Nurix Therapeutics

Blazing a New Path in Medicine

Investor Presentation

April 2022

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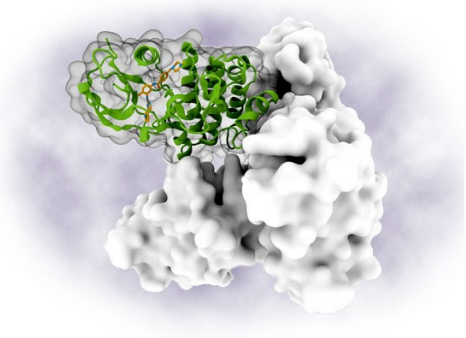
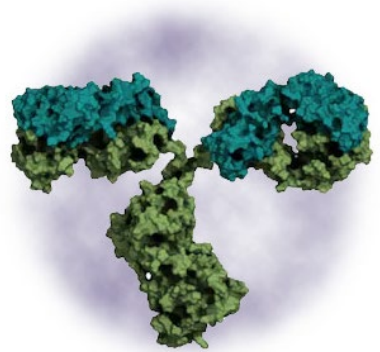
Working to Create a New Category of Medicine

Evolution of new therapeutic modalities

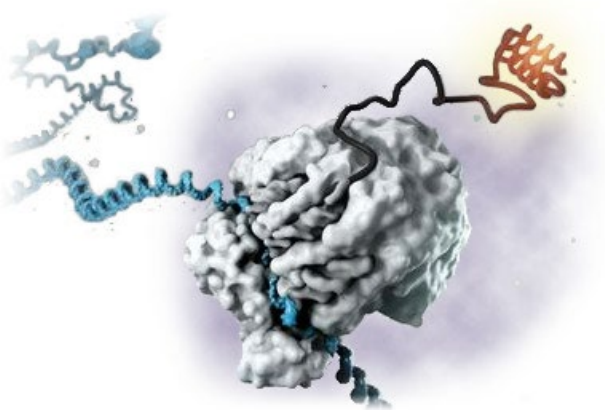


Small Molecule Inhibitors

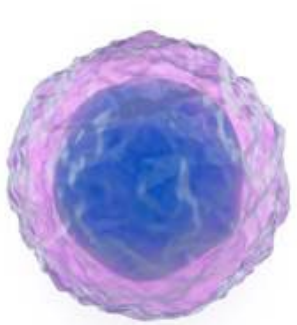


Antibodies

Therapeutic Proteins

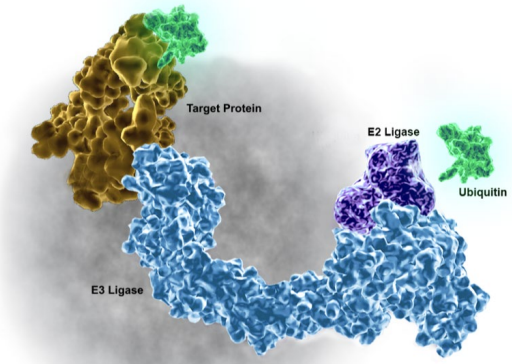


Nucleic Acid-Based Therapies:
Antisense, RNAi
Gene Therapy
CRISPR



Adoptive Cell Therapy

DeTIL

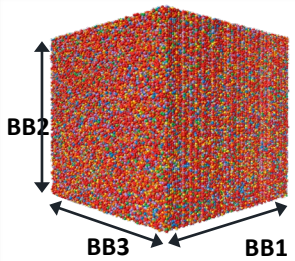


Nurix Protein Modulation Drugs to *Increase* or *Decrease* Specific Protein Levels

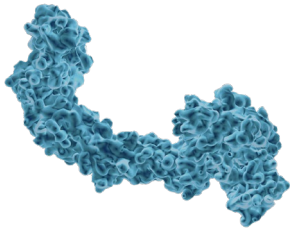
Nurix's DELigase Platform: Leading the Industry in DNA-Encoded Libraries for Targeted Protein Modulation

- DELigase™ is a versatile drug discovery platform comprised of massive DNA-encoded libraries (DEL) now containing over 5 billion compounds
- Nurix can rapidly screen an expanded universe of E3 ligases and proteins previously thought to be undruggable
- Nurix can modulate specific protein levels up or down with its drug discovery platform

DELigase Protein Modulation Platform



Proprietary DNA-Encoded Libraries, > $5x10^9$ compounds



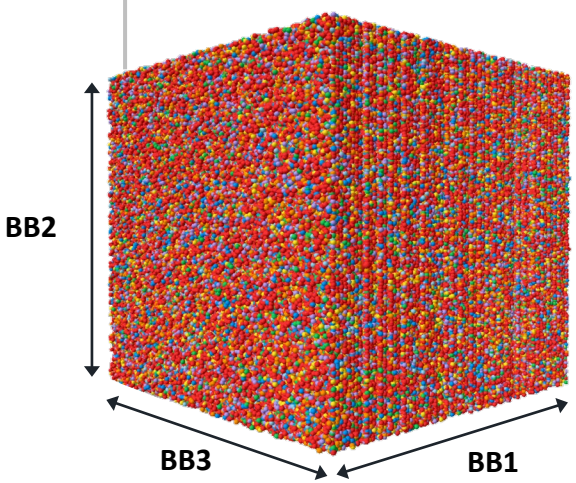
>30 E3 ligases currently in discovery

Chimeric Targeting Molecules (CTMs) ***Decrease*** **specific protein levels**

Ligase Inhibitors ***Increase*** **specific protein levels**

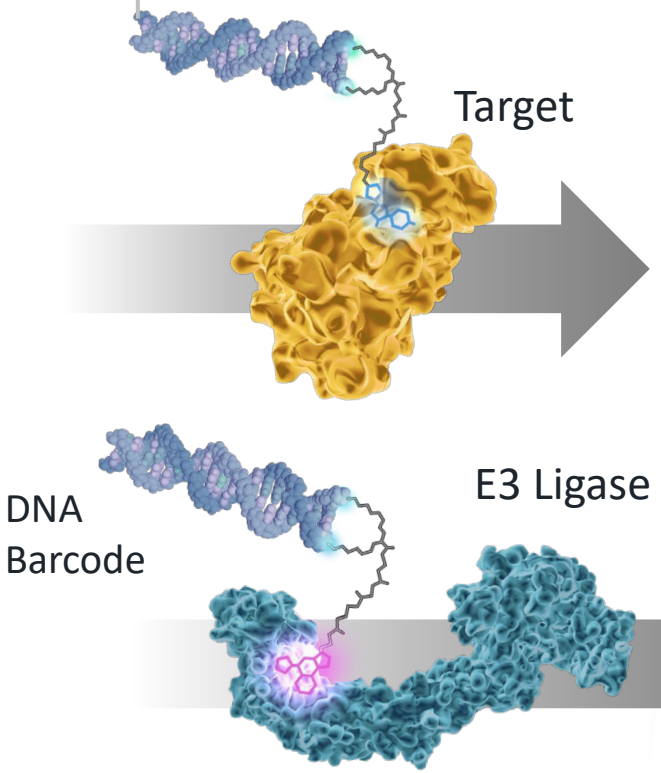
DELigase® Enables Efficient Chimeric Targeting Molecule Discovery and Design

1 Billions of proprietary DNA-Encoded Library (DEL) compounds

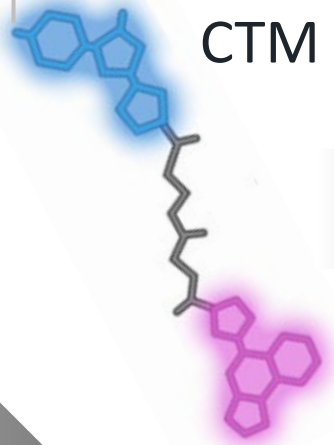


BB = Chemical Building Blocks

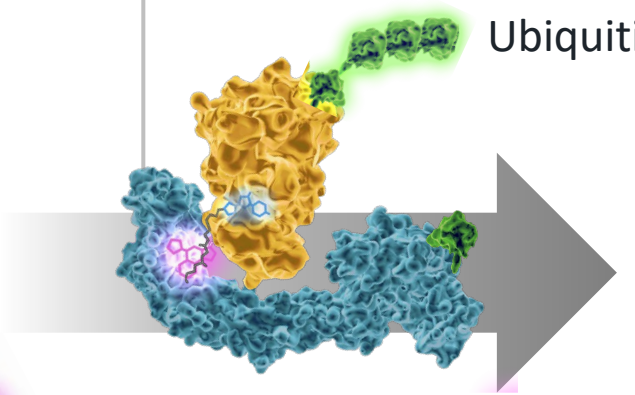
2 Target proteins and E3 ligases are screened using DEL



3 Binders from DEL are joined via a linker to construct CTMs



4 CTM recruits E3 ligase to target protein, triggering ubiquitin transfer and degradation



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

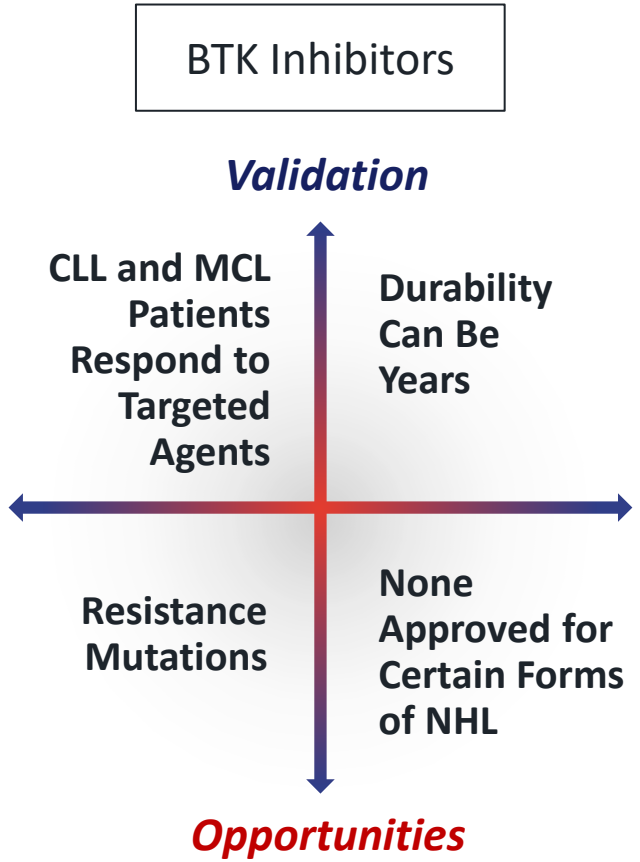
Drug Program	Target / Delivery	Therapeutic Area	Discovery	IND enabling	Phase 1	Phase 2	Phase 3
NX-2127 Degrader	BTK + IKZF *Oral*	B-cell Malignancies					
NX-5948 Degrader	BTK *Oral*	B-cell Malignancies and Autoimmune Diseases					
NX-1607 Inhibitor	CBL-B *Oral*	Immuno-oncology					
DeTIL-0255 Cell therapy	Adopted cell therapy with *Ex vivo CBL-B inhibition*	Gynecologic malignancies					
Discovery pipeline							
Wholly owned	Degraders and inhibitors of multiple targets including E3 ligases, T cell kinase, hematology & oncology drivers, and viral proteins						
Gilead Sciences	5 targets						
Sanofi	5 targets						

Nurix's BTK Degrader Portfolio: A Differentiated Approach to B-Cell Malignancies

- **BTK is standard of care target however mutational escape represents a major unmet need**
  - BTK inhibitors are approved for CLL/SLL, mantle cell lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, with 2021 sales of approximately $8.4 billion
  - Next generation BTK inhibitors continue to be susceptible to mutational escape
- **Opportunities to meet unmet need with BTK degraders differentiated action**
  - Catalytic nature of targeted protein degraders provide a new MOA with fundamentally different PK/PD from inhibitors and demonstrated ability to overcome resistance mutations
  - Unique dual activity: NX-2127 combines the activities of BTK degradation and immunomodulation which may be beneficial across a range of hematologic malignancies

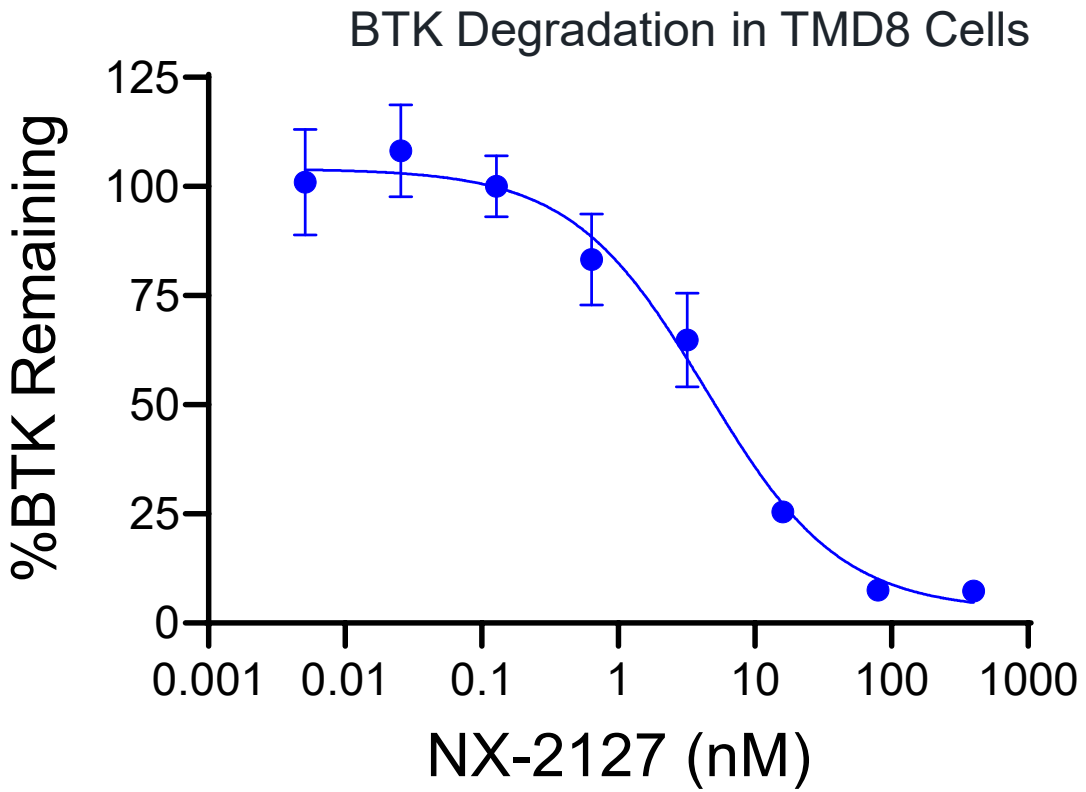
NX-2127: BTK + IKZF degrader. Developing across multiple B-cell malignancies (CLL, MCL, WM, MZL, DLBCL, FL)

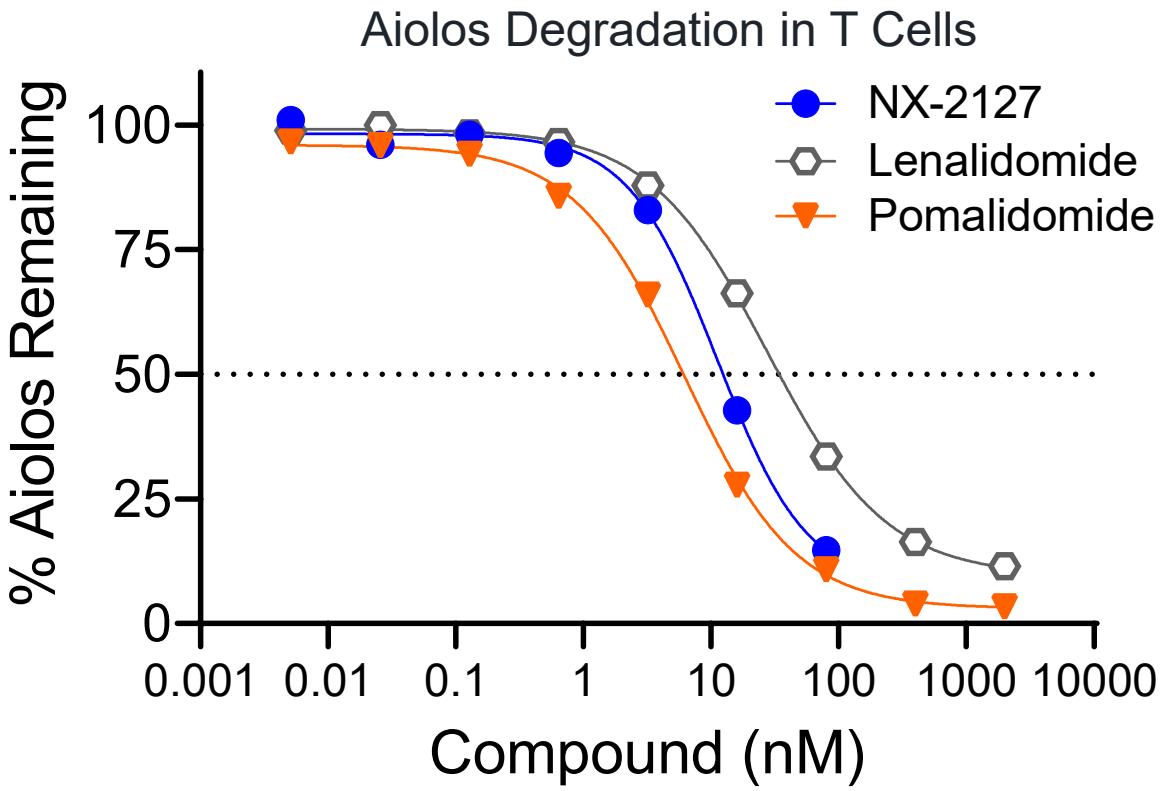
NX-5948: BTK degrader. Developing for targeted B-cell malignancies and autoimmune diseases



BTK, Bruton tyrosine kinase; IKZF, Ikaros zinc finger transcription factor ; DLBCL, Diffuse large B cell lymphoma; CLL, Chronic lymphocytic leukemia, SLL, small lymphocytic lymphoma; MCL, Mantle cell lymphoma; WM, Waldenstrom's macroglobulinemia; MZL, Marginal zone lymphoma; FL, Follicular lymphoma; NHL, non-Hodgkin lymphoma

NX-2127 Degrades Both BTK and Cereblon Neo-Substrates

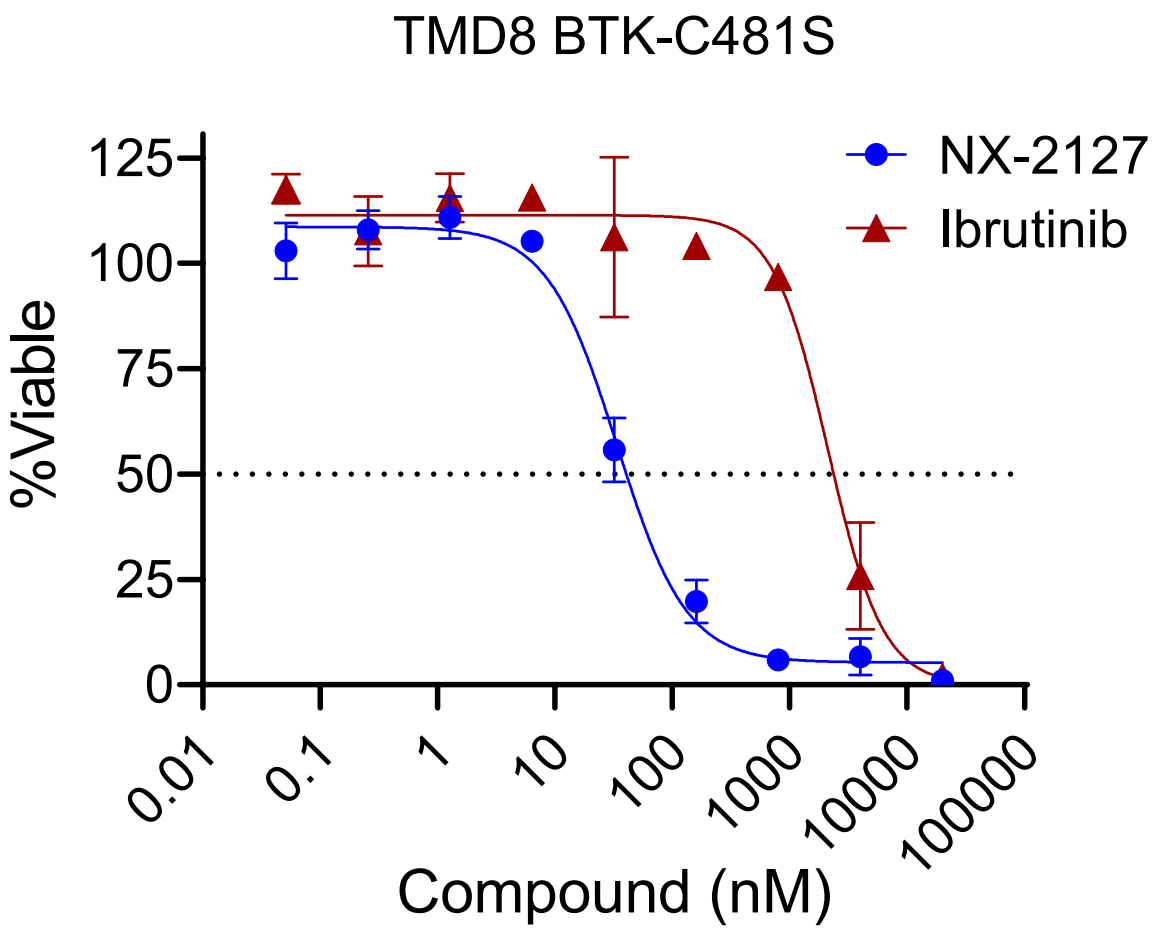




NX-2127 shows potent BTK degradation in TMD8 cells (human DLBCL cell line)

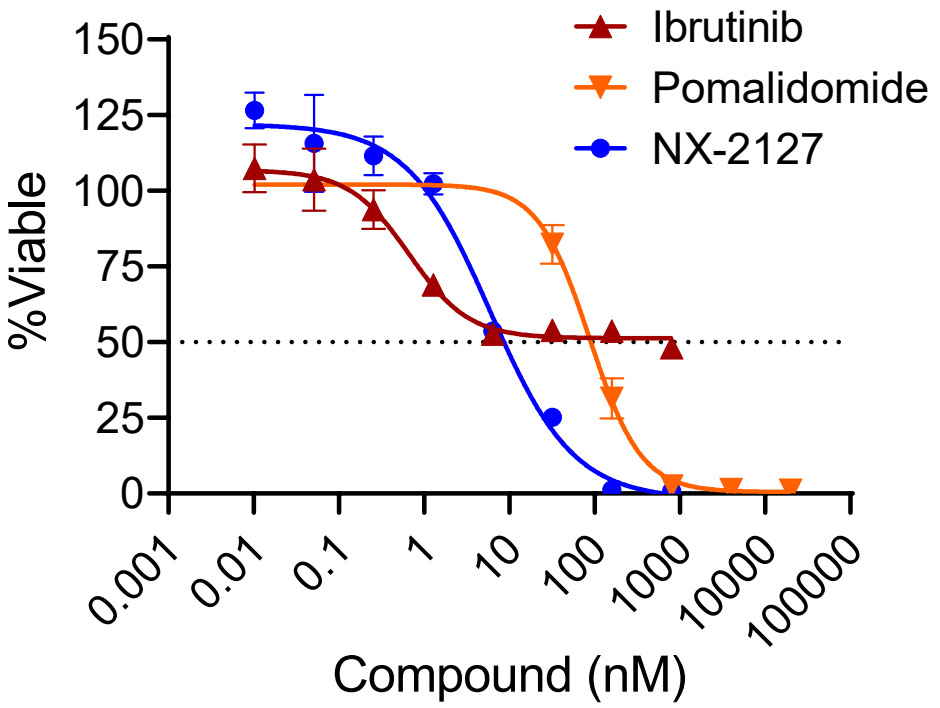
NX-2127 degradation of Aiolos in human T cells occurs at a similar potency to lenalidomide and pomalidomide

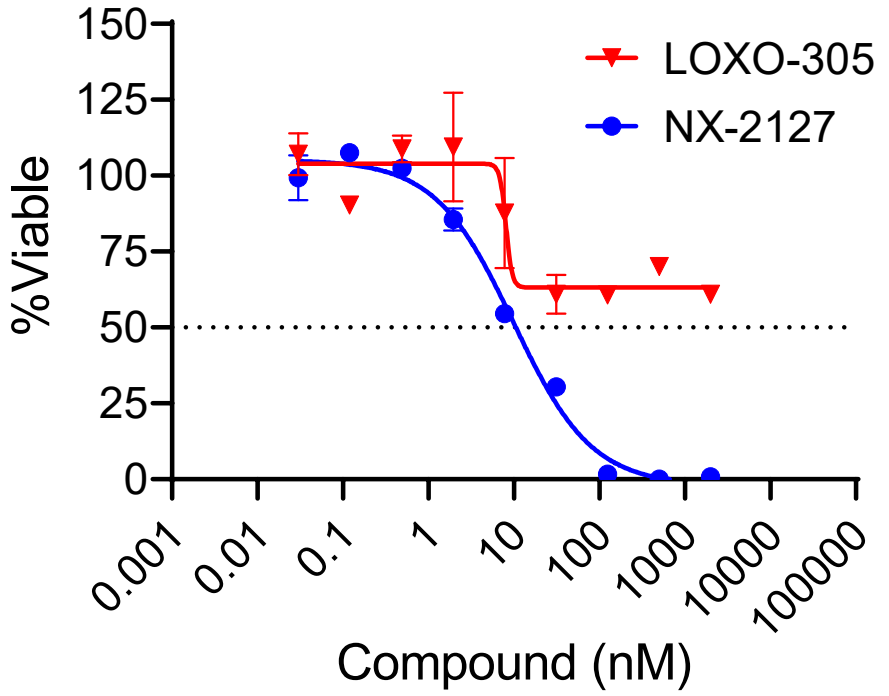
NX-2127 Potently Inhibits Growth of Ibrutinib-Resistant Tumor Cell Lines



- NX-2127 retains potent growth inhibition relative to BTK inhibitors in a tumor cell line carrying the C481S mutation
- Degradation of BTK with NX-2127 may offer a therapeutic option for patients who develop resistance to BTK inhibitors
- NX-2127 also shows superior activity to BTK inhibitors in wild-type TMD8 cells

The Advantage of Immunomodulatory Activity Plus BTK Degradation in Mantle Cell Lymphoma Cells: Complete Cell Killing by NX-2127

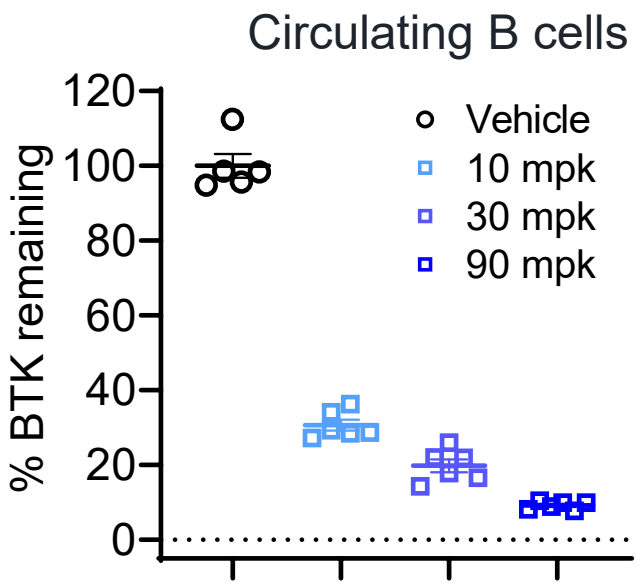


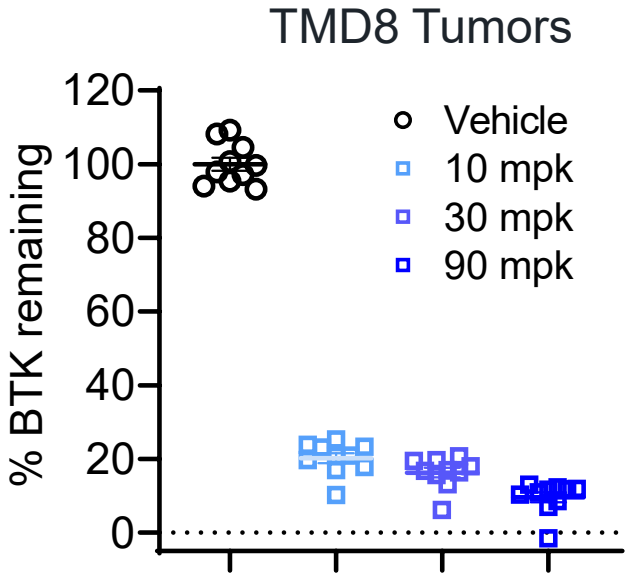


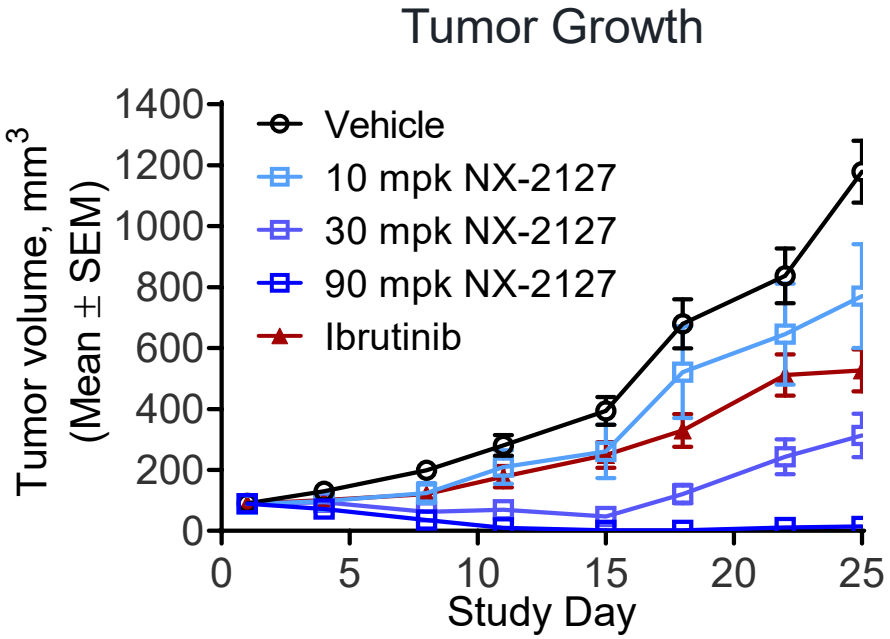
- Compounds active against BTK reduce cell viability at low doses, but this effect plateaus
- Pomalidomide promotes more complete killing but require higher doses to reduce cell viability
- BTK and IKZF1/3 degradation by NX-2127 allow it to potently and completely kill REC-1 cells

- The next generation non-covalent BTK inhibitor, pirtobrutinib, has an activity curve similar to other BTK inhibitors
- NX-2127 shows similar potency and greater depth of cell killing compared to pirtobrutinib

Increasing BTK Degradation Correlates with Significant Tumor Growth Inhibition





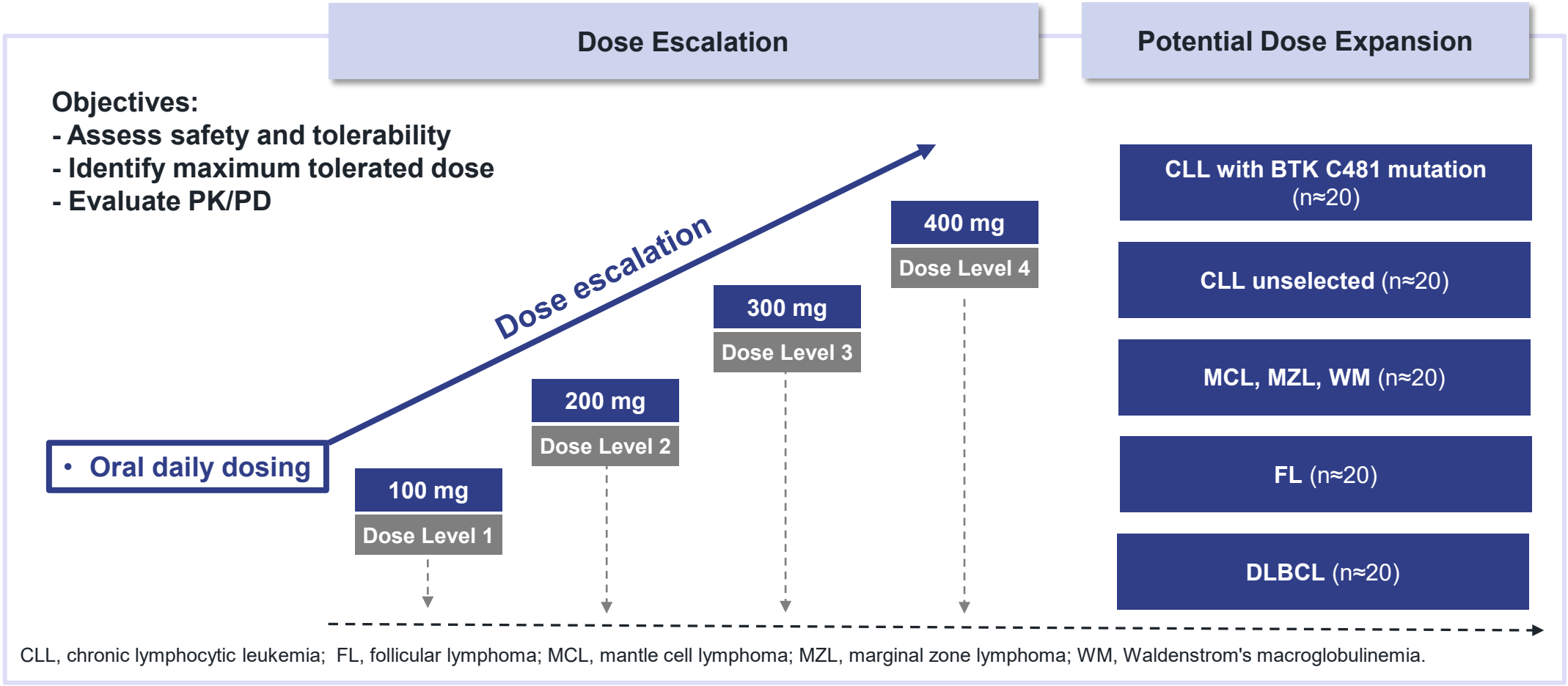


Treatment	Oral gavage dose (mg/kg)	% BTK degradation in circulating B cells	% BTK degradation in TMD8 tumor tissue	% TGI vs Vehicle (Day 24)	*P* value vs Vehicle
Vehicle	0	0.0±3.2	0.0±1.8	N/A	0
NX-2127	10	69.3±1.5	79.8±1.4	58%	0.0492
	30	80.2±1.8	83.7±1.3	74%	<0.0001
	90	90.8±0.4	90.4±1.4	100%	<0.0001
Ibrutinib	30	N/A	N/A	62%	0.0004

N/A: Not applicable; TGI: tumor growth inhibition.

NX-2127-001: Phase 1 First-in-Human Clinical Trial Design

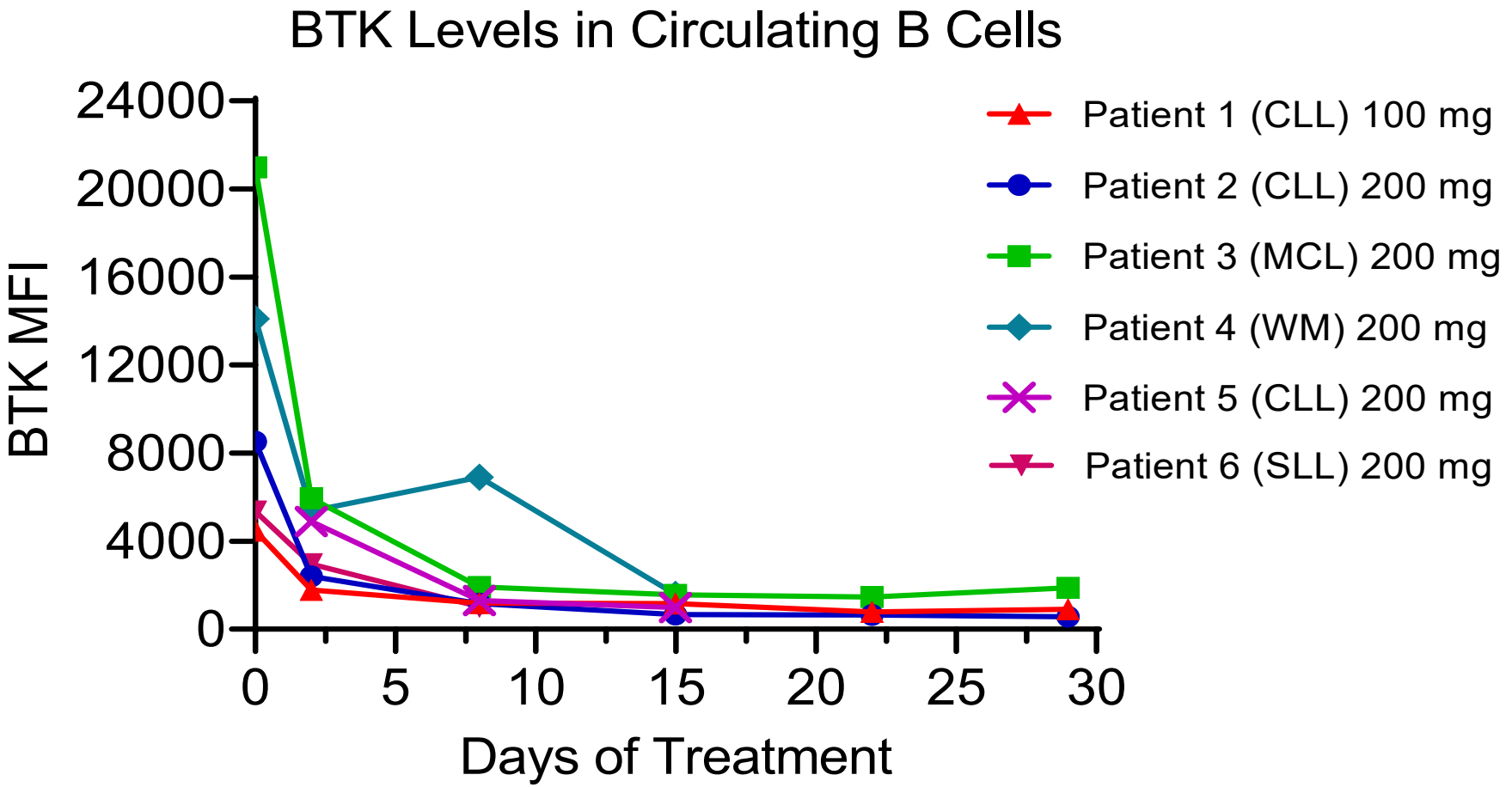
Two-Part Phase 1 Monotherapy Trial of NX-2127 in Relapsed or Refractory B-Cell Malignancies



CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenstrom's macroglobulinemia.

Robust BTK Degradation Observed in All Patients Dosed Regardless of Baseline BTK Protein Levels

- Oral daily treatment of NX-2127 induced a rapid and significant decrease in BTK levels that was sustained throughout dosing
- Patients have varying levels of BTK in B cells at the start of treatment



MFI: geometric mean fluorescence intensity in circulating CD19+ B cells.

BTK Degradation Table of Enrolled Patients

Dose	Patient	% BTK Degraded							
		Baseline	Day 2	Day 8	Day 15	Day 22	Day 29	**Average Steady State***	Day 56
100 mg	Patient 1 (CLL)	0	62.8	76.9	78.0	85.5	82.0	**81.8**	81.4
200 mg	Patient 2 (CLL)	0	75.1	90.5	96.1	95.4	96.1	**95.9**	96.0
	Patient 3 (MCL)	0	74.0	92.7	94.6	95.4	92.3	**94.1**	94.7
	Patient 4 (WM)	0	63.6	56.8	91.5			**91.5**	
	Patient 5 (CLL)	N/A	✓	✓	✓				
	Patient 6 (SLL)	0	6.9	85.1					

Cohort 2, Patient 4: Last dose given on Cycle 1 Day 15, discontinued due to disease progression
Cohort 2, Patient 5: Baseline sample was not collected due to inclement weather (Hurricane Ida), thus % degradation could not be calculated.
*Average steady state is calculated with available % BTK degraded values from Day 15, Day 22 and Day 29

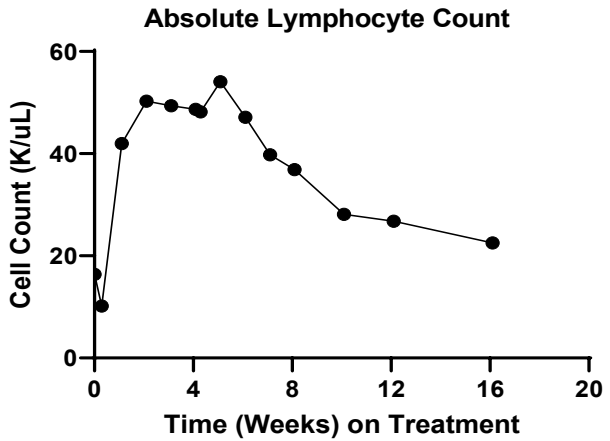
Clinical Response Observed in Patient 1

Patient History:
78-year-old male with stage IV CLL

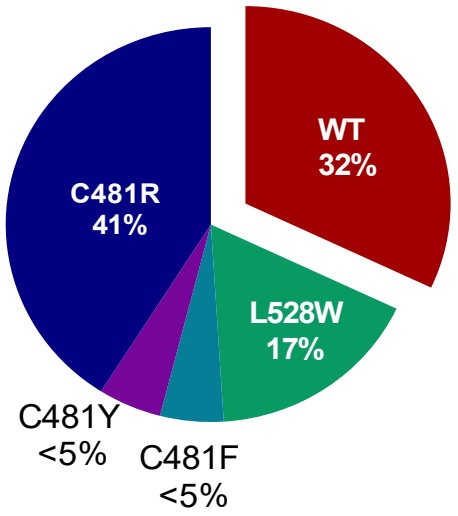
Prior Treatments:
1. Rituximab, 2015
2. Ibrutinib, 2015-2021

Disease at Study Entry:
Bone Marrow Involvement: 85.4%
Spleen: Enlarged (15.7 cm)
Nodal Lesions: Several, largest 4.2 cm
Multiple resistance mutations

Safety	
Exposure	No dose interruptions or modifications
DLT's	None
SAE's	None
Grade 3 or > AE	Neutropenia (ANC = 860), resolved without intervention



Up to 68% of Leukemia Cells with BTK Mutations

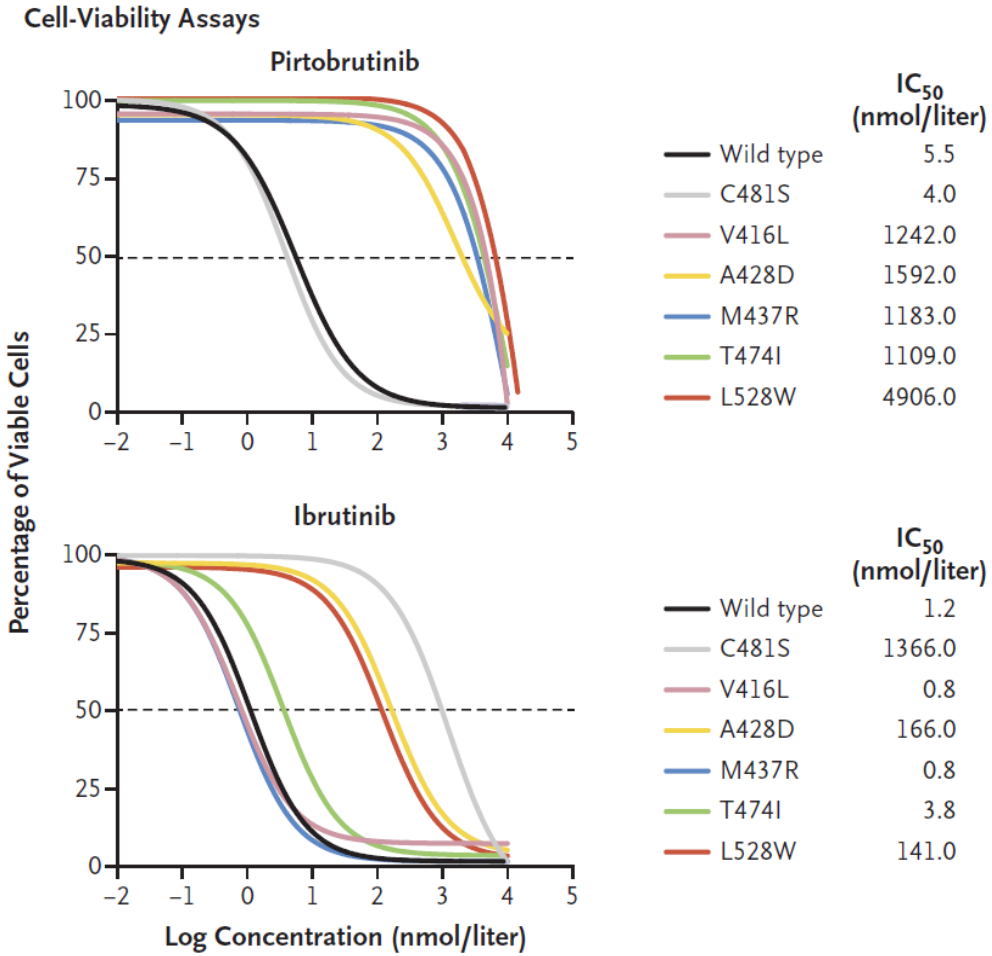


Disease Assessment

Time Point	Hgb (g/dL)	Plt (K/uL)	ALC (K/uL)	Spleen (cm)	Spleen % change[a]	Lymph Node SPD (cm^2)	Nodal SPD % Change	Response[b]
Baseline	14.3	112	16.4	15.7	---	27.1	---	----
Week 8	13.2	133	36.9	14.8	-33%	13.4	-51%	Stable Disease[c]
Week 16	14.1	114	22.5	14.2	-56%	10.8	-60%	Partial remission with lymphocytosis

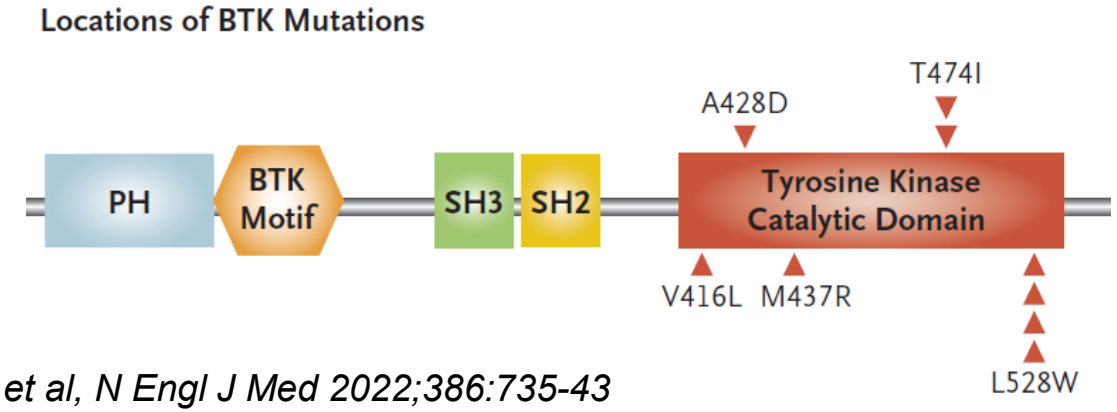
[a] Spleen % change is the percent change to a reference "normal" of 13 cm.
[b] Response for this patient as per International working group on chronic lymphocytic leukemia (iwCLL)
[c] Listed as partial remission in database.
DLT: dose limiting toxicity; SAE: serious adverse event; AE: adverse event; ANC: absolute neutrophil count; Hgb: hemoglobin, Plt: platelet count, ALC: absolute lymphocyte count, SPD: sum of product diameters

L528W is Among New Mutations Identified That Confer Resistance to Noncovalent BTK Inhibitors



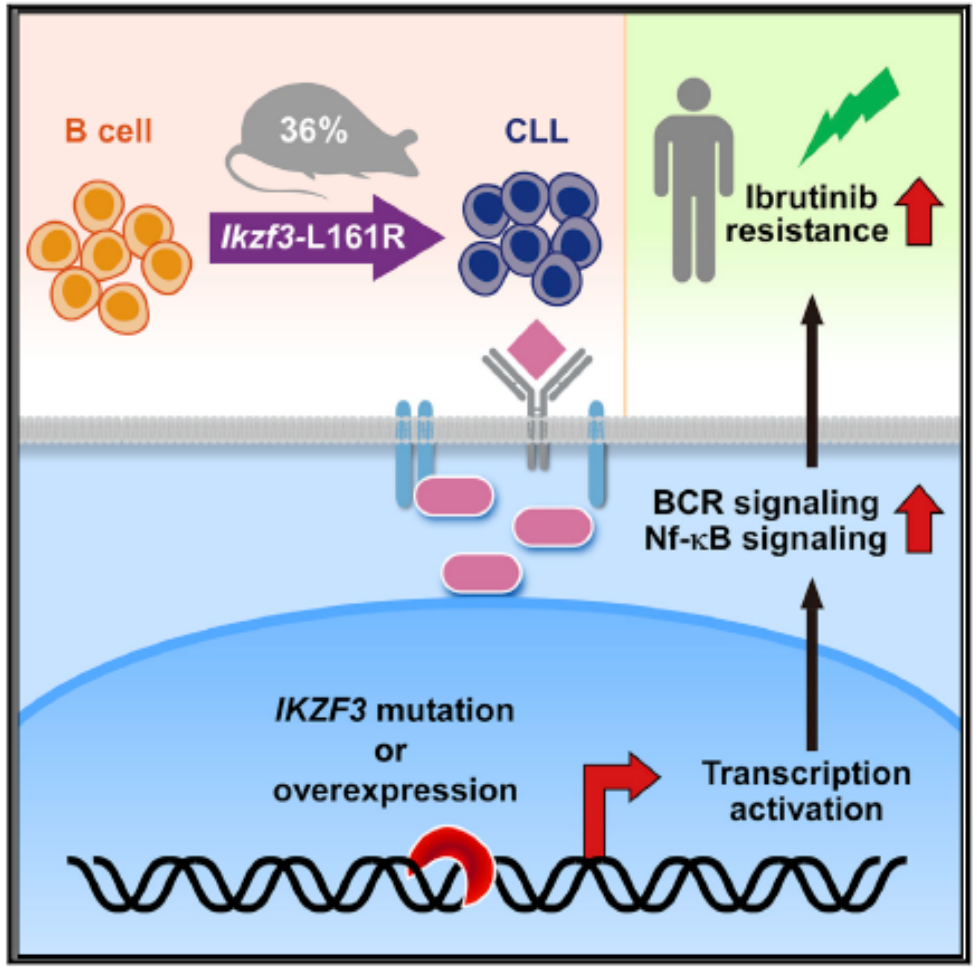
The NEW ENGLAND JOURNAL of MEDICINE

"Our data suggest potential new therapeutic approaches to overcome the newly described BTK inhibitor resistance mechanisms. For example, these data provide a rationale for therapies aimed at addressing the potential scaffold function of BTK rather than inhibiting BTK kinase activity."



Source: Wang et al, N Engl J Med 2022;386:735-43

Aiolos (IKZF3) Overexpression Drives BTK Inhibitor Resistance in CLL, a Rationale for a Combination Strategy



Article

Cancer Cell

A hotspot mutation in transcription factor *IKZF3* drives B cell neoplasia via transcriptional dysregulation

"Our results thus highlight IKZF3 oncogenic function in CLL via transcriptional dysregulation and demonstrate that this pro-survival function can be achieved by either somatic mutation or overexpression of this CLL driver. This emphasizes the need for combinatorial approaches to overcome IKZF3-mediated BCR inhibitor resistance."

Source: Lazarian et al; Cancer Cell 39, 380–393, March 8, 2021

NX-5948 is a Differentiated BTK Degrader Being Developed for CLL/NHL and Autoimmune Diseases

Differentiated profile

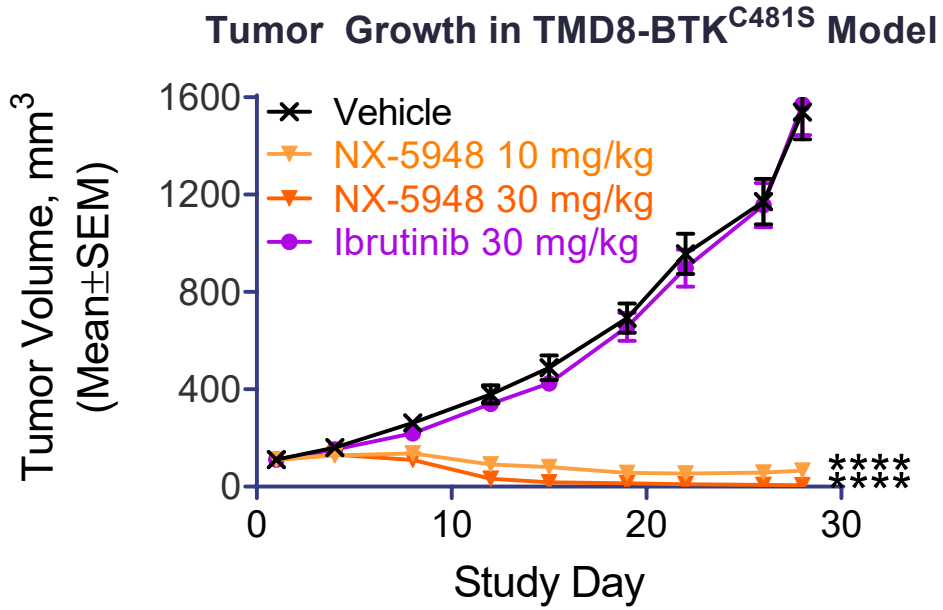
- NX-5948 retains potent activity against both wild type and mutant BTK
- NX-5948 lacks cereblon immunomodulatory activity, unlike NX-2127
- NX-5948 crosses the blood brain barrier in animal models and degrades BTK in both brain-resident lymphoma cells and microglia

Strategy and Implications

- Establish safety and preliminary clinical activity in B-cell malignancies
- Explore the treatment of patients with CNS+ B-cell malignancies
- Further explore potential for autoimmune indications

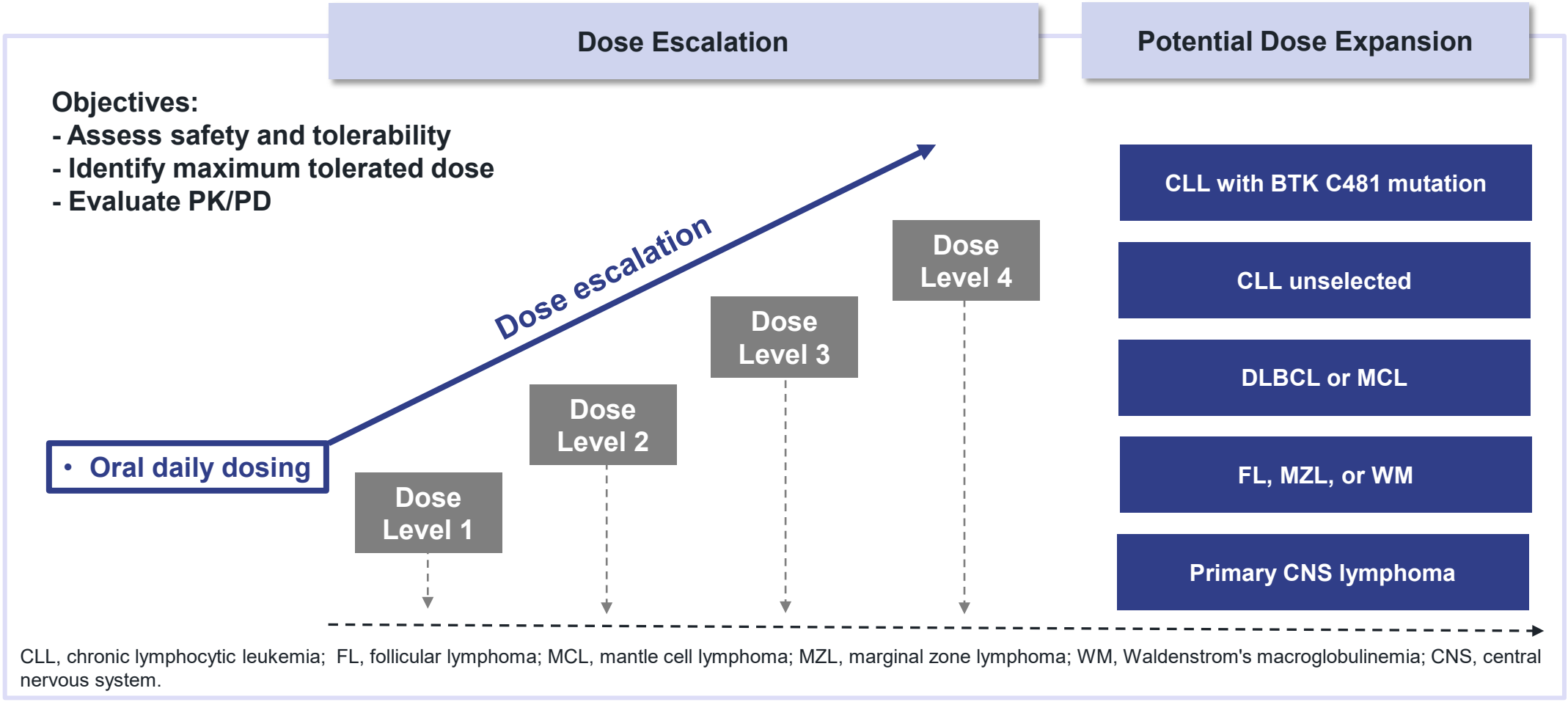
Next Steps

- Anticipate dosing first patient in Phase 1a trial in H1 2022
- Initial proof of mechanism PK/PD data anticipated in H2 2022



NX-5948-301: Phase 1 First-in-Human Clinical Trial Design

Two-Part Phase 1 Monotherapy Trial of NX-5948 in Relapsed or Refractory B-Cell Malignancies



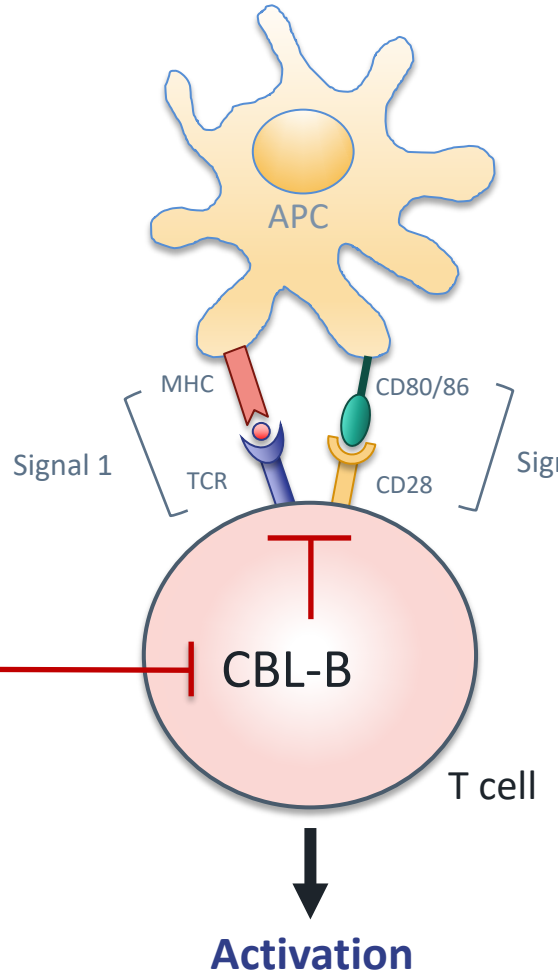
CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenstrom's macroglobulinemia; CNS, central nervous system.

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

- CBL-B is an E3 ligase that regulates the immune system by specifically ubiquitinating proteins involved in signaling through the T cell antigen receptor
- Blocking CBL-B removes a brake on the immune system enhancing both T cell and NK cell responses
- CBL-B function is supported by mouse and human genetics

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.



CBL-B inhibition

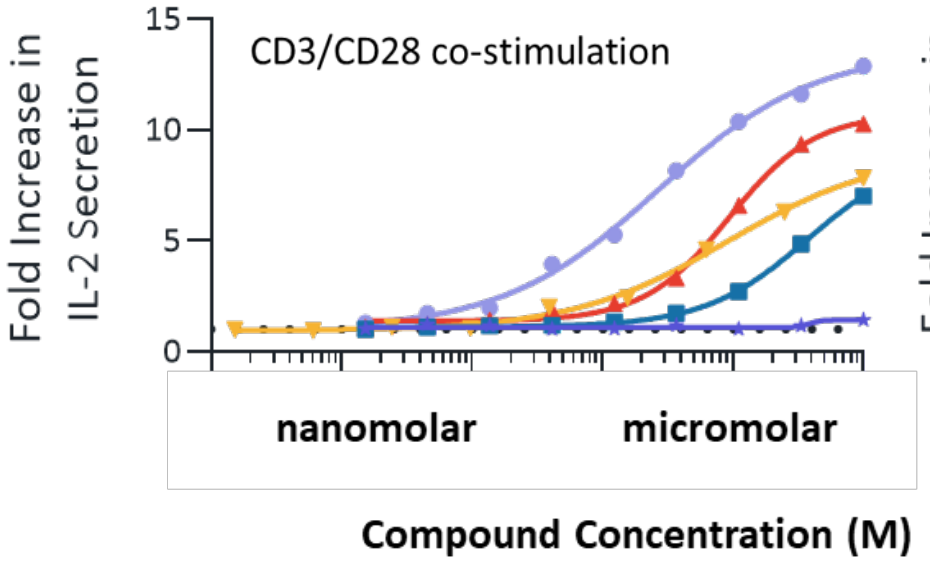
- IL-2 production
- Proliferation
- Central memory phenotype
- Anti-tumor activity
- Threshold of activation
- T cell exhaustion

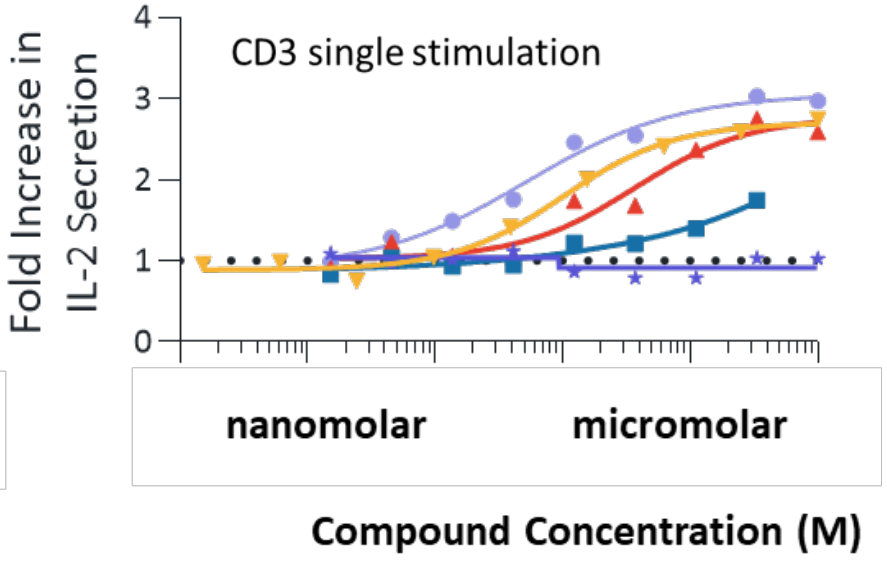
Synergy with anti-PD-1

CBL-B Inhibitor NX-1607 Elevates Cytokines Including IL-2 in Human Donor T Cells

- NX-1607 increases stimulation-dependent production of key activation cytokines
- NX-1607 has no impact in the absence of T cell stimulation
- Oral NX-1607 is expected to produce key cytokines locally in tumors, driving a more robust anti-tumor response

IL-2 secretion increases with concentration and potency of CBL-B inhibition





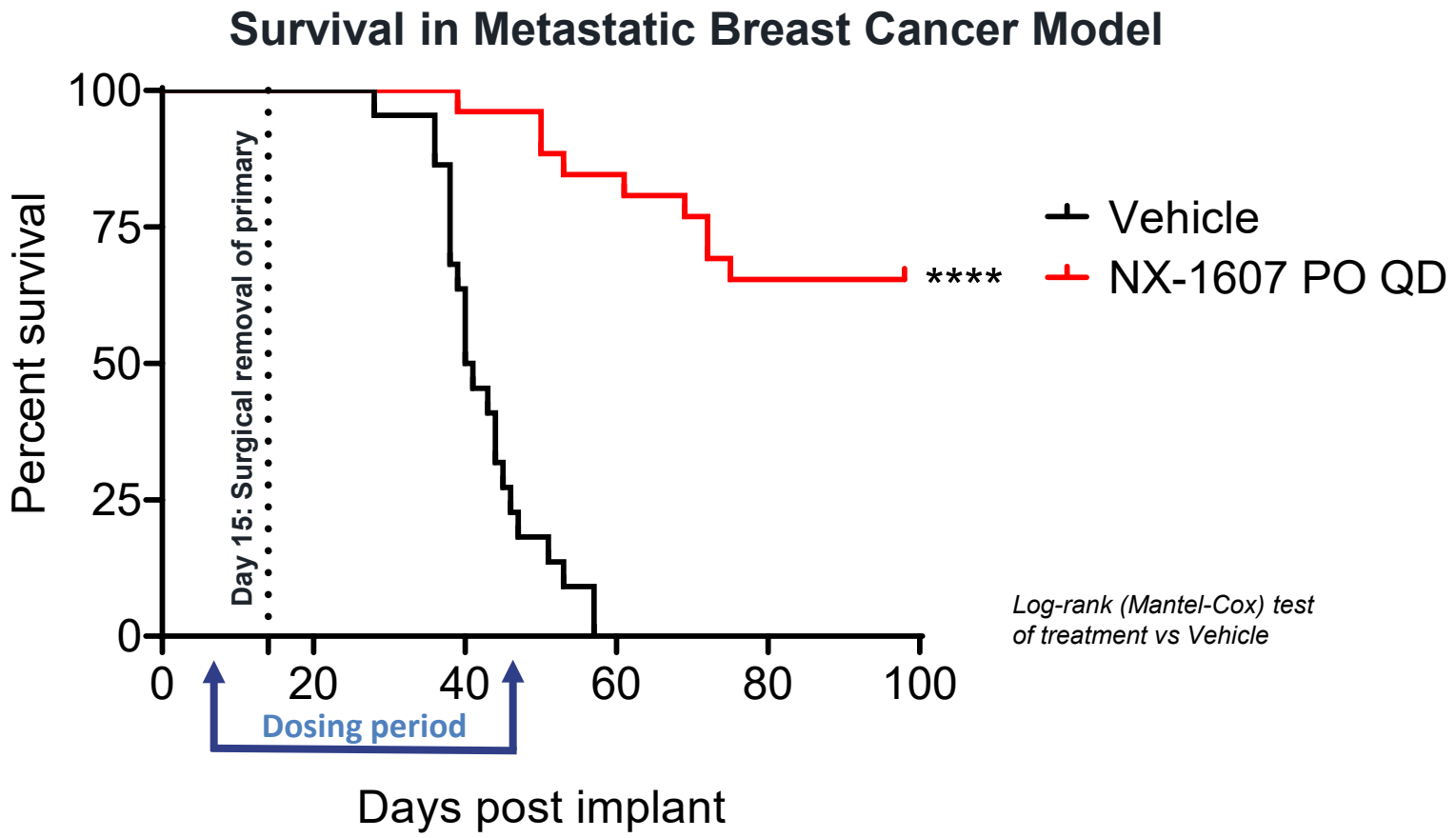
Biochemical Activity

Compound	IC_{50} nM
NRX-5	5
NRX-4	15
NRX-3	26
NRX-2	112
NRX-1 (inactive enantiomer of NRX-4)	1,191

T cell activity ranks orders with biochemical activity

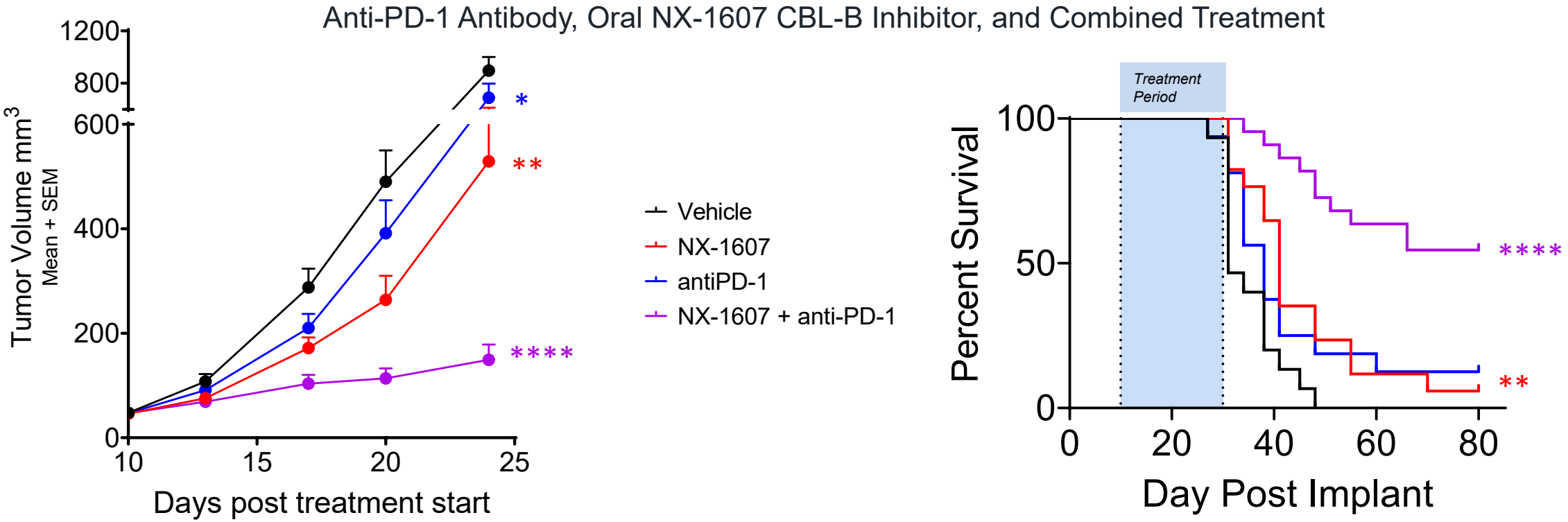
Single-Agent NX-1607 Induces Long Term Survival in Metastatic, Triple Negative, Breast Cancer Model

- Once daily oral dosing of NX-1607
- Tumors implanted at Day 0
- Surgical removal of primary tumor at Day 15
- NX-1607 was given before the surgery from day 7 to day 15 (neo-adjuvant phase) and continued after surgery (adjuvant phase) until day 46



4T1 breast carcinoma cells metastasize from subcutaneous space to distant sites

Combination of NX-1607 and Anti-PD-1 Synergize to Enhance Anti-Tumor Effects and Survival of Tumor-bearing Mice



Combination of NX-1607 and anti-PD-1 treatment significantly improves anti-tumor response and survival in mice bearing two tumors relative to vehicle or anti-PD-1 alone

Tumors from both flanks plotted
Two-way ANOVA of treatment group vs vehicle control

Log-rank (Mantel-Cox) test of vehicle vs treatment

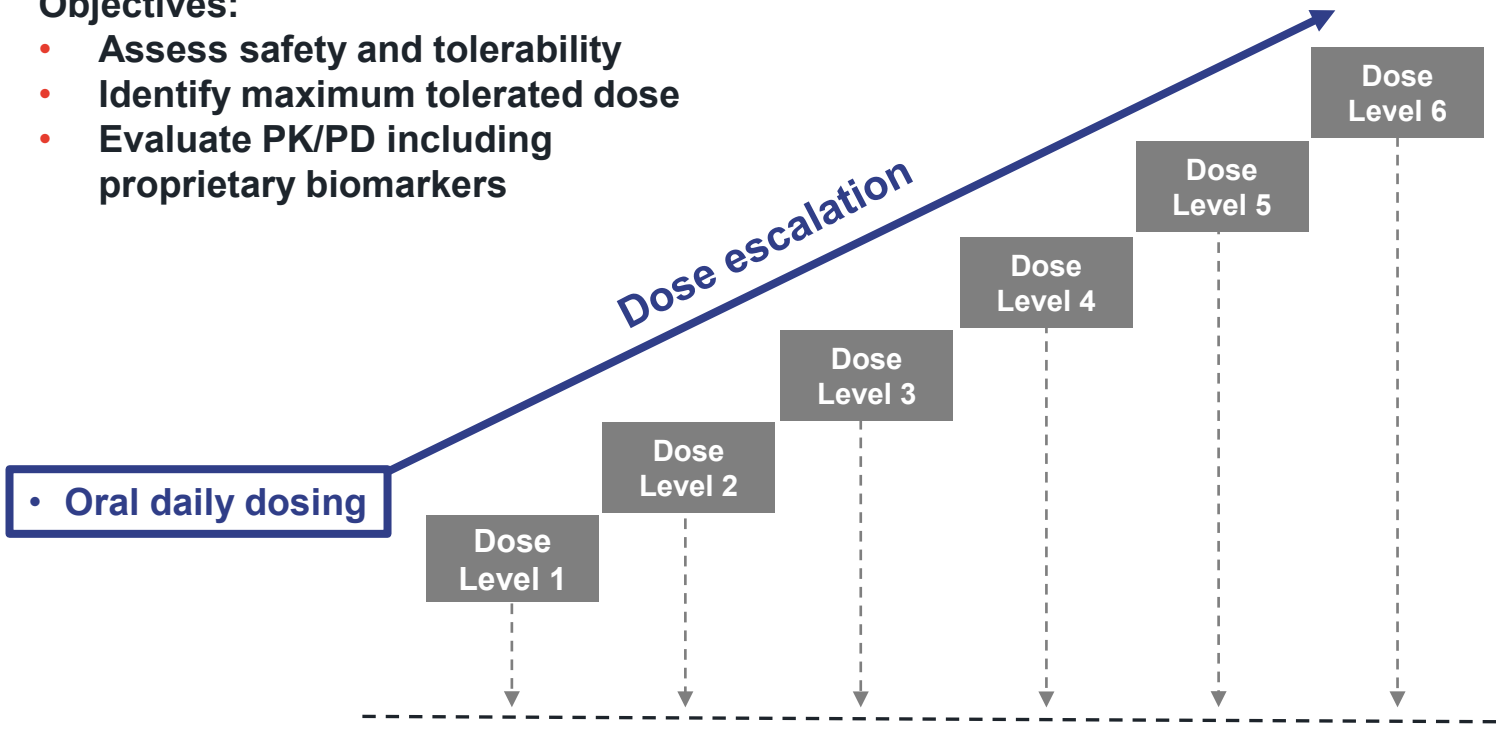
NX-1607-101: Phase 1 First-in-Human Clinical Trial Design

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

Dose Escalation

Objectives:

- Assess safety and tolerability
- Identify maximum tolerated dose
- Evaluate PK/PD including proprietary biomarkers



Potential Dose Expansion

- Melanoma
- Squamous Cell Carcinoma of the Head and Neck (HNSCC)
- Non-small Cell Lung Cancer (NSCLC)
- Platinum Resistant Epithelial Ovarian Cancer (EOC)
- Gastric Cancer
- Metastatic Castration Resistant Prostate Cancer (mCRPC)
- Mixed Solid Tumor Cohort
- Diffuse Large B-cell Lymphoma with Richter Transformation (DLBCL-RT)

Checkpoint resistant tumors
Immunosuppressive microenvironment
Poorly immunogenic tumors

Drug Enhanced Tumor Infiltrating Lymphocytes (DeTIL-0255)

DeTIL

Drug-**E**nhanced

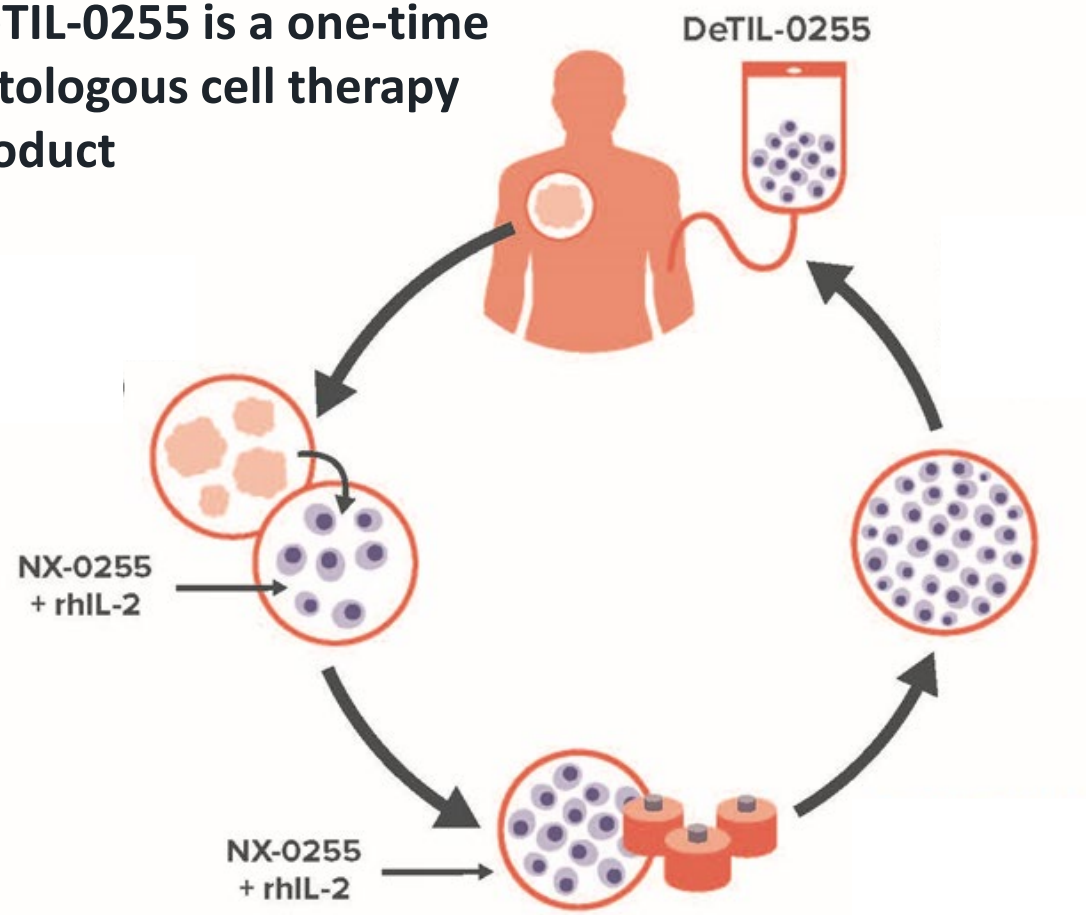
Tumor **I**nfiltrating **L**ymphocytes

DeTIL-0255 is created by *ex vivo* CBL-B inhibition with small-molecule NX-0255, producing a TIL cell therapy product with enhanced characteristics that overcomes the major limitations of current TIL therapy

Major limitations of TIL:

1. Suboptimal manufacture success rate
2. Exhausted phenotype after *in vitro* expansion
3. Unpredictable efficacy and durability

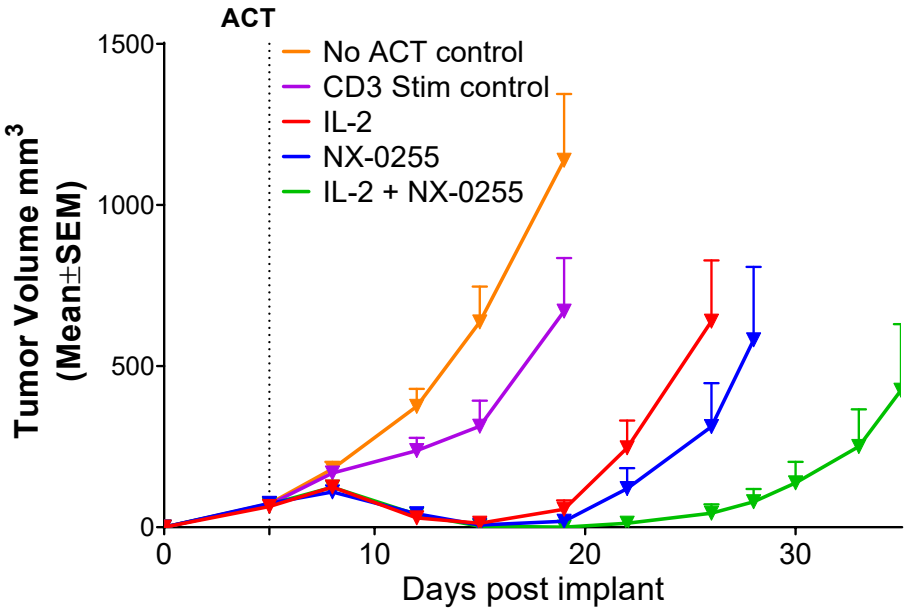
DeTIL-0255 is a one-time autologous cell therapy product



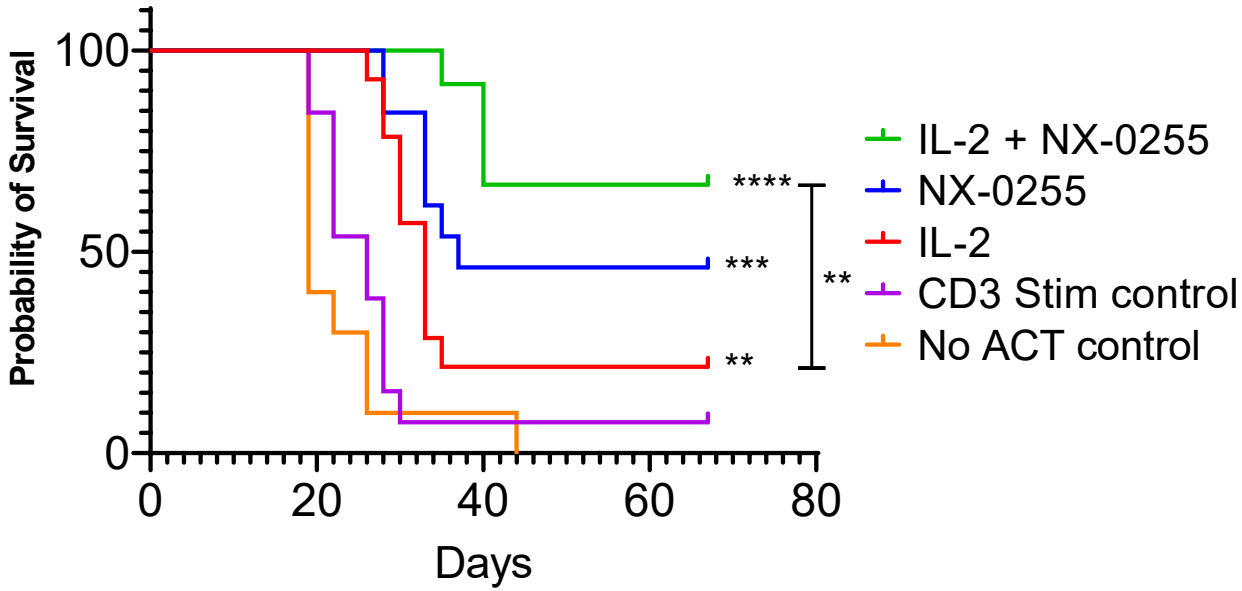
nurix

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

Reduction in Tumor Growth in Mouse ACT Tumor Model



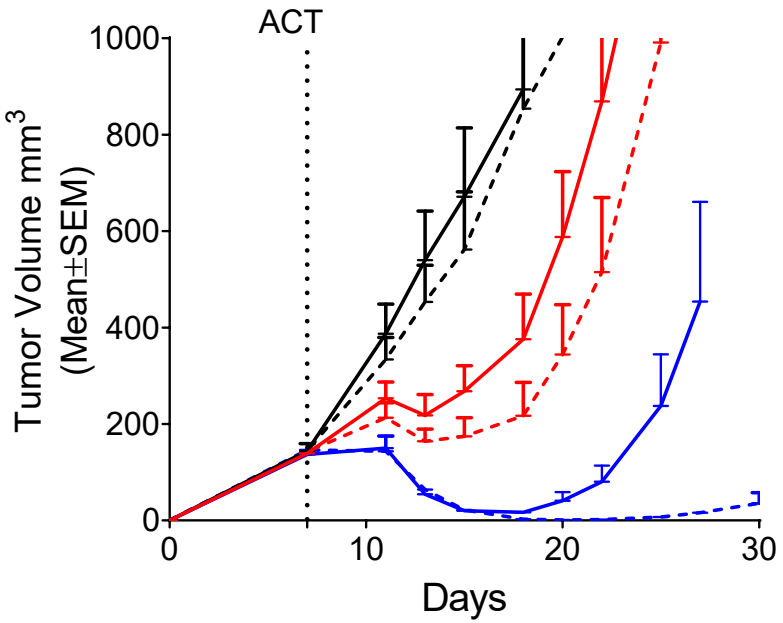
Improvement in Conditional Survival in Mouse ACT Tumor Model



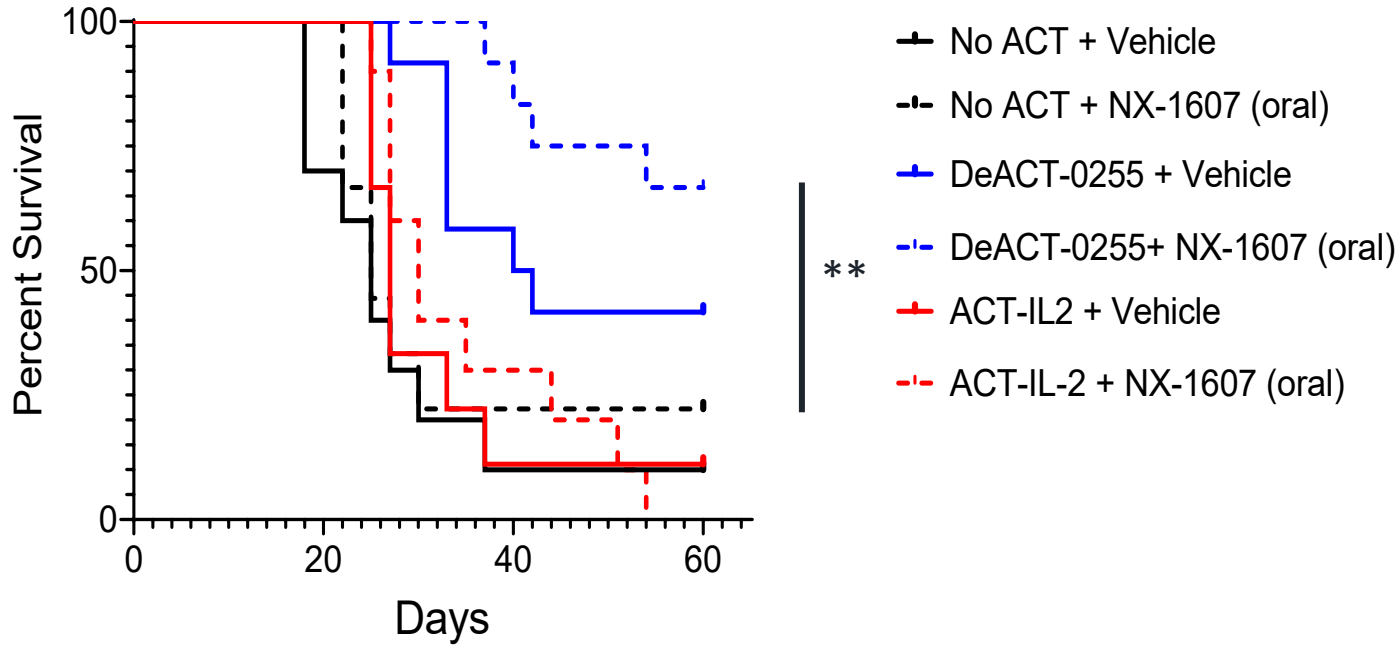
- CD8+ cells exposed to NX-0255 alone *ex vivo* resulted in superior conditional survival compared to using IL-2 alone
- CD8+ cells exposed to NX-0255 and IL-2 combined *ex vivo* exert a deeper anti-tumor response
- NX-0255 *ex vivo* exposure period is only three days, anti-tumor effects persist for over a month after engraftment
- Animals that rejected tumor were rechallenged 80 days post ACT, and all animals rejected tumor
- One-year post infusion, tumor-specific T cells in recipient mice remained enhanced

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
- The combination of oral CBL-B inhibition with DeTIL-0255 will be explored as a means to improve outcomes and potentially reduce the need for systemic IL-2

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

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

Safety Run in (3-6 patients)

Cohort Expansion

Objectives:
- **Assess safety and tolerability**
- **Assess preliminary efficacy**

In-hospital treatment (~3 weeks)

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**

Platinum Resistant Epithelial Ovarian Cancer (~ 15 patients)

Recurrent, Metastatic or Persistent Cervical Cancer (~ 15 patients)

Advanced or Recurrent Endometrial Cancer (~ 15 patients)

Cy, Cyclophosphamide; Flu, Fludarabine; IL-2, Interleukin-2

Advancing Our Proprietary and Partnered Pipelines with Financial Strength

Financial Highlights

- $386 million in cash as of February 28, 2022
- $518 million raised in equity financings in 2020-2021
- $276 million to date from partnership upfront payments
- $32.5 million to date in partnership progress milestones

Gilead Sciences

June 2019

- Upfront payment of $45M and up to $2.3B in additional payments, including early discovery milestones

Sanofi

December 2019

- Upfront payment of $55M, expansion option payment of $22M in January 2021, and up to $2.5B in additional payments, including early discovery milestones

- Two premier partnerships, each with five targeted protein degradation discovery programs
- Nurix has option for 50/50 U.S. co-development for two drug candidates from each partner
- Nurix internal programs excluded

Advancing Our Pipeline to Multiple Clinical Milestones in 2022

NX-2127

- Initiate Phase 1b trial in mid-2022
- Present additional Phase 1a clinical results in H2 2022

NX-5948

- Dose first patient in Phase 1a trial in H1 2022
- Establish Phase 1a PK/PD in H2 2022

NX-1607

- Establish Phase 1a PK/PD in mid-2022

DeTIL-0255

✓Dose first patient in Phase 1 trial in H1 2022

- Phase clinical update from safety run in H2 2022

Investor R&D day

- Planned for Q2 2022 (May 26 in NYC)

Note: All anticipated timing is based on calendar-year periods

Thank you

Nurix Therapeutics