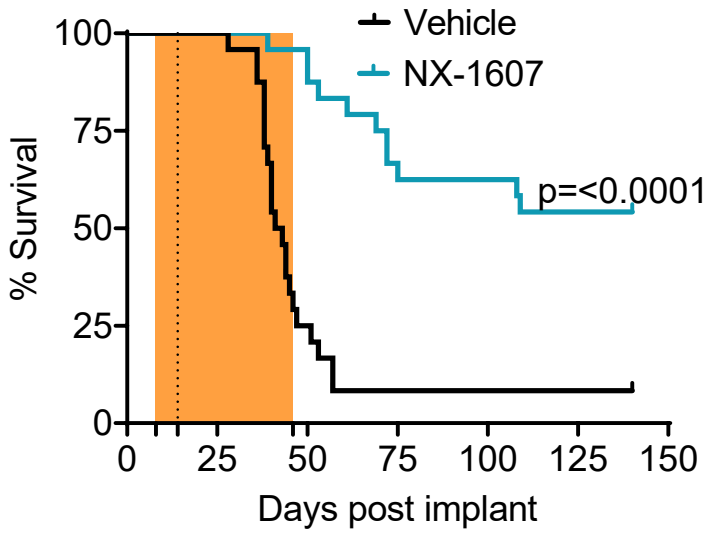
- 1 hour compound pre-treatment prior to addition of K562s target cells
- 6 hour NK/K562 coculture

Single-Agent NX-1607 Induces Antitumor Response in Multiple Models

NX-1607
Reduced Tumor Volume
Colorectal (CT26)

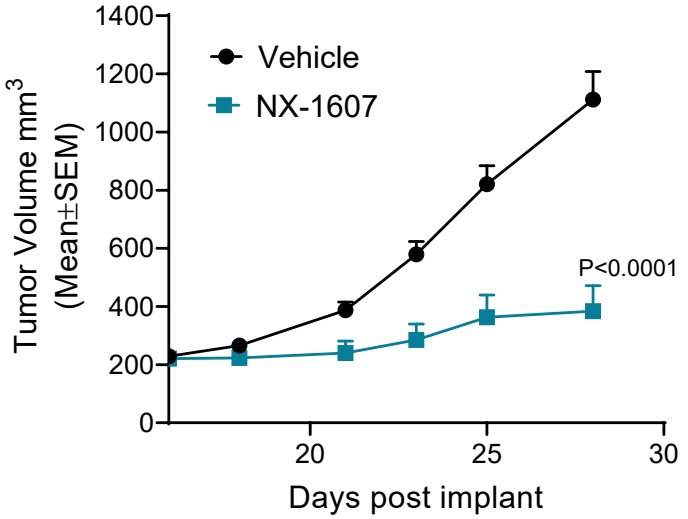


NX-1607
Prolonged Survival
Triple-Negative Breast (4T1)



NX-1607 30 mg/kg day 7 to 46

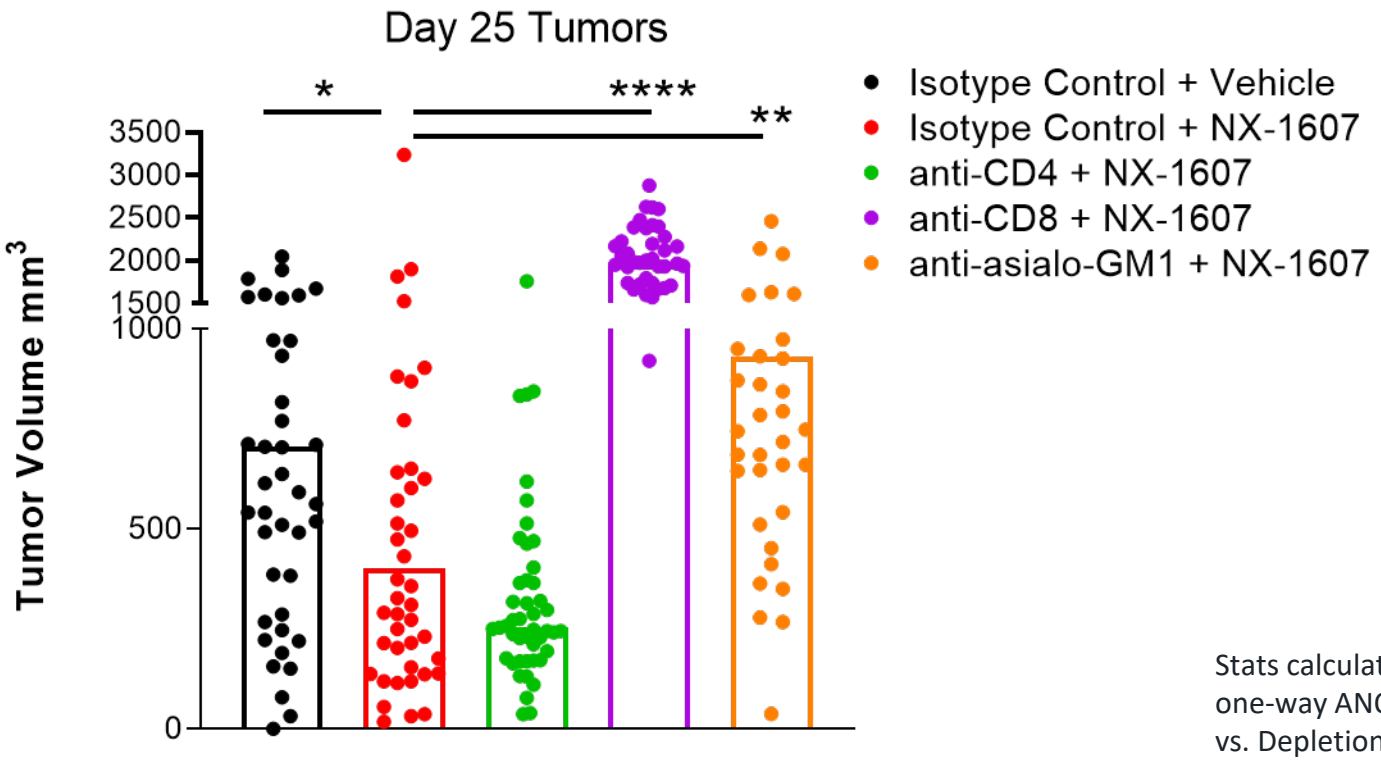
NX-1607
Reduced Tumor Volume
B Cell Lymphoma (A20)



NX-1607 30 mg/kg day 16 to 28

Shaded area indicates dosing period

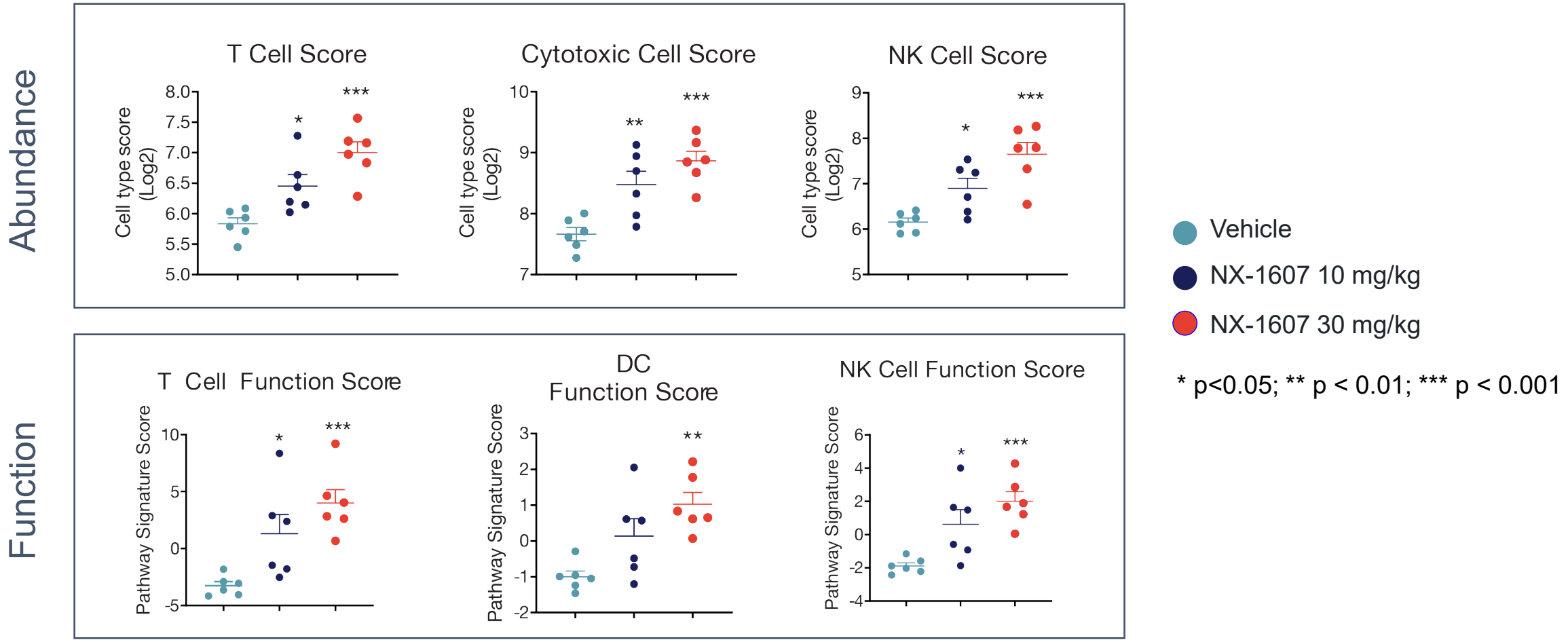
NX-1607 Antitumor Efficacy is Dependent on CD8+ T Cells or NK Cell Activity



Stats calculated with Mann-Whitney (Vehicle vs. NX-1607) or one-way ANOVA with Dunn's multiple comparisons test (NX-1607 vs. Depletion groups); * $P \leq 0.05$, ** $P \leq 0.01$, **** $P \leq 0.0001$.

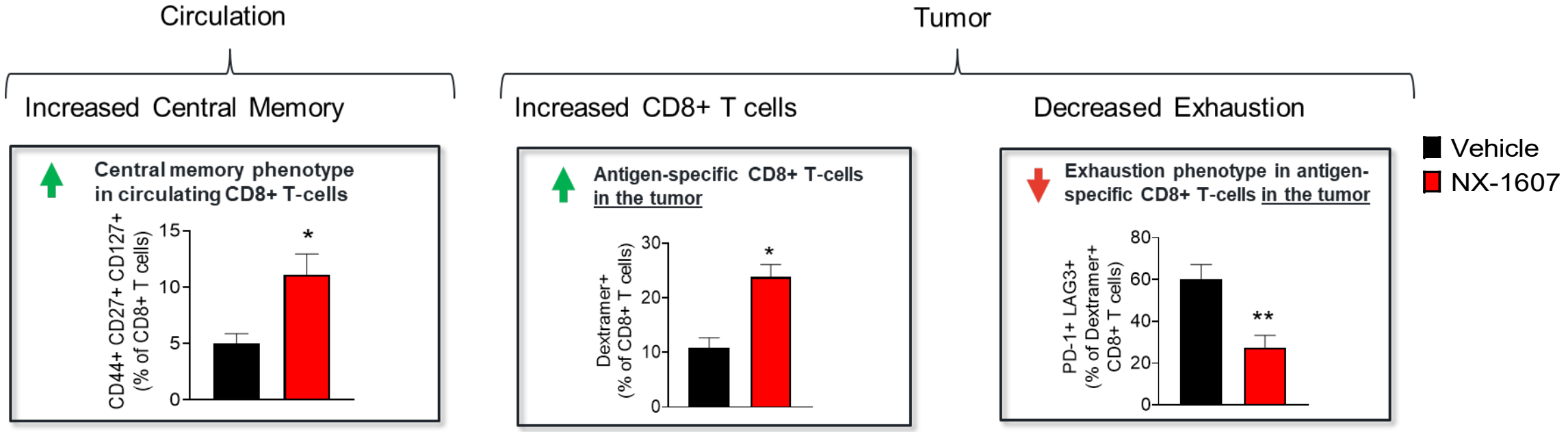
- CT26 colorectal tumor on left and right flanks treated from Day 9 to Day 25 with oral NX-1607 at 30 mg/kg, PO QD in the presence of depleting antibodies for CD4+ cells, CD8+ cells, or NK cells (anti-asialo-GM1)

NX-1607 Treatment Induces Dose Dependent T and NK Cell Intratumoral Infiltration and Enhanced Function



CT26 tumor-bearing mice treated for 18 days with NX-1607 at 10 or 30 mg/kg. Tumor microenvironment profiled using NanoString technology.

NX-1607 Treatment Increases Tumor Antigen Specific Response in a Metastatic Triple Negative Breast Cancer Tumor Model

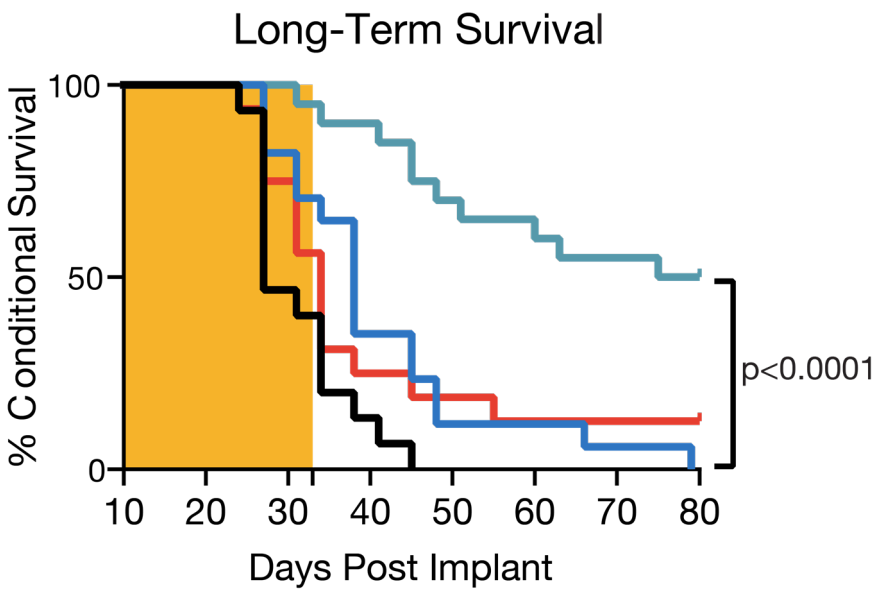


4T1 breast cancer model. ANOVA test with post-hoc Dunn's multiple comparisons test * $p<0.05$; **$p<0.01$

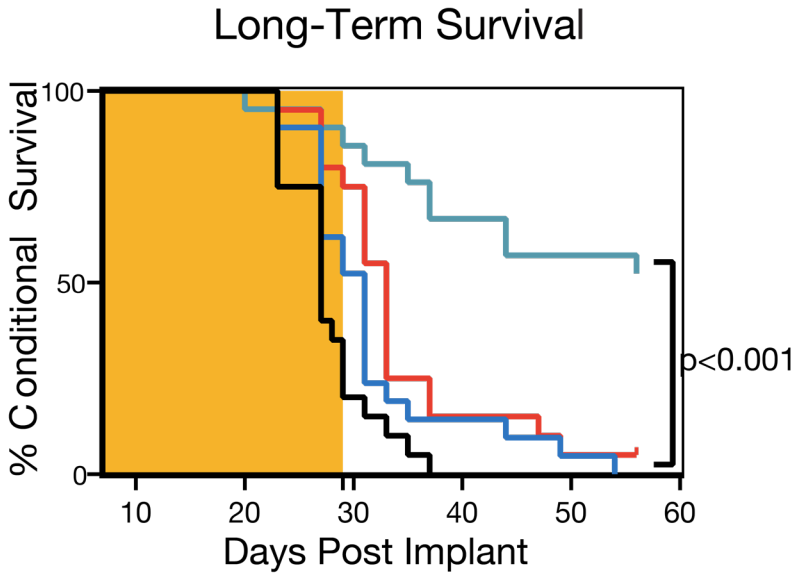
- NX-1607 treatments result in immune cell phenotypic changes, both in the tumor microenvironment (TME) and in peripheral blood in animal models
- Similar changes have been associated with extended survival and better prognosis in cancer patients

NX-1607 and Anti-PD-1 Synergize to Enhance Anti-tumor Effects and Survival of Mice in Multiple Tumor Models

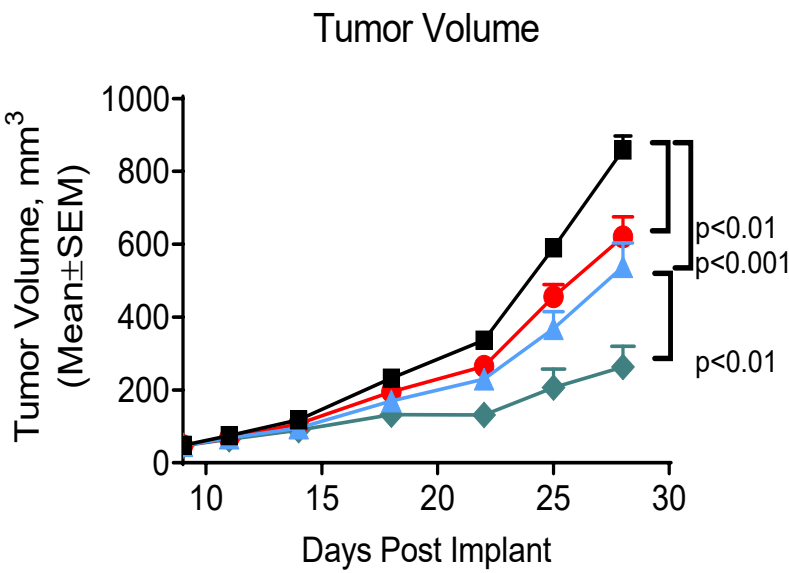
Colorectal (CT26)



Colorectal (MC38)



Triple-Negative Breast (4T1)

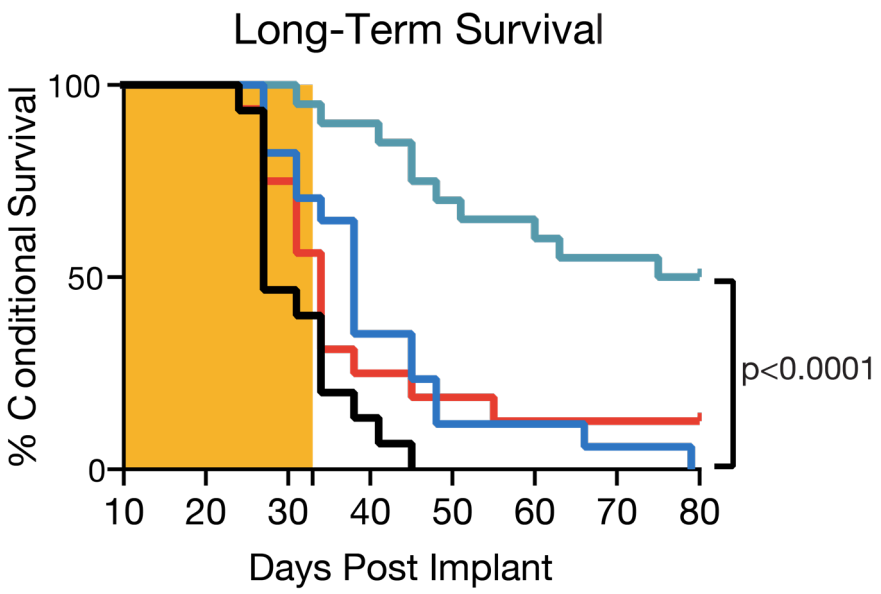


Vehicle NX-1607 anti-PD-1 NX-1607+anti-PD-1

Shaded area indicates dosing period: NX-1607 (30 mg/kg, PO daily) and anti-PD-1 twice a week at 10 mg/kg dosing period

NX-1607 and Anti-PD-1 Synergize to Enhance Anti-tumor Effects and Survival of Mice in Multiple Tumor Models

Colorectal (CT26)



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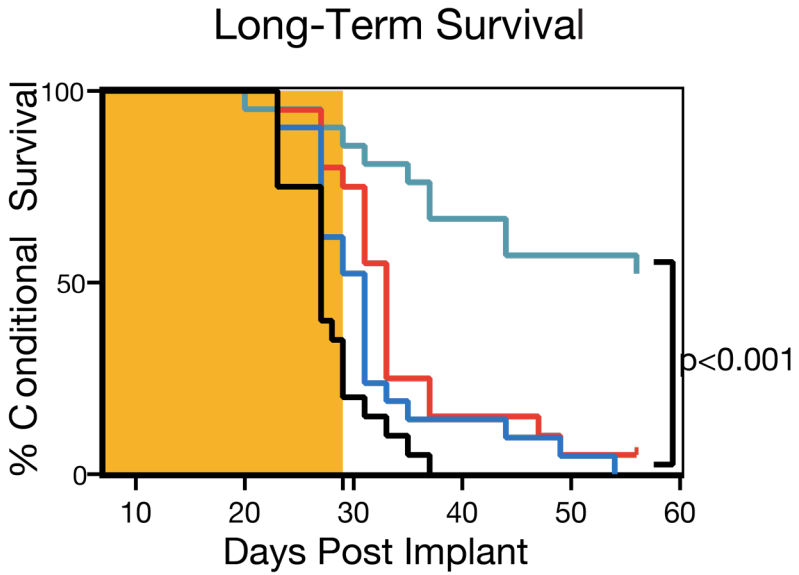

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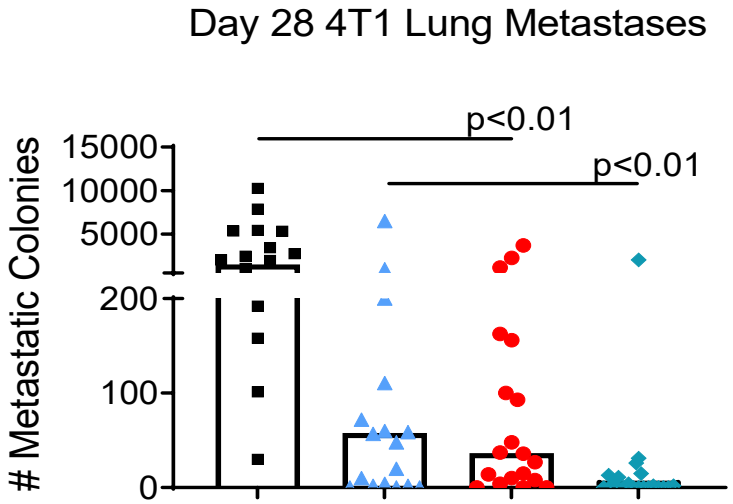


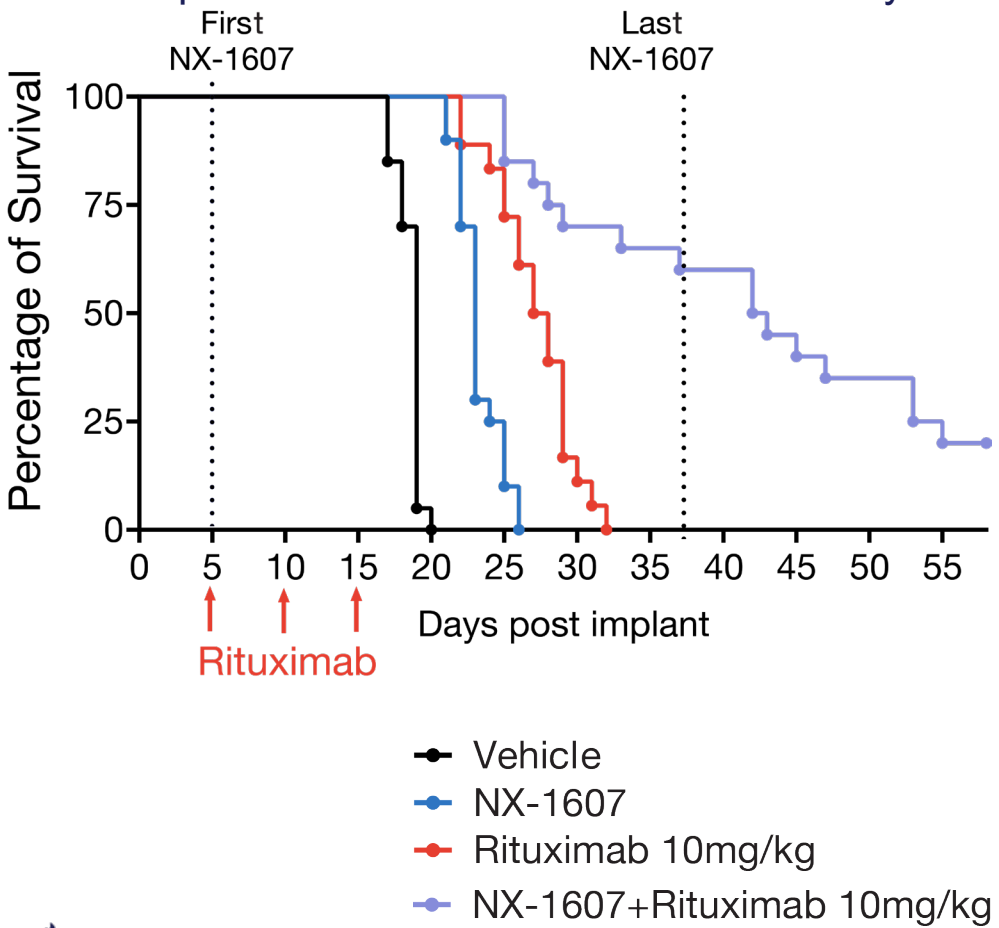
Vehicle NX-1607 anti-PD-1 NX-1607+anti-PD-1

Shaded area indicates dosing period: NX-1607 (30 mg/kg, PO daily) and anti-PD-1 twice a week at 10 mg/kg dosing period

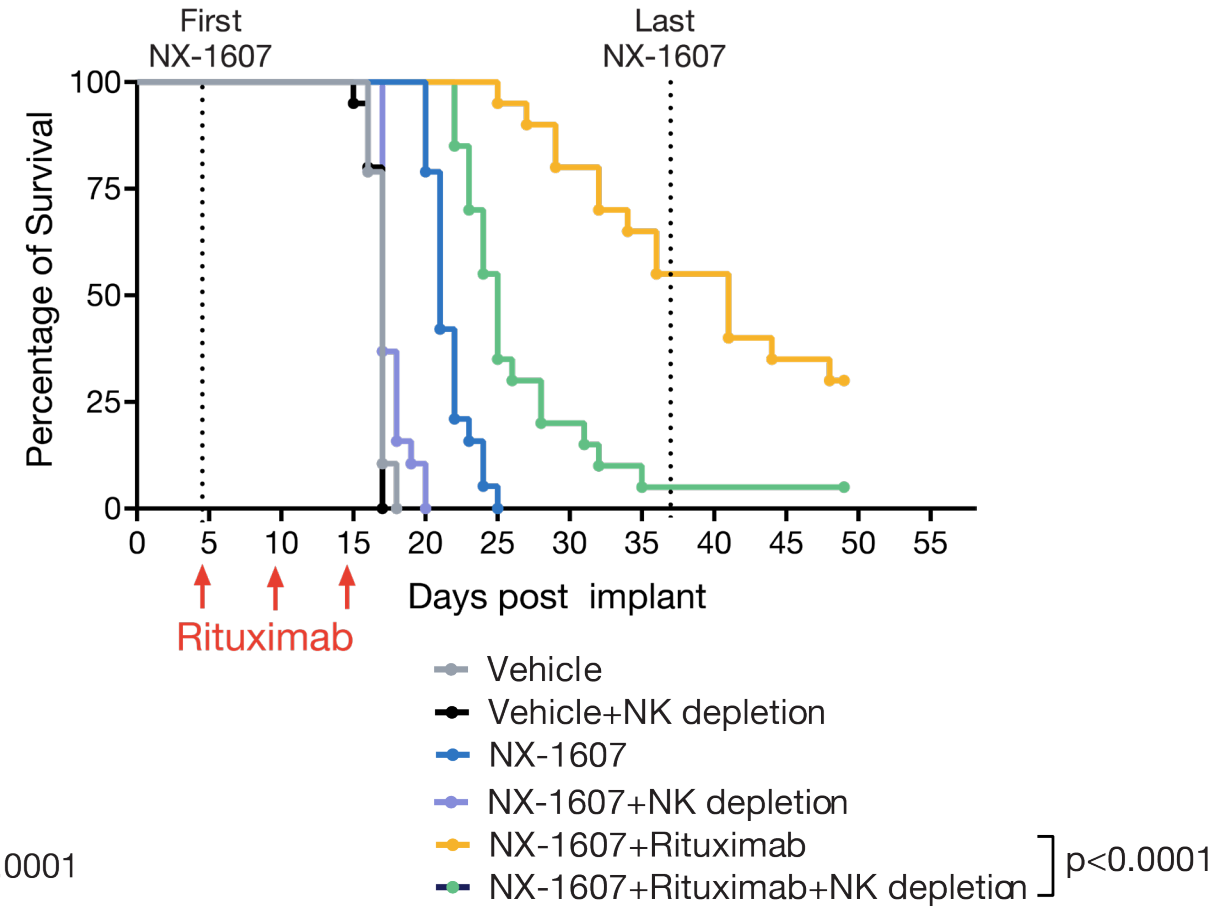
Combination of NX-1607 and Rituximab Enhances Anti-tumor Activity in a Human NHL Animal Model

NX-1607 Strongly Potentiates Rituximab-Directed NK Cell ADCC Against Raji Tumor Cells

NX-1607-mediated NK activation potentiates rituximab antitumor activity

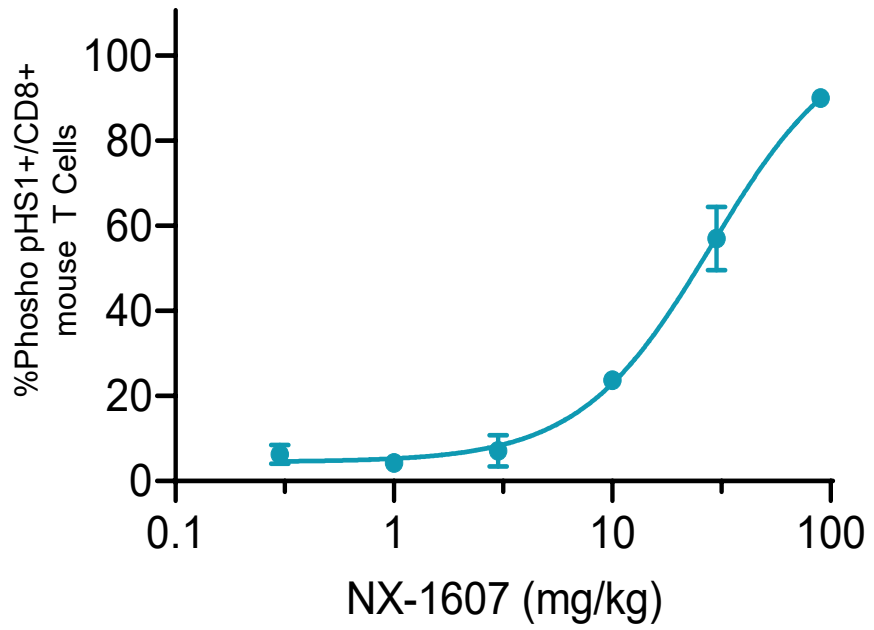


NK depletion abrogates NX-1607 and NX-1607 + Rituximab antitumor activity

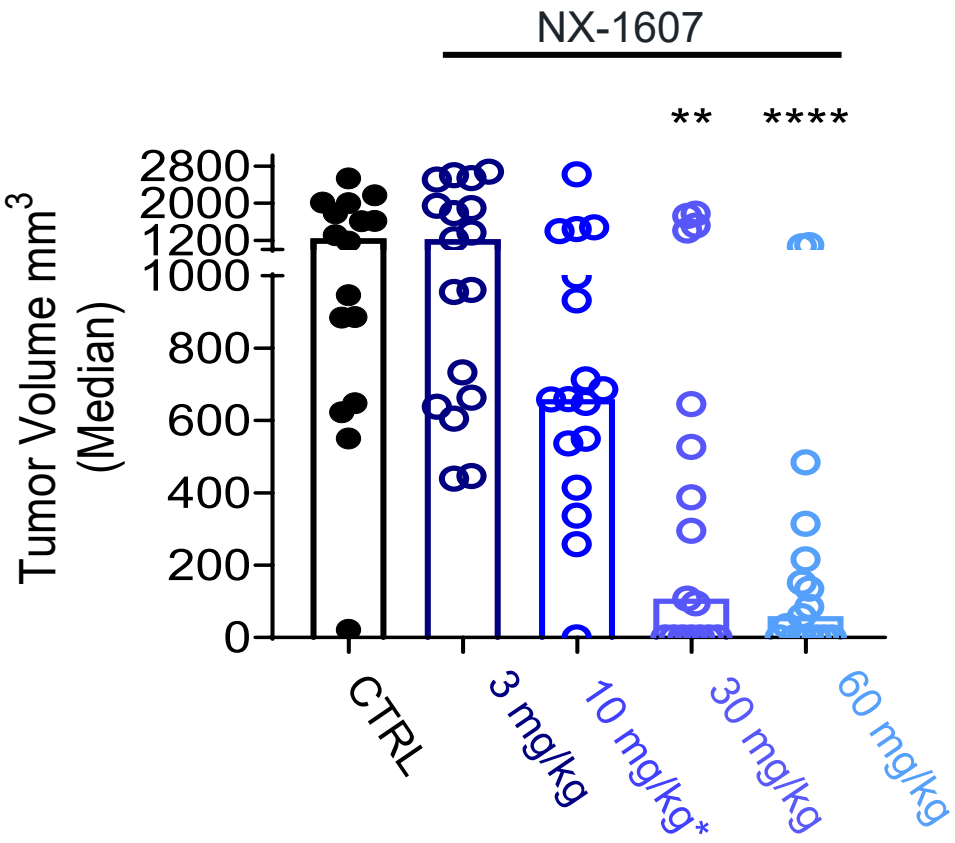


Dose Dependent Increases of CBL-B Proximal Biomarker Correlates with Antitumor Effects of NX-1607

Pharmacodynamic relationship in mice following NX-1607 dosing



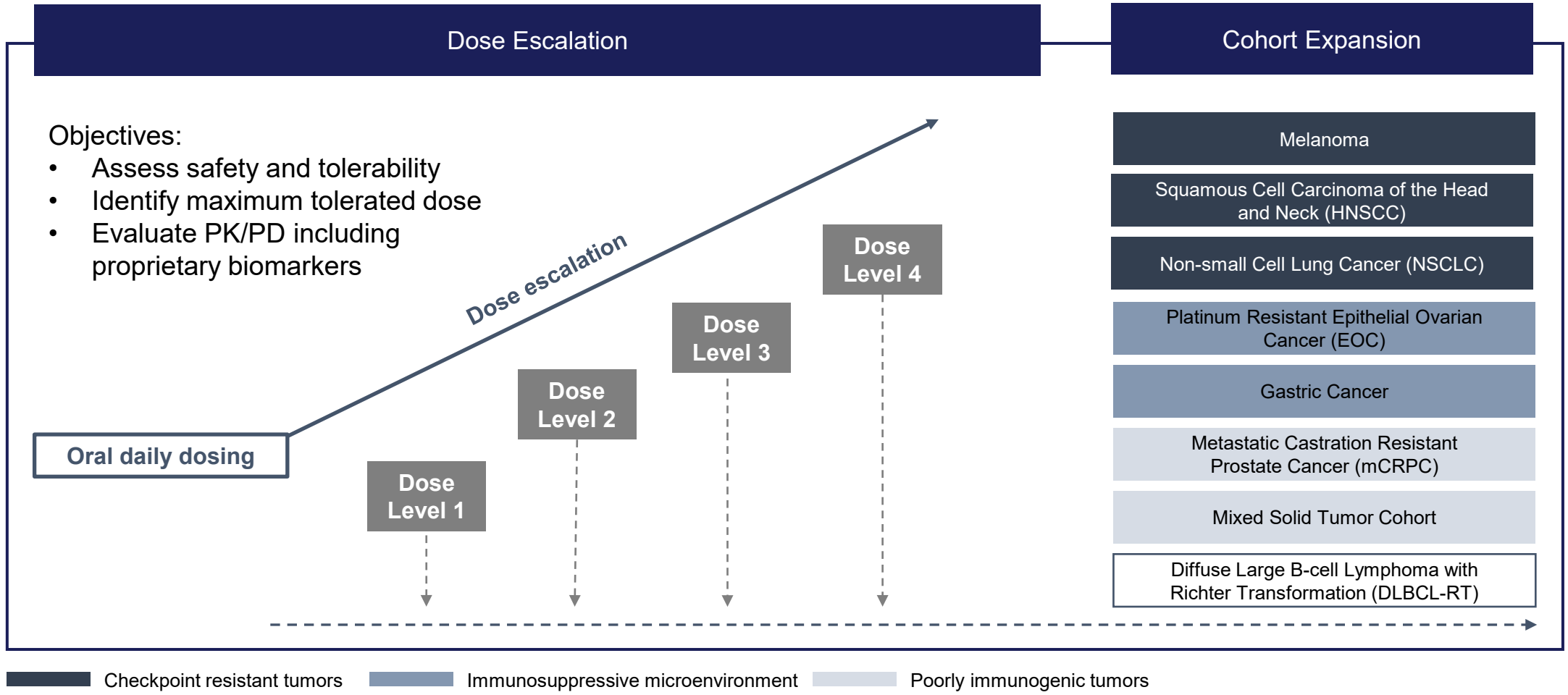
Antitumor activity in mice



A20 - B cell lymphoma model

NX-1607-101: Phase 1 first-in-human clinical trial design

Two-Part Phase 1 Monotherapy Trial of NX-1607 in Relapsed or Refractory Tumors



Summary NX-1607

- Pharmacological inhibition of CBL-B with NX-1607 recapitulates the anti-tumor effects observed in the genetic model of ligase inhibition
- NX-1607 exerts potent single agent anti-tumor activity which is dependent on CD8+ T cells and NK cells
- NX-1607 promotes infiltration of activated T cells with a lower exhausted phenotype in the tumor microenvironment
- NX-1607 strongly synergizes with PD-1 blockade to increase the rate of complete rejection and long-term survival of tumor bearing mice
- A Phase 1a clinical trial of NX-1607 is currently on going

Thank you