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Leader in Targeted Protein Modulation

Combining TIL with Small Molecule Inhibitors to Enhance T-Cell Expansion & Phenotypes

4th TIL Therapies Summit

Boston, MA

October 25th, 2022

nxact

Nurix Adoptive Cell Therapy
Living Drugs

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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				

TPD=Targeted Protein Degradation; TPE=Target Protein Enhancement

Topics for Consideration

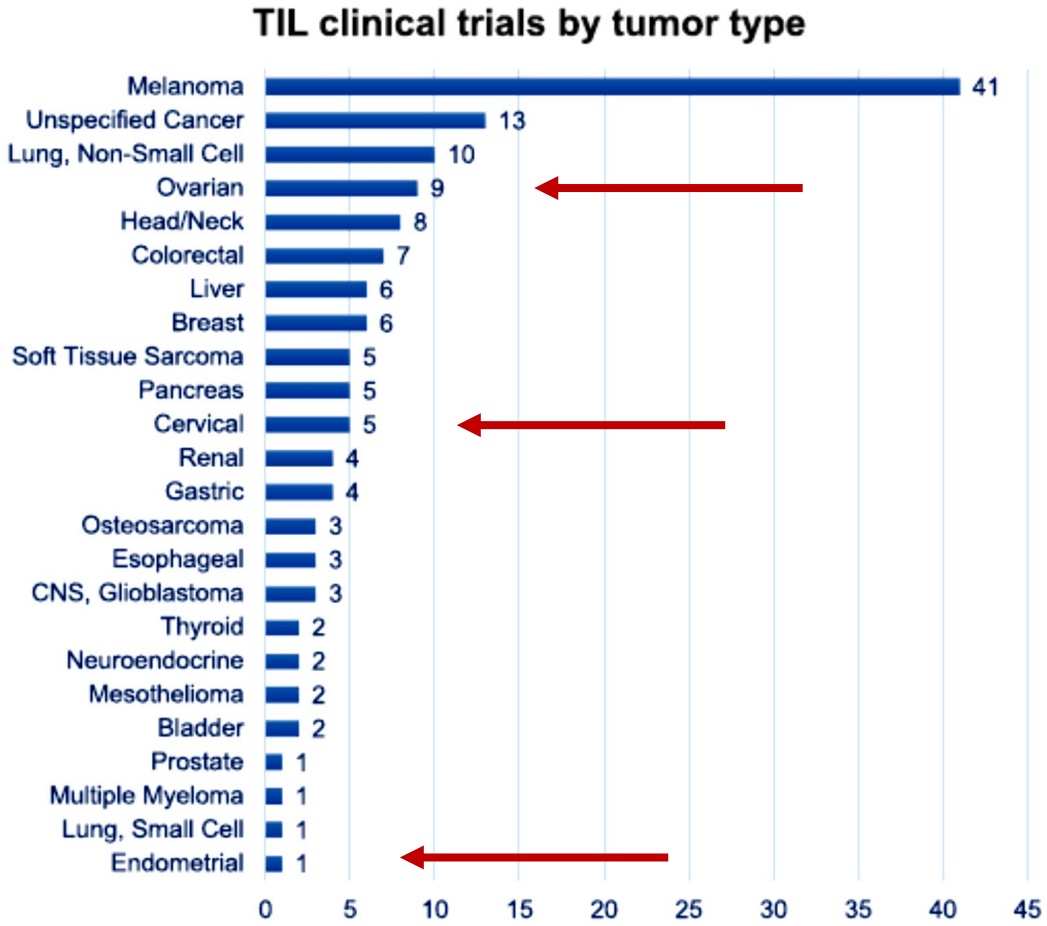
- Expanding the scope of indications to include gynecological malignancies by combining with small molecule inhibitors
- Applying targeted protein modulation to adoptive cell therapy
- Inhibiting CBL-B to stimulate IL-2 secretion, reduce T cell exhaustion and improve clinical outcomes

Current Limitations of TIL Therapy: How Can We Improve?

Current limitations:

Limited effectiveness in the post-checkpoint era due to:

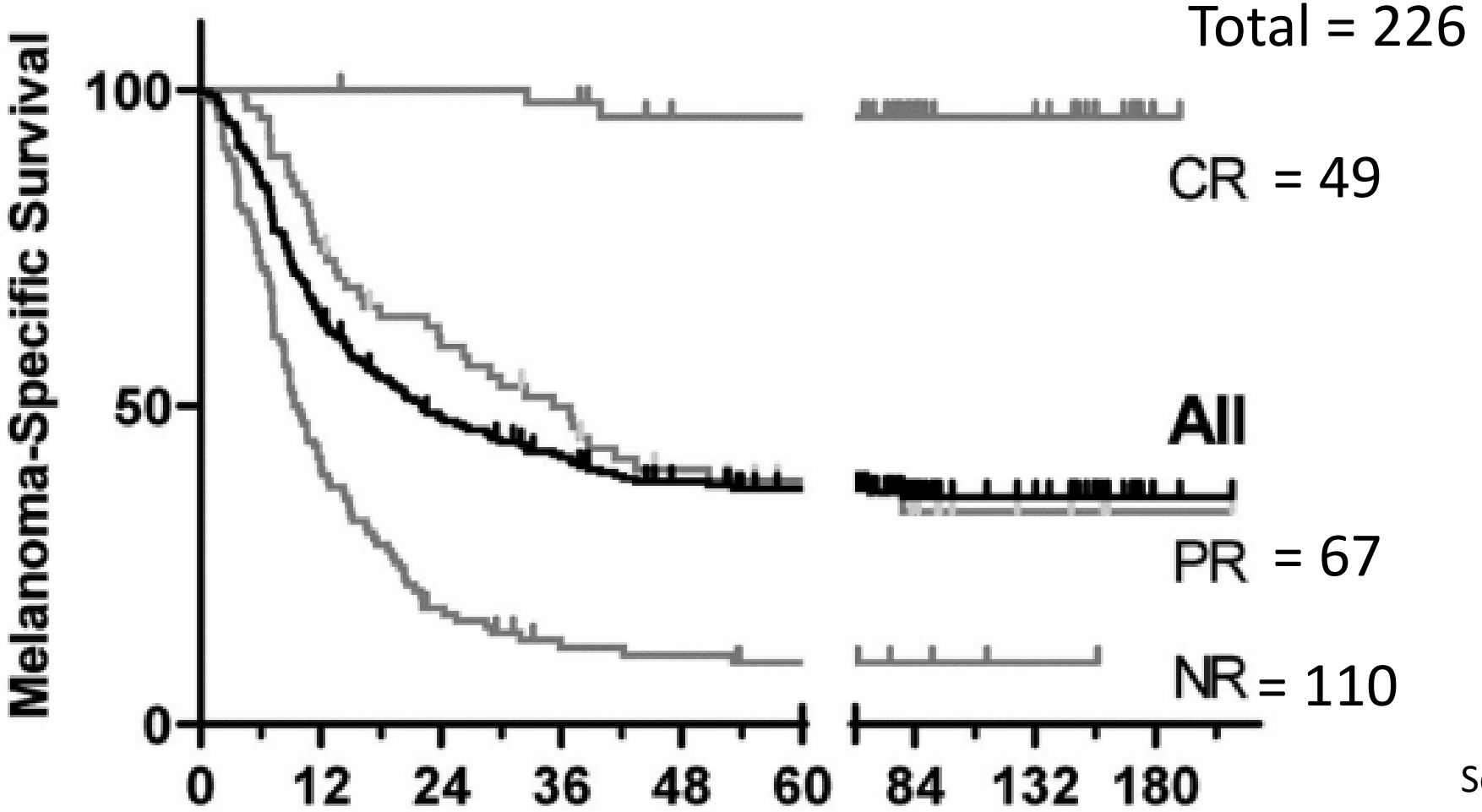
- Lower tumor mutation burden, fewer neoantigens
- Significant loss of TCR diversity
- Lower rate of tumor reactive TIL
- Lower tumor infiltration
- Lower success rate of TIL expansion
- Rapid exhaustion and terminal differentiation



Perspectives of tumor-infiltrating lymphocyte in solid tumors. *BMC Med*, 2021

TIL Therapy Melanoma Suggests that Complete Responses Could Equate with Cure Is it Possible to Achieve in Other Tumor Types ?

2000 – 2018 NCI Melanoma TIL Experience



2 of 49 CR patients developed melanoma recurrence with a median follow-up of 7 years

Seitter et al. *CCR* © 2021

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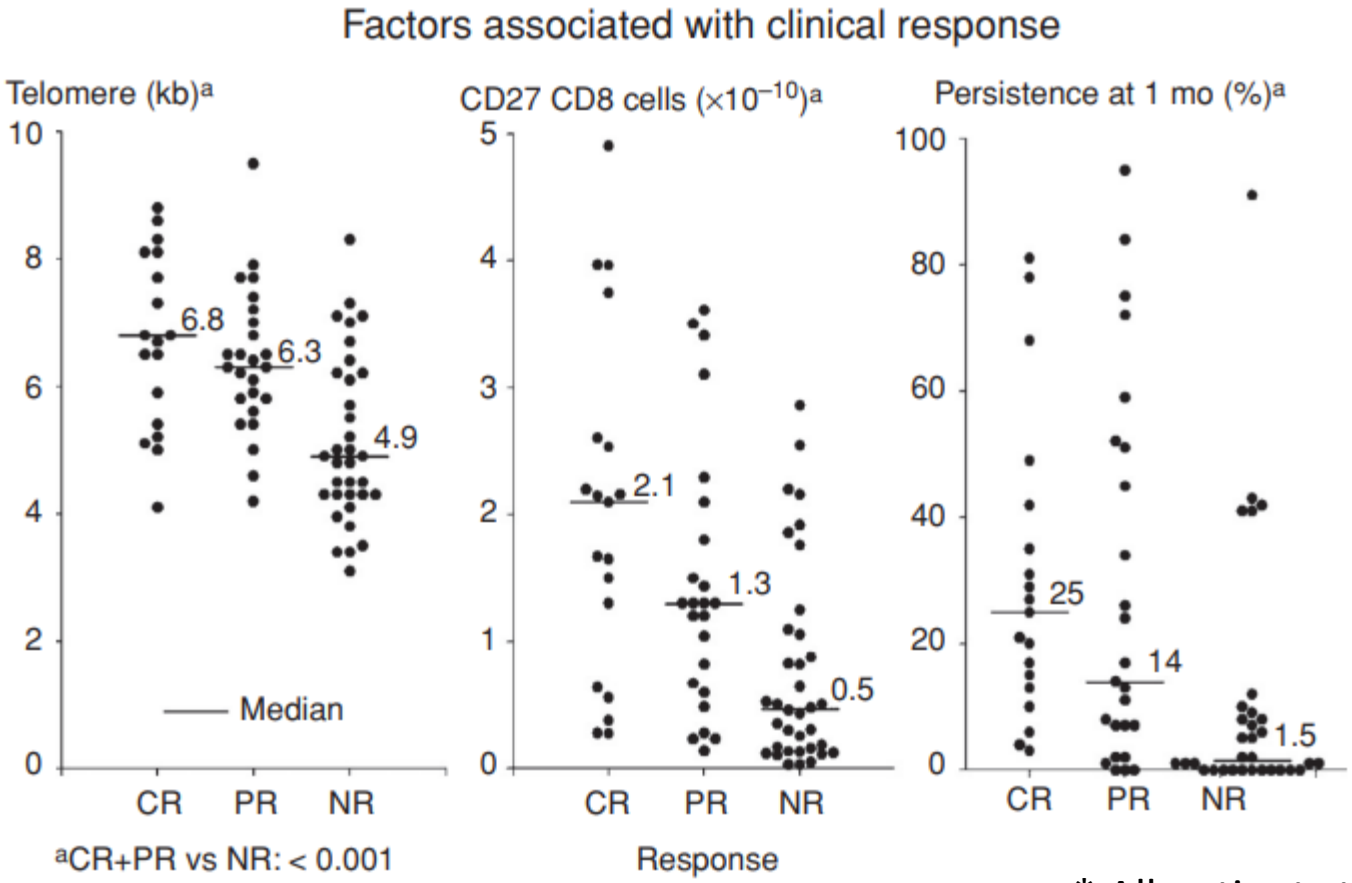
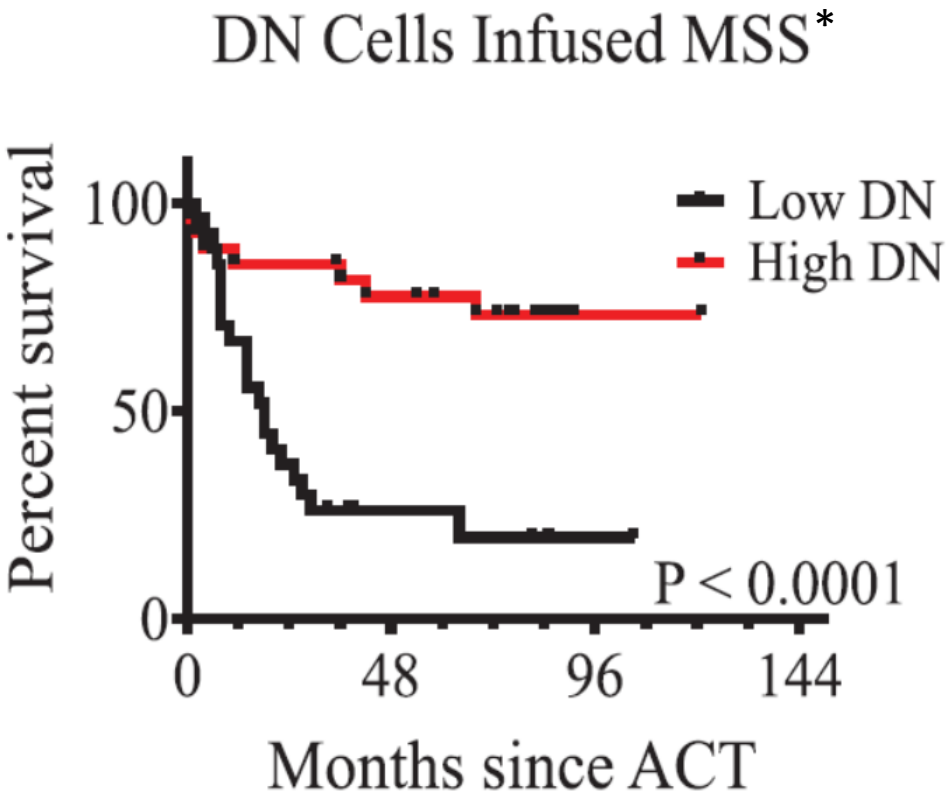
Memory Phenotype Is Associated with Clinical Response Following TIL Therapy in Melanoma Patients

↑ Telomeres, CD8 CD27+, CD8 CD39- CD69- DN Cells Is Associated with Persistence





Rosenberg et al. *CCR* © 2011
Krishna et al. *Science* © 2021

* All patients treated were checkpoint therapy naïve prior to therapy

CBL-B Inhibitor Program

Nurix has optimized two CBL-B inhibitors for oral and *ex vivo* applications

- **NX-1607** is an orally bioavailable small molecule drug candidate currently in Phase 1 clinical testing as an oral immuno-oncology agent. It is currently being developed as a single agent but has the potential to combine with other anti-tumor modalities including checkpoint inhibitors, cell therapies, chemotherapy, and other targeted oncology agents.

- **NX-0255** is optimized for *ex vivo* applications and is currently in Phase 1 clinical testing as part of the manufacturing process for our drug-enhanced tumor infiltrating lymphocyte (DeTIL-0255) program. Preclinical data supports its utility in enhanced CAR-T and potentially NK cell therapy.

Both agents work through the same mechanism of action and share similar in vitro properties. The primary difference is that NX-1607 is optimized for oral bioavailability.

Value Proposition for CBL-B Inhibition in Manufacturing and Administration of Cell Therapy Products

How can CBL-B inhibitors improve response rate and durability in cell therapy?

- Increased proliferation – applications across T cell and NK cell therapies
- Increased T cell homing, infiltration, and persistence within the tumor
- Greater cytotoxicity
- Enhanced potency – potential for higher response rates
- Longer persistence – potential for prolonged clinical responses
- Enriched T stem cell memory

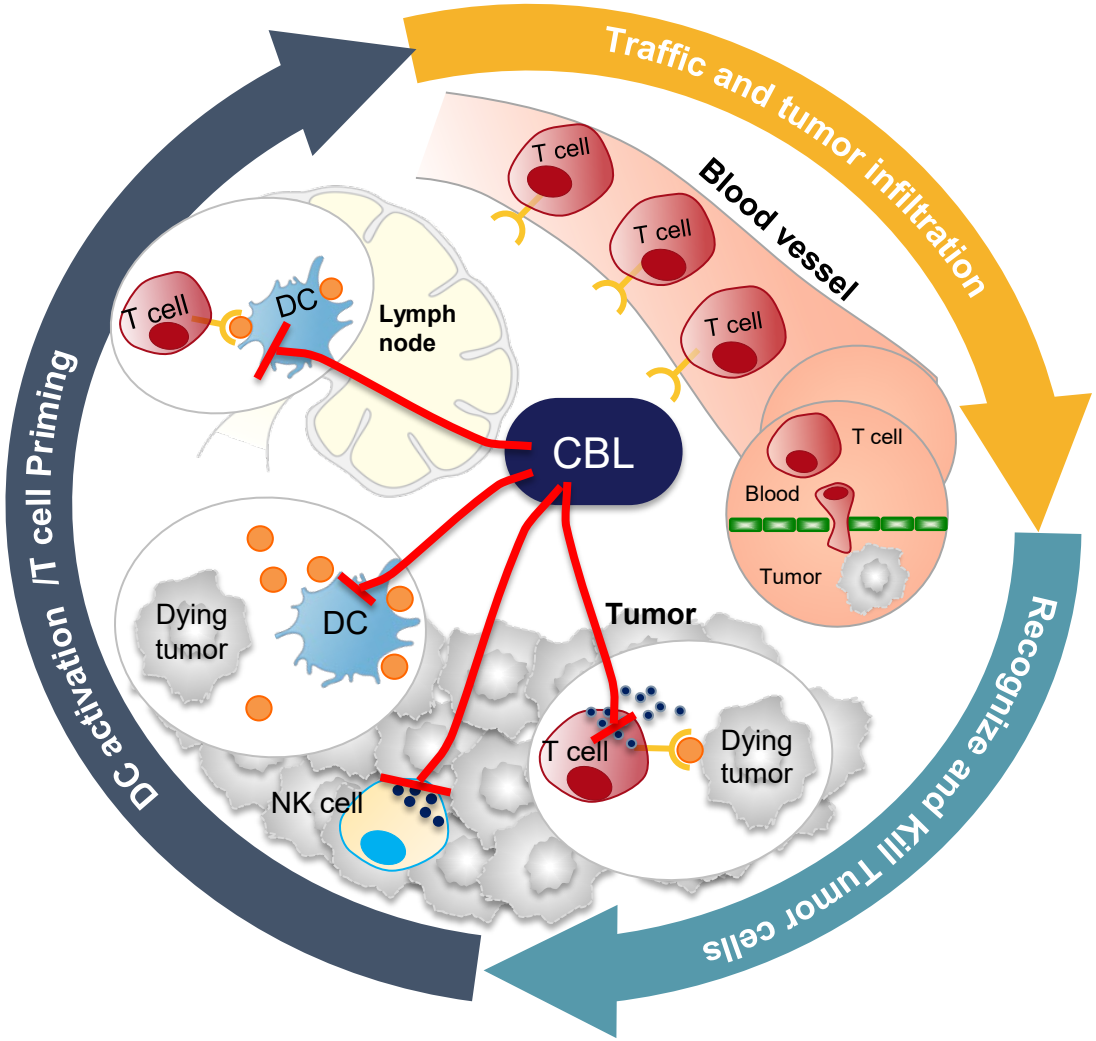
Targeting CBL-B Enhances Antitumor Response

A Master Orchestrator of the Immune System

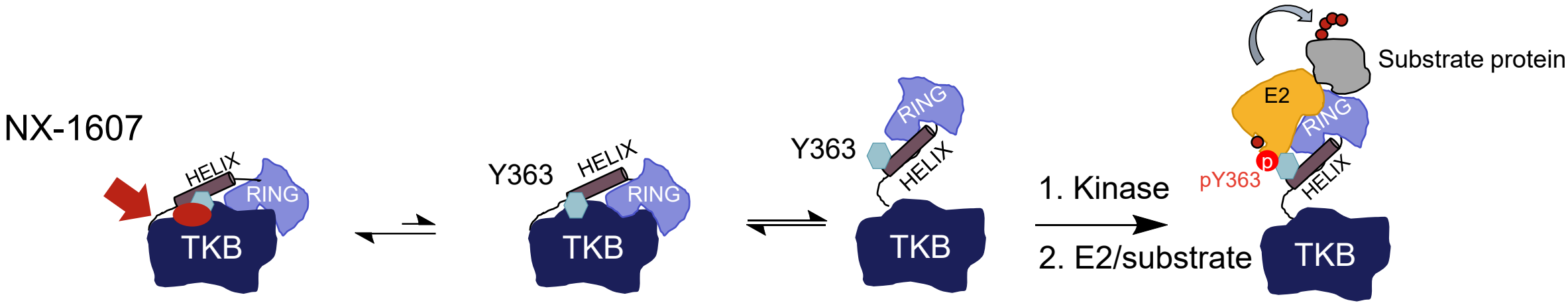
CBL-B mediated mechanisms strongly restrains a productive anti-tumor response

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



NX-1607 Mechanism of Action: Intramolecular Glue



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

Closed State **INACTIVE**

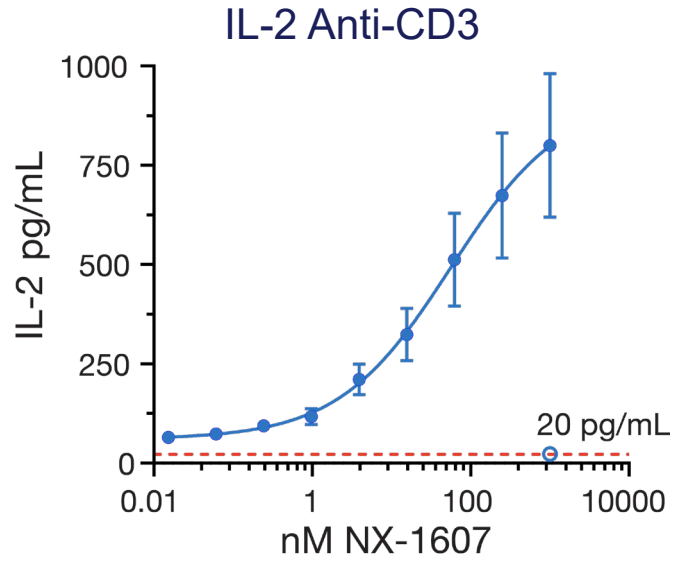
Opened State

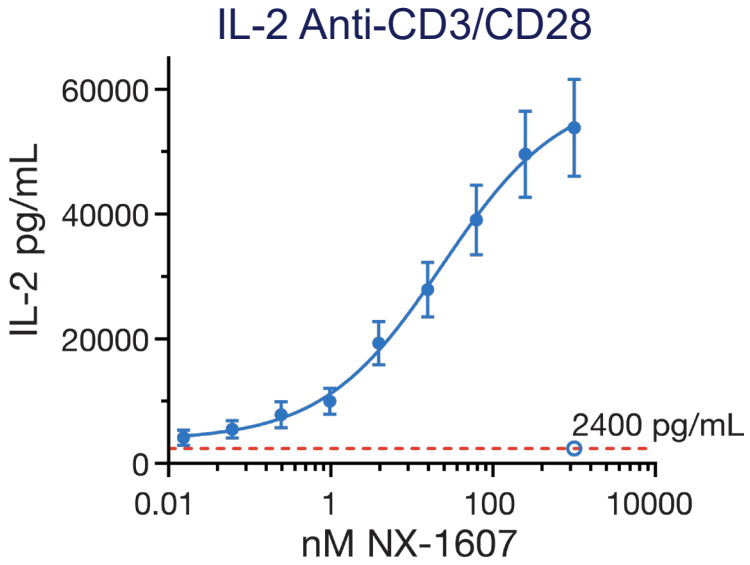
Phosphorylation locks CBL-B in the **ACTIVE** Conformation

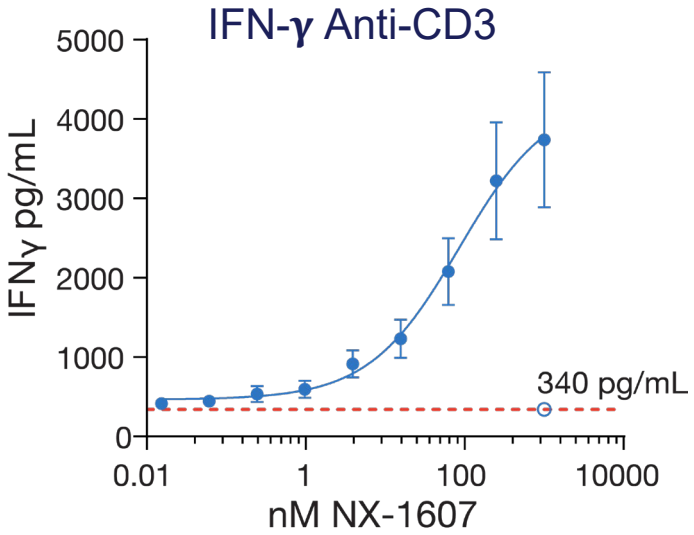
Immune Response

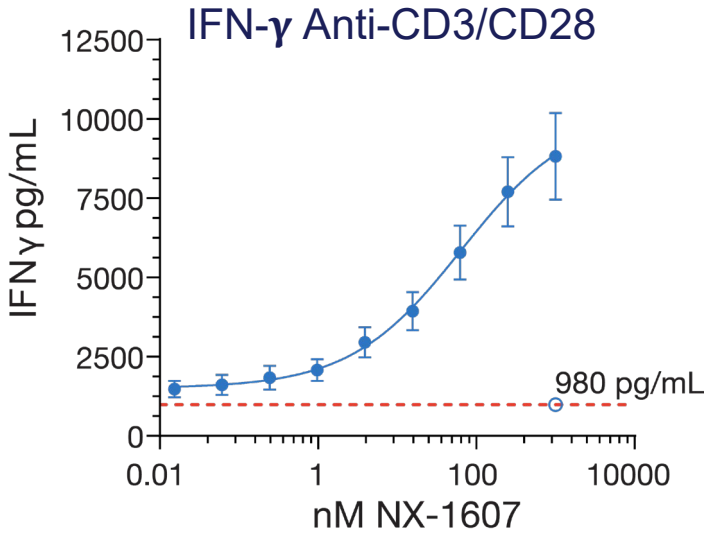
Immune Response

CBL-B Inhibition Increases IL-2 and IFN-γ Secretion in TCR Stimulated Primary Human T cells







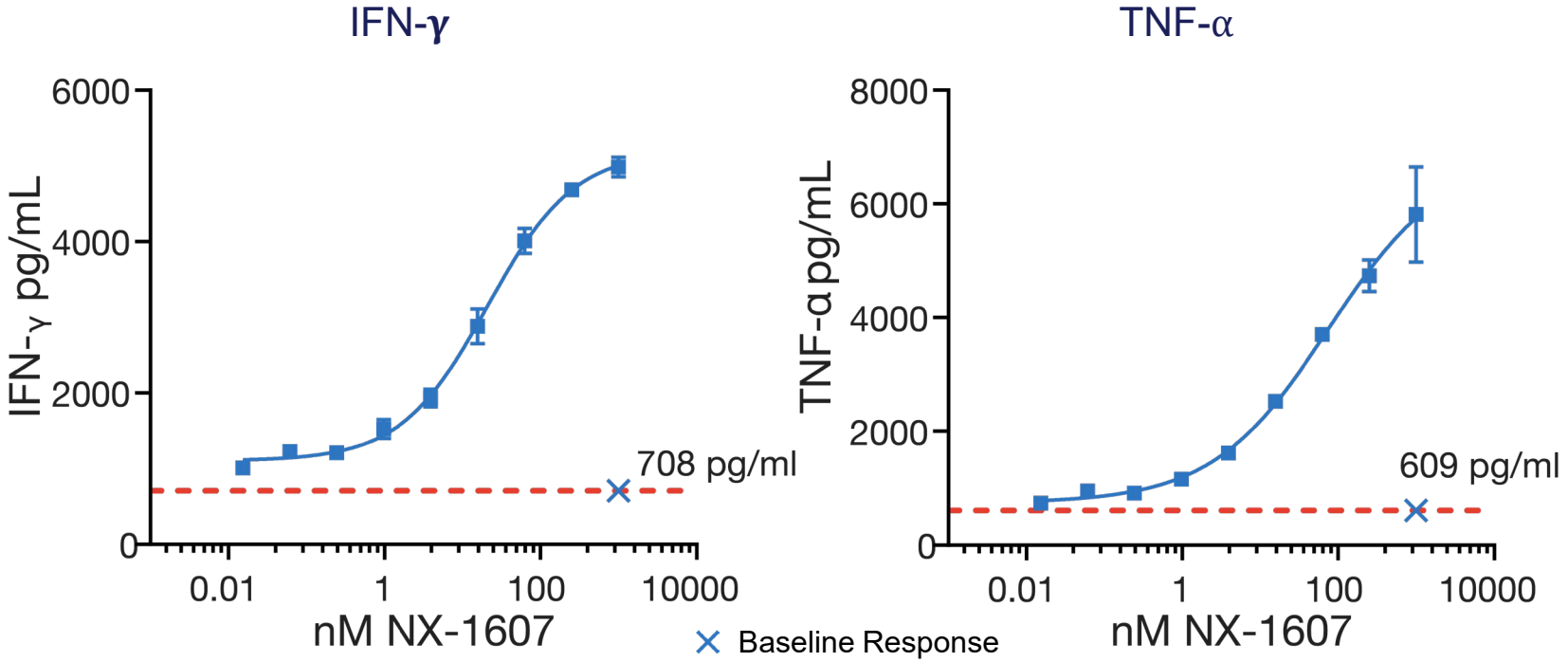


Increases TCR stimulation-dependent production of IL-2 and IFN-γ in primary human T cells

No impact in the absence of T cell stimulation as measured by proliferation, activation, or cytokine release

Cytokine Response
Baseline Response

CBL-B Inhibition Also 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

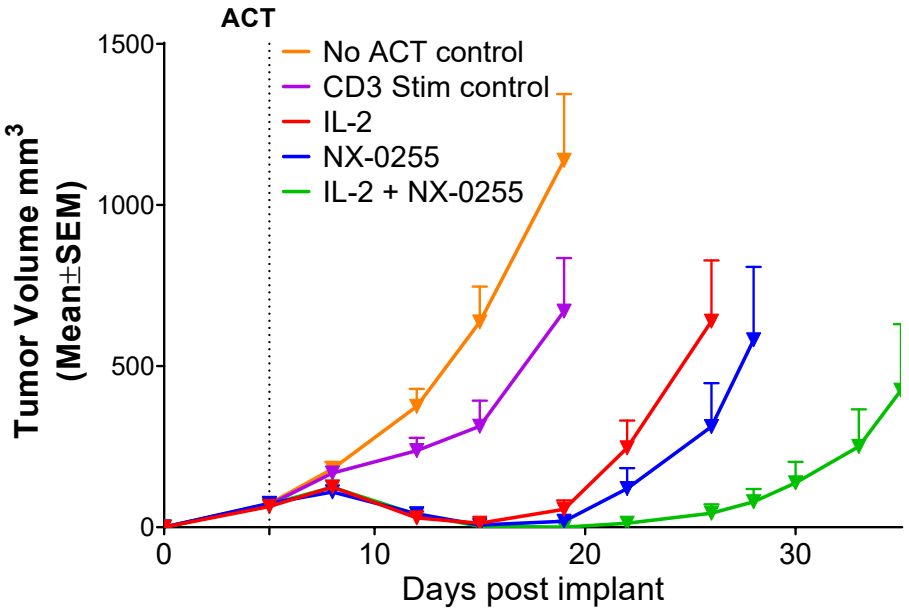
NX-1607 has no impact in the absence of NK cell stimulation (with K562), as measured by cytokine release

NK K562 Killing Assay

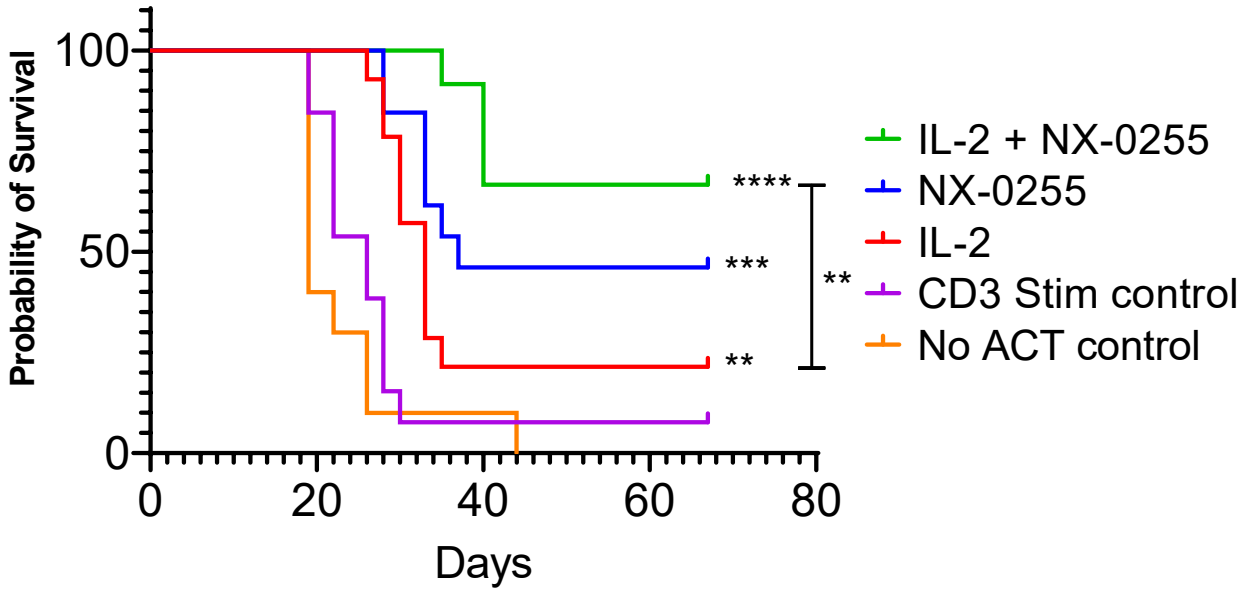
- 1 hour compound pre-treatment prior to addition of K562 target cells
- 6 hour NK/K562 coculture

NX-0255 *ex vivo* Treatment Provides Robust Anti-Tumor Activity in OT-1 Mouse Model of Adoptive T Cell Therapy

Reduction in Tumor Growth in Mouse ACT Tumor Model



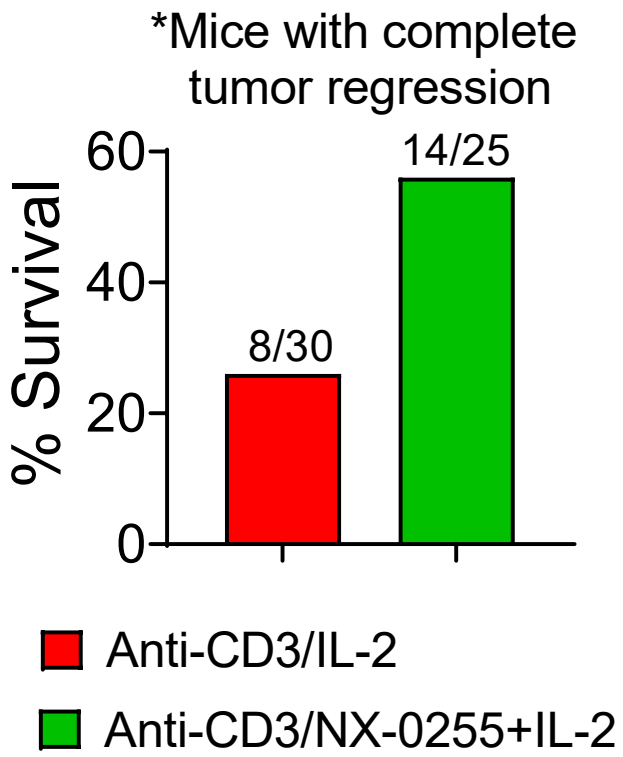
Improvement in Conditional Survival in Mouse ACT Tumor Model



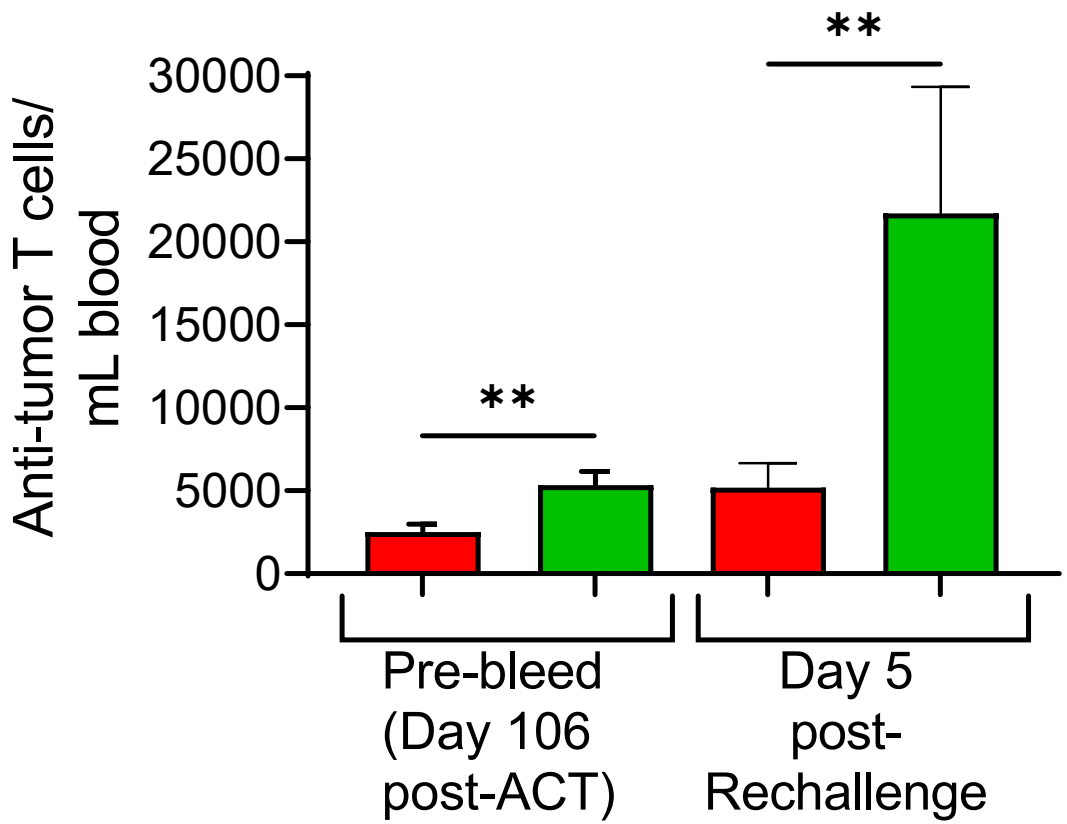
- CD8+ cells exposed to NX-0255 alone *ex vivo* resulted in superior conditional survival compared to using IL-2 alone
- CD8+ cells exposed to NX-0255 and IL-2 combined *ex vivo* exert a deeper anti-tumor response
- NX-0255 *ex vivo* exposure period is only three days, anti-tumor effects persist for over a month after engraftment
- Animals that rejected tumor were rechallenged 80 days post ACT. All animals rejected tumor, demonstrating immunological memory

NX-0255-Treated OT-I Cells Persist at Day 106, Mediating More Rapid Recall Response Following Re-challenge Than IL-2-Alone Treated OT-I Cells

Greater Number of Long-term Surviving Animals

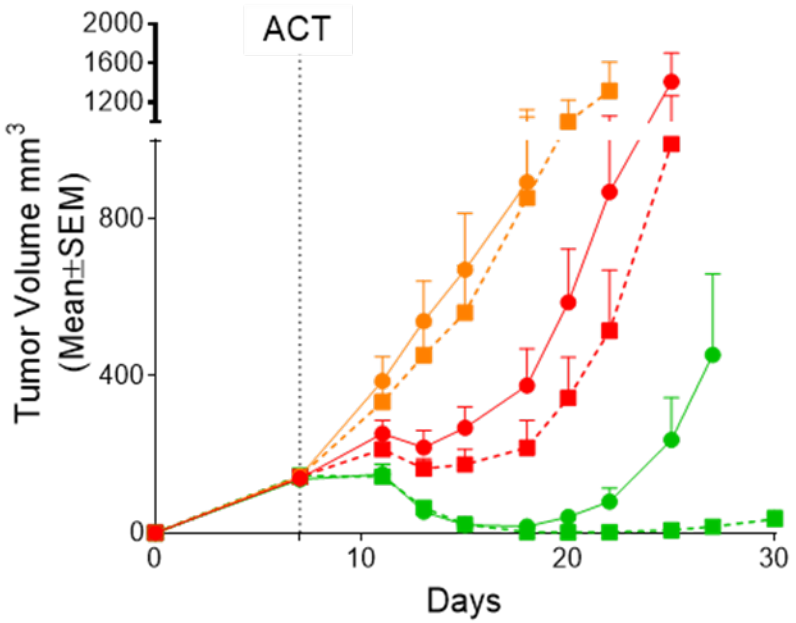


Increased Persistence and More Rapid Response to Re-Challenge

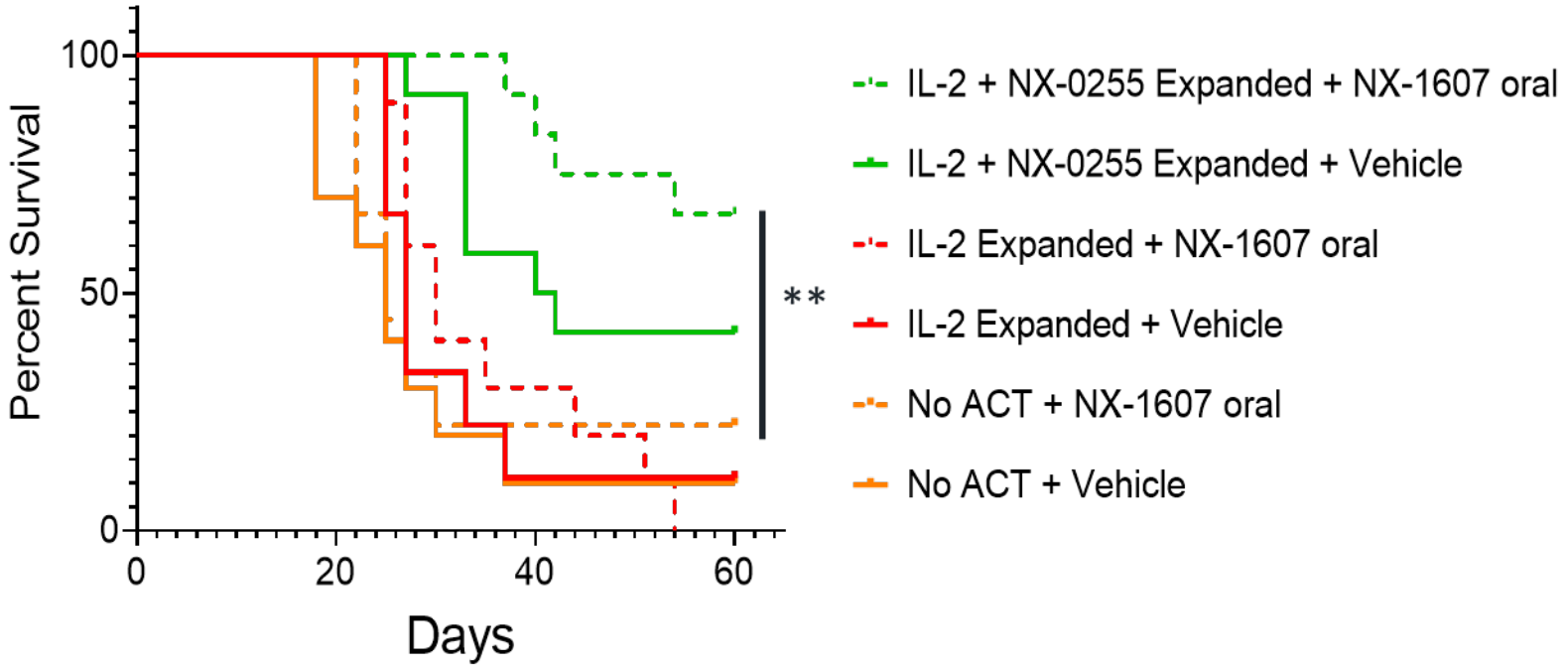


Oral NX-1607 Augments Anti-Tumor Activity Observed with *ex vivo* NX-0255 Combination in ACT Mouse Model

Reduction in Tumor Growth in Mouse ACT Tumor Model



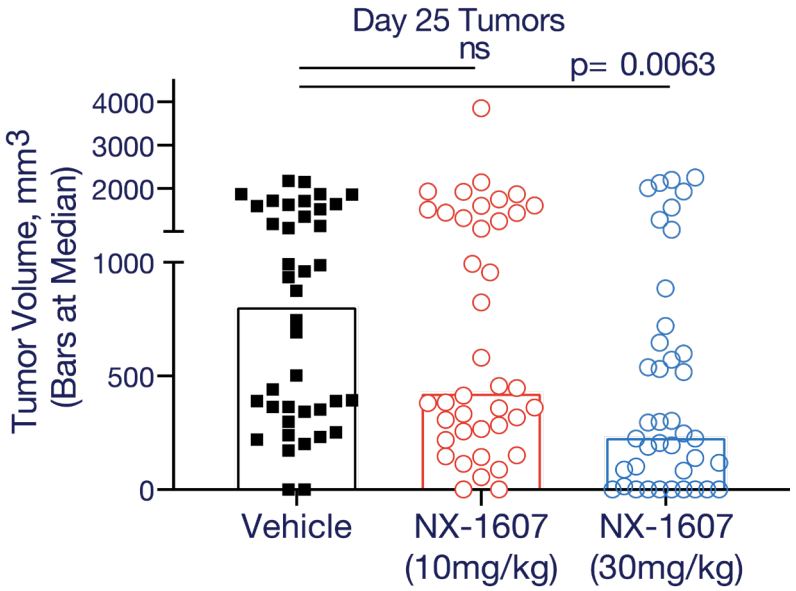
Improvement in Conditional Survival in Mouse ACT Tumor Model



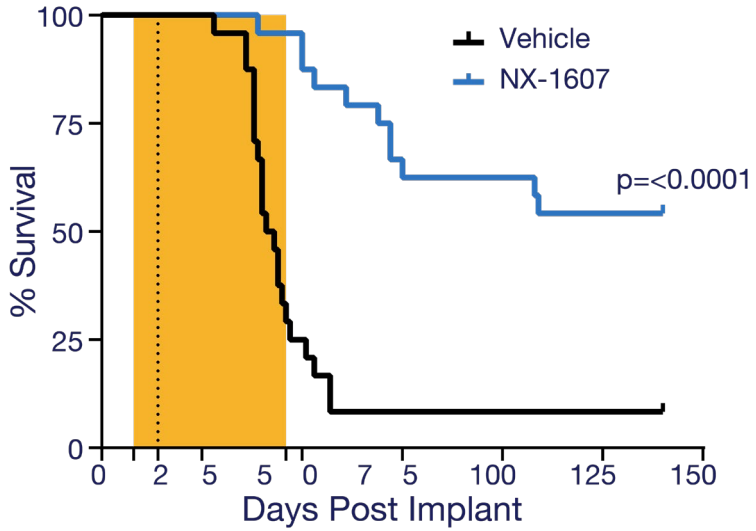
- Oral NX-1607 treatment once daily further enhances conditional survival and anti-tumor activity of T cells expanded for three days with recombinant IL-2 plus NX-0255 *ex vivo* in adoptive cell therapy mouse model

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

NX-1607
Reduced Tumor Volume
Colorectal

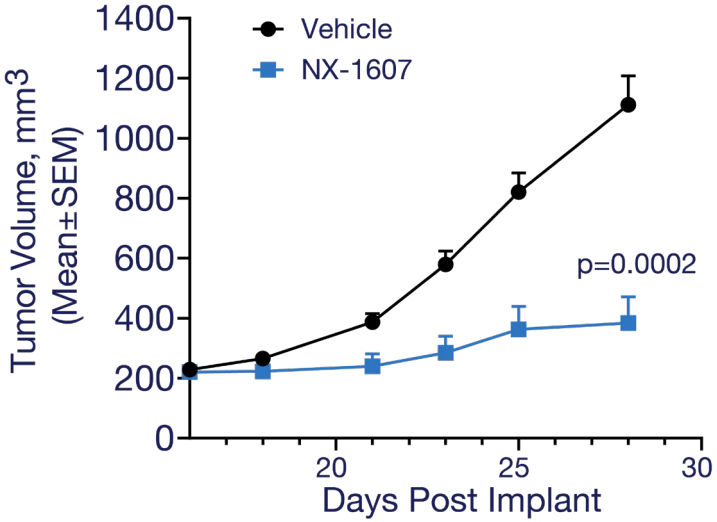


NX-1607
Prolonged Survival
Triple-Negative Breast



NX-1607 30 mg/kg day 7 to 46

NX-1607
Reduced Tumor Volume
B Cell Lymphoma



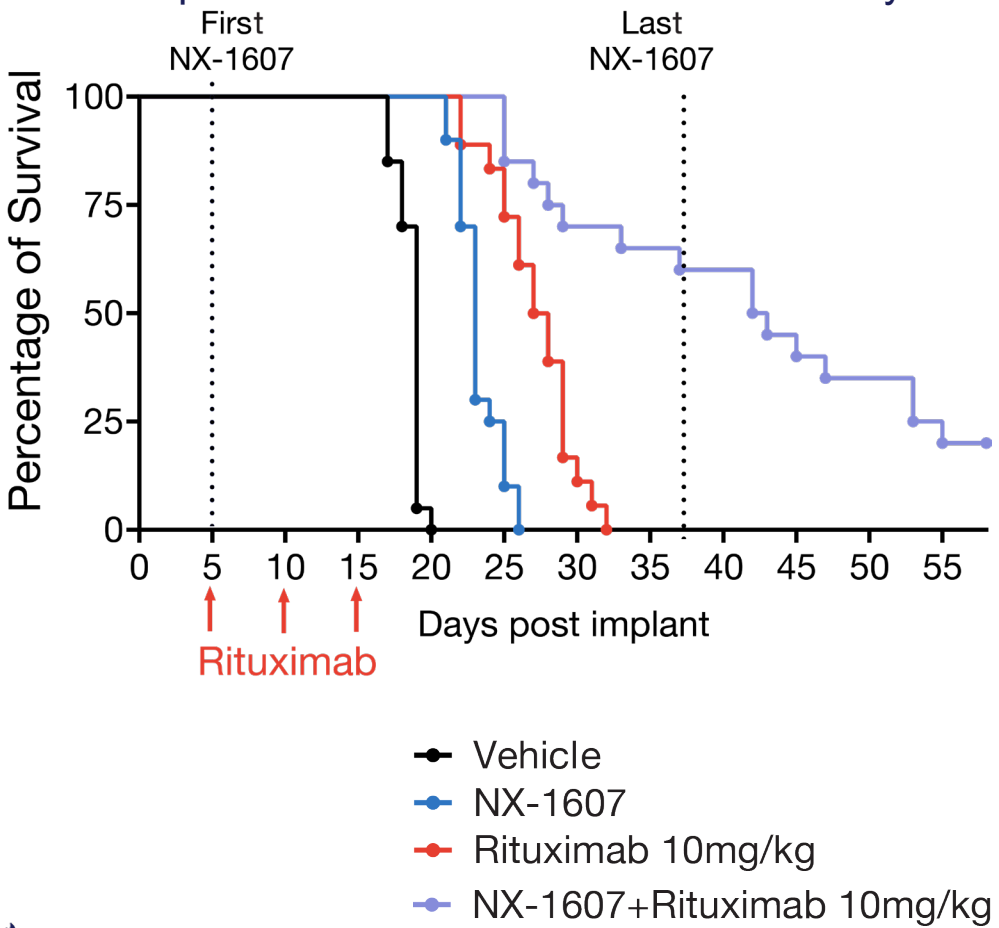
NX-1607 30 mg/kg day 16 to 28

Shaded area indicates dosing period

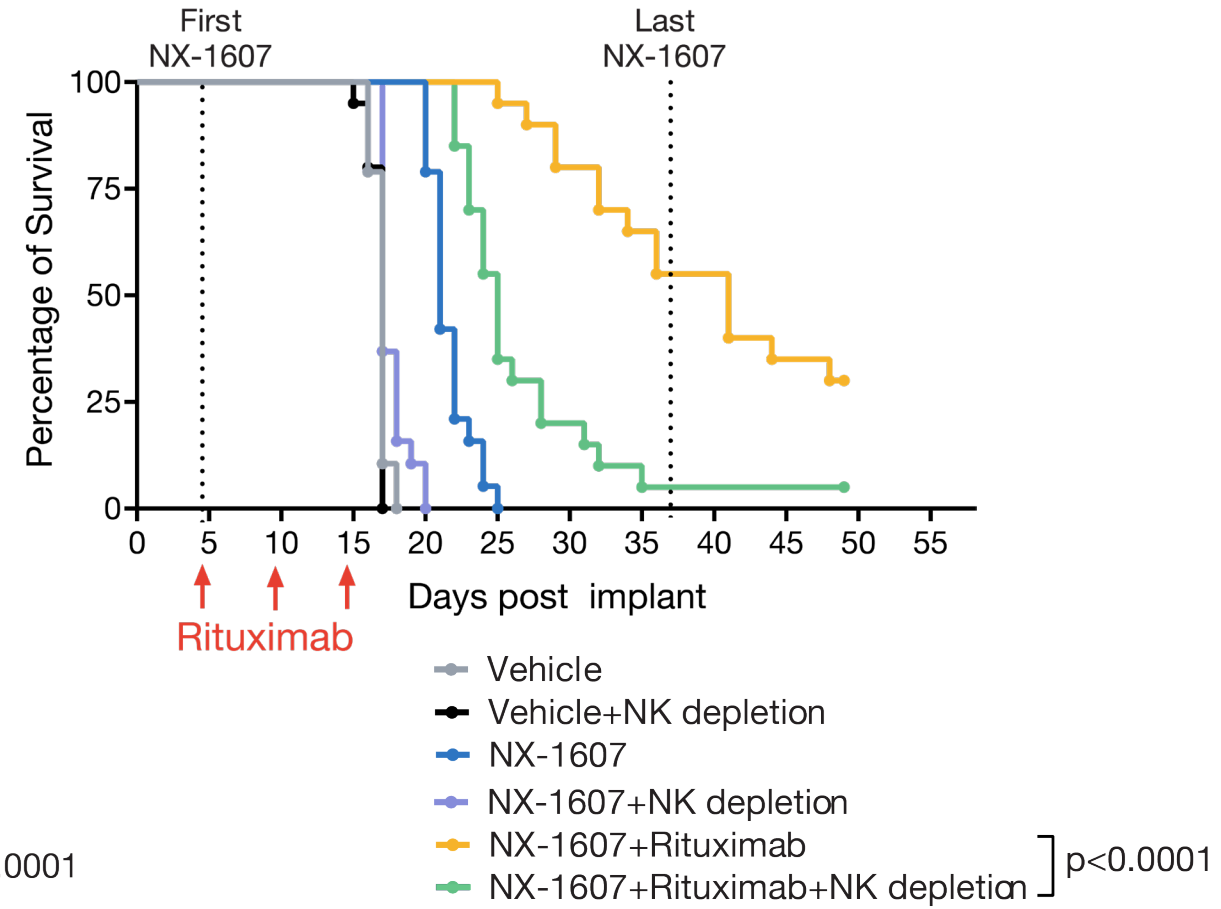
Combination of NX-1607 and Rituximab Enhances Antitumor Activity in a Human NHL Animal Model

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

NX-1607-mediated NK activation potentiates rituximab antitumor activity



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



NX-0255 Enhances Human TIL

Drug-enhanced TIL (DeTIL)

- More effective expansion of potent and stem-like human DeTIL-0255 compared with conventional TIL
- Enhances DeTIL proliferation
- Enhances DeTIL activation
- Limits T cell exhaustion

More Effective Expansion of Potent and Stem-like Human DeTIL-0255 Compared with TIL

Increased Diversity, Cell Number, and Stem-Like Properties

- Decreased exhaustion
- Enhanced effector function
- Increased activation

Whelan *et al* SITC 2021

Exhaustion	
Marker	% of CD8+
Total PD-1+	↓
Total PD-1+ TIM-3+	↓
Total PD-1+ LAG-3+	↓

Tumor Reactivity	
CD8	% of CD8+
Total 41BB+	↑

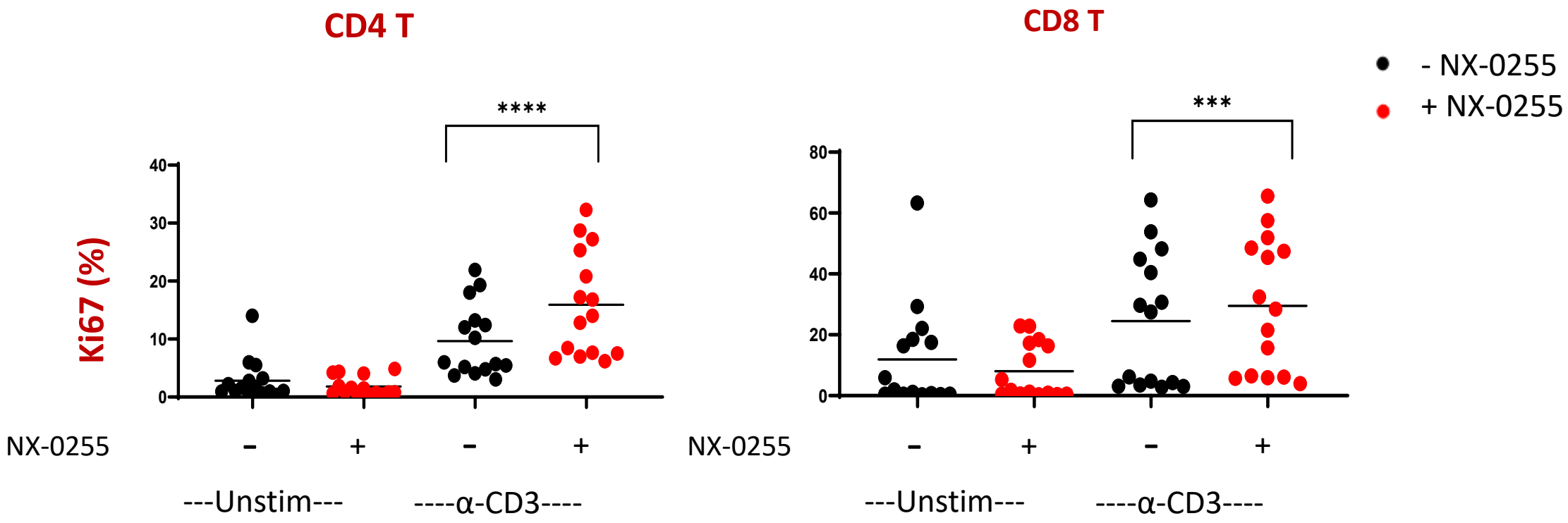
Cytotoxic Function	
Marker	Absolute No. of CD8
CD107a+	↑
GrB+	↑
Perforin+	↑
CD107a+ GrB+	↑
CD107a+ Perforin	↑
GrB+ Perforin	↑
GrB+ Perforin CD107A+	↑

Chemokine Secretion	
Secretion	pg/mL
RANTES	↑
MCP-1	↑
IL-8	↑

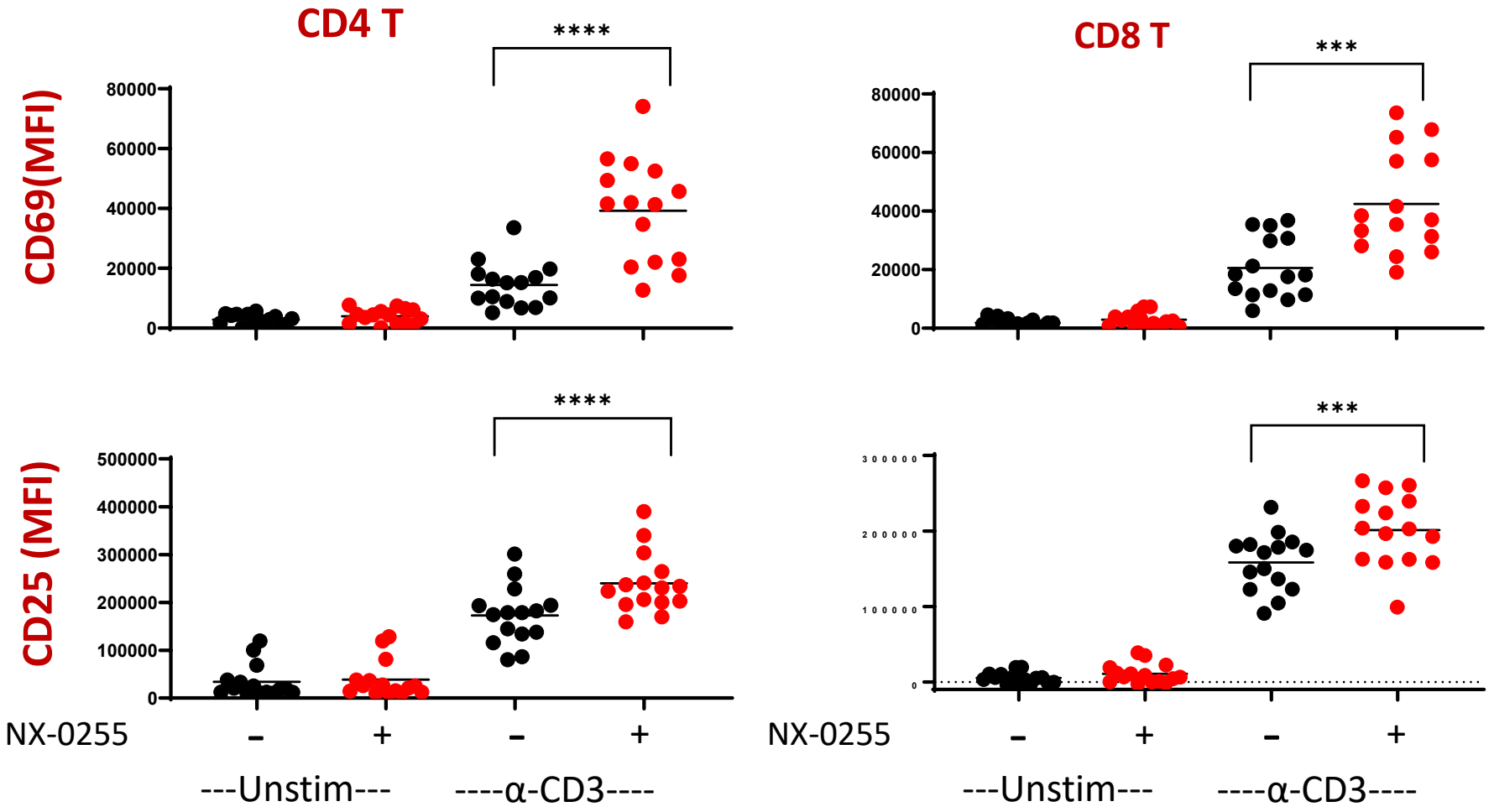
Cytokine Secretion	
Secretion	pg/mL
7 CRS-associated cytokines (IL-2, IL-4, IL-6, IL-9, IL-10, IFN-γ, TNF-α)	—

Arrows indicate a statistically significant ($P<0.05$) change in DeTIL-0255 compared with TIL.

NX-0255 Enhances TIL Proliferation in CD4 and CD8 T Cells Following αCD3 Activation



NX-0255 Enhances TIL Activation (CD69 and CD25) Following αCD3 Activation



- NX-0255
- + NX-0255

Other activation markers that are increased:

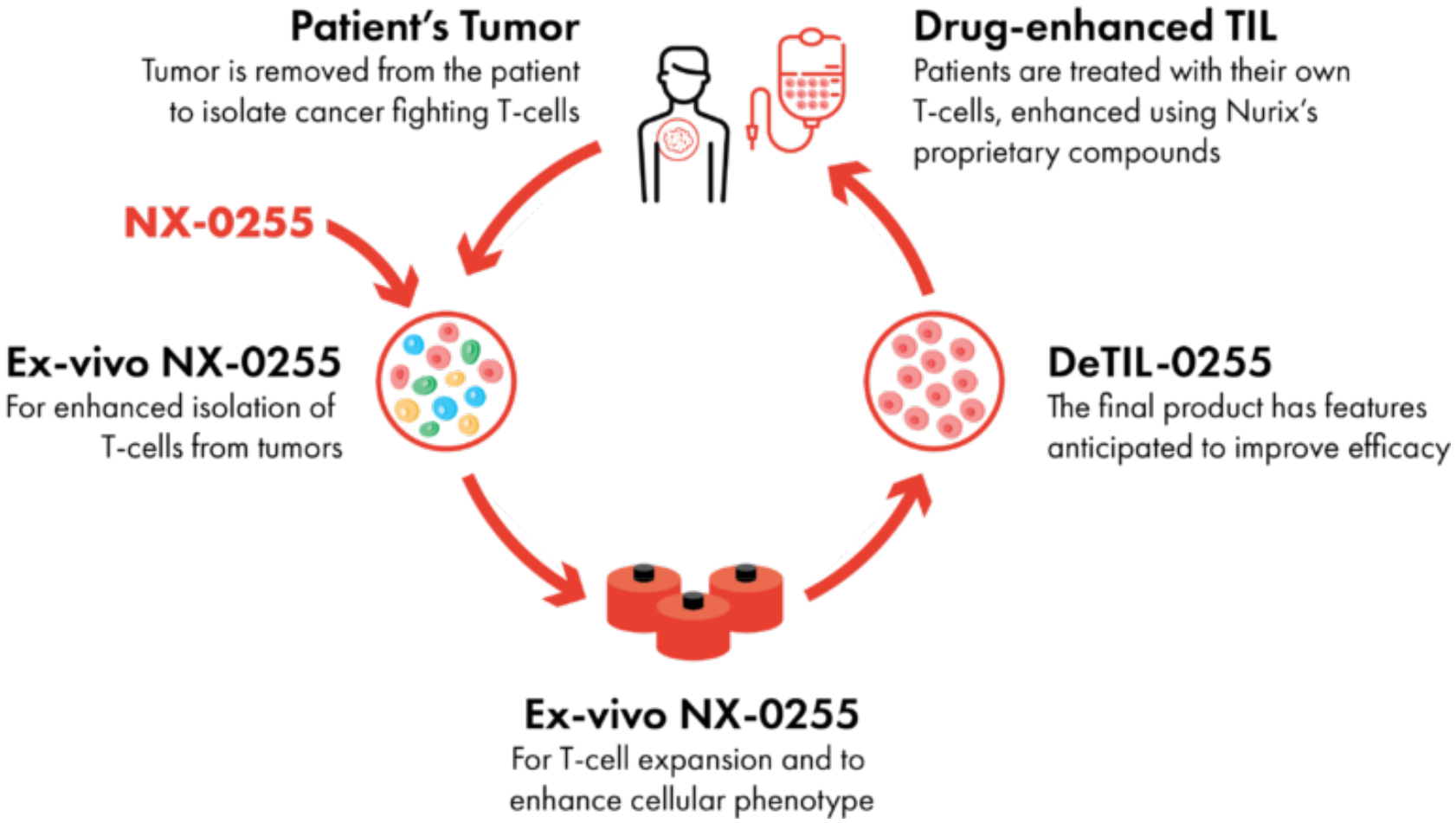
- CD134
- CD137
- CD226

Introduction of DeTIL-0255 into the Clinic

- Drug-enhanced TIL product utilizes our proprietary CBL-B inhibitor in manufacturing
- Cellular therapy with phenotypic and functional properties associated with superior activity in conventional TIL therapies
- Potency assay designed to meet all regulatory requirements with anticipated validation in ongoing clinical trial
- Successfully manufactured DeTIL and have initiated treatment in a safety run-in in patients with gynecologic malignancies

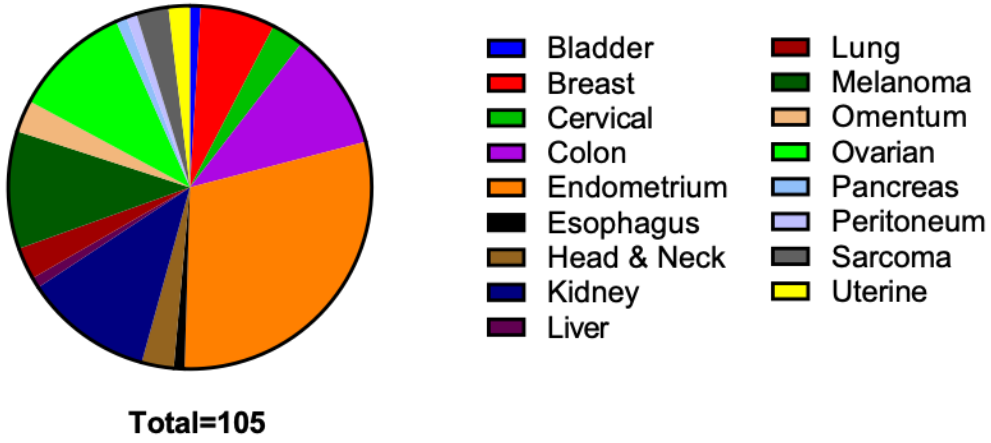
Drug-Enhanced Tumor Infiltrating Lymphocytes (DeTIL-0255)

A one-time patient-derived cell therapy



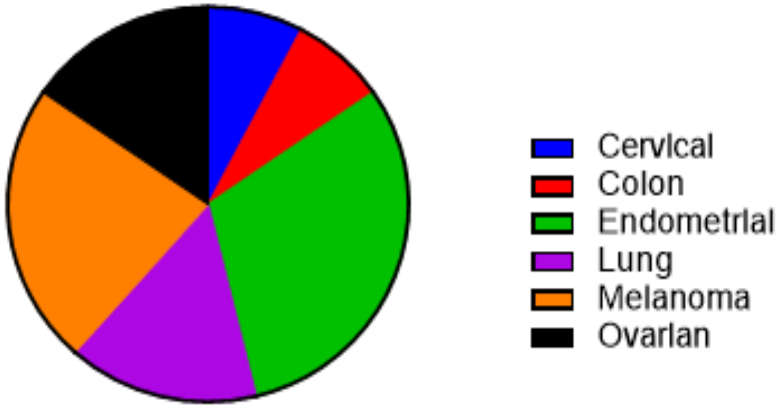
Universal DeTIL-0255 Expansion Allows Application to Multiple Tumor Types

Pilot Runs



Total=105

Full-scale runs



Total=13

All tumors harbor TIL which can be expanded in pilot and full-scale runs

Pilot scale:
T-cell expansion has been demonstrated in 105 tumors

Full-scale:
DeTIL-0255 production has been demonstrated on 13 tumors

DeTIL-0255-201: Phase 1 First-in-Human Clinical Trial Design

Two-Part Phase 1 Monotherapy Trial of DeTIL-0255 in Patients with Relapsed or Refractory Gynecological Cancers

Safety Run in (3-6 patients)

Objectives:
- Assess safety and tolerability
- Assess preliminary efficacy

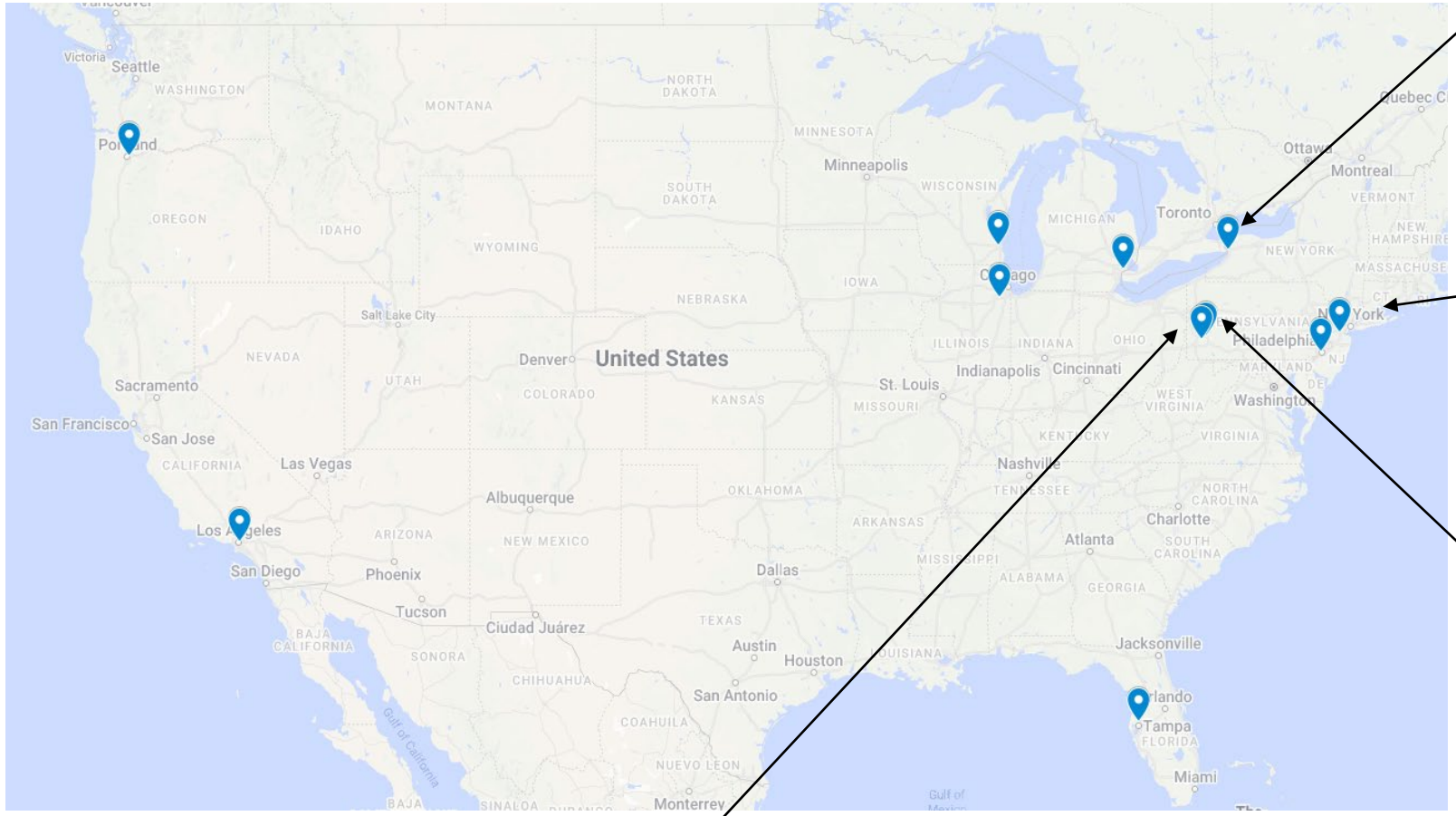
In-hospital treatment (~3 weeks)

Excisional Biopsy → DeTIL production (22 days) → Conditioning chemotherapy (Cy / Flu) → DeTIL infusion 1 x 10^9 cells to 150 x 10^9 cells → IL-2 infusions

Cohort Expansion

- Platinum Resistant Epithelial Ovarian Cancer (~ 18 patients)
- Recurrent, Metastatic or Persistent Cervical Cancer (~ 18 patients)
- Advanced or Recurrent Endometrial Cancer (~ 18 patients)

Clinical Sites for DeTIL-0255



ROSWELL PARK
COMPREHENSIVE CANCER CENTER

RUTGERS
Cancer Institute of New Jersey
RUTGERS HEALTH
NCI Designated Comprehensive Cancer Center

AHN Cancer Institute – Allegheny General

UPMC | HILLMAN CANCER CENTER

Conclusions:

CBL-B inhibitors promotes T cell antitumor response and enhances cell therapy

- Promotes major antitumor effects in murine models of TCR antitumor transgenic T cells
- Enhances multipotent T cell effector function with enhanced stem-like properties
- Increases potency in *in vitro* studies
- Promotes and activates NK, NKT, and T cells
- Enhances expansion of T cells