Nurix Therapeutics

Blazing a New Path in Medicine

40th Annual J.P. Morgan Healthcare Conference

January 10, 2022

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Leading the Field of Targeted Protein Modulation

Key Accomplishments in 2021

- Industry leading targeted protein modulation platform over 5 billion DEL compounds
- 15 targeted protein degradation drug discovery programs advancing from DELigase platform
- Regulatory clearance to initiate four wholly owned clinical programs (two INDs, two CTAs)

Goals for 2022

- Advance four programs through Phase 1a and initiate Nurix's first Phase 1b/2 clinical trial
- Advance Nurix's drug discovery pipeline with a new development candidate entering IND-enabling studies
- Continue to lead the targeted protein modulation field supported by premier partners, investors, and employees

Nurix Delivered on Key Milestones in 2021, a Year of Significant Execution

	H1 2021*	H2 2021*
NX-2127 (oral BTK degrader / IMiD)	✓ **Initiate Phase 1 trial** IND accepted by FDA Enrollment ongoing	✓ **Present initial dose escalation data** Positive proof of mechanism
NX-5948 (oral BTK degrader)	✓ **Define differentiated profile** Crosses blood brain barrier in animals Active in autoimmune animal models	✓ **Initiate Phase 1 trial** CTA accepted by MHRA Enrollment anticipated in H1 2022
NX-1607 (oral CBL-B inhibitor)	✓ **Present additional preclinical data** Poster presented at 2021 AACR Annual Meeting	✓ **Initiate Phase 1 trial** IND accepted by FDA Enrollment ongoing
DeTIL-0255 (drug-enhanced TIL)	✓ **Complete engineering manufacturing runs**	✓ **Initiate Phase 1 trial** IND accepted by FDA Enrollment anticipated in H1 2022

* All anticipated timing was based on calendar-year periods

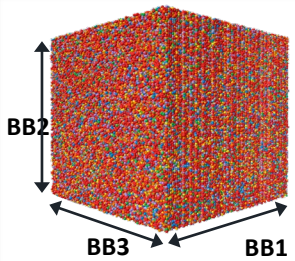
Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

Drug Program	Target / Delivery	Therapeutic Area	Discovery	IND enabling	Phase 1	Phase 2	Phase 3
NX-2127 Degrader	BTK + IMiD activity *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						

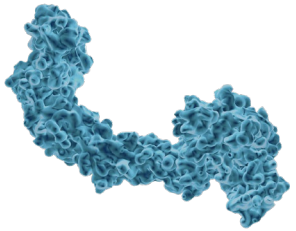
Nurix's DELigase Platform: Leading the Industry in DNA-Encoded Libraries for Targeted Protein Modulation

- 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



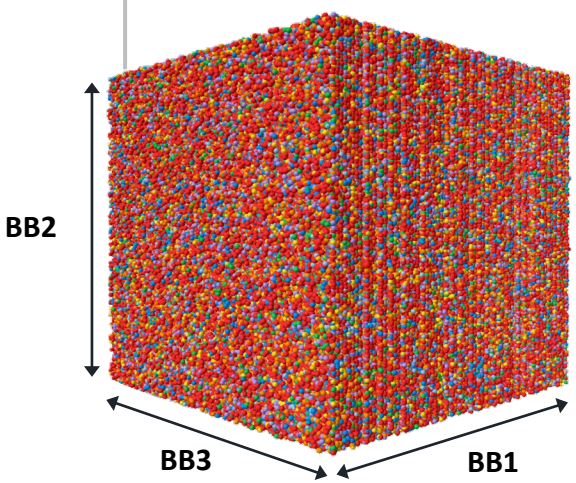
>30 E3 ligases currently in discovery

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

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

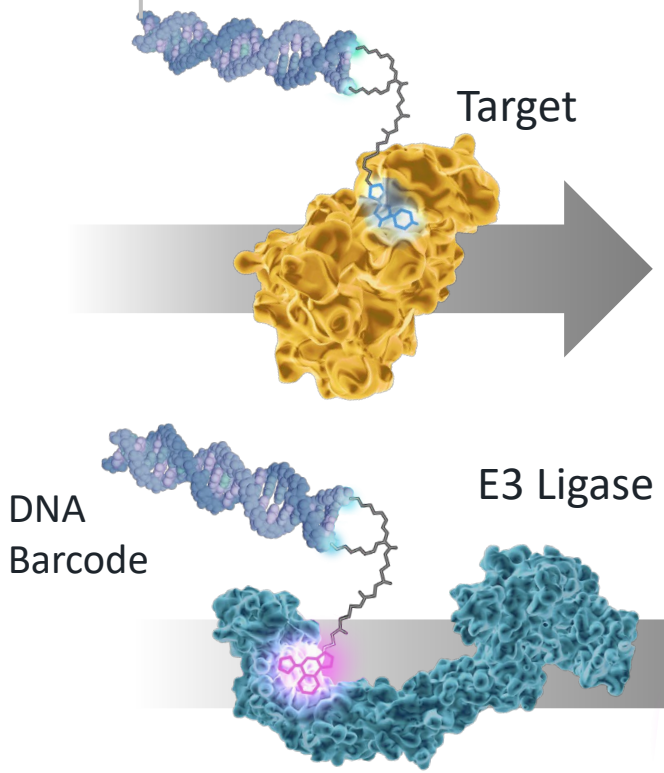
DELigase® Enables Efficient Chimeric Targeting Molecule Discovery and Design

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

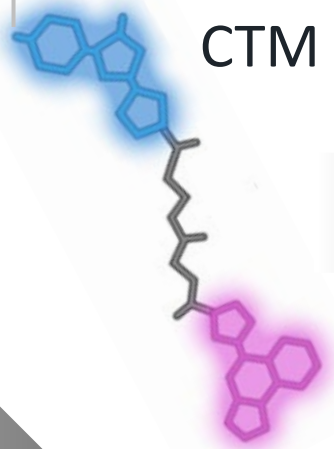


BB = Chemical Building Blocks

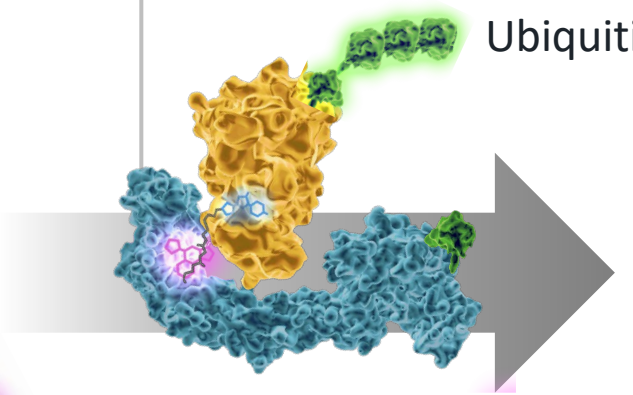
2 Target proteins and E3 ligases are screened using DEL



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



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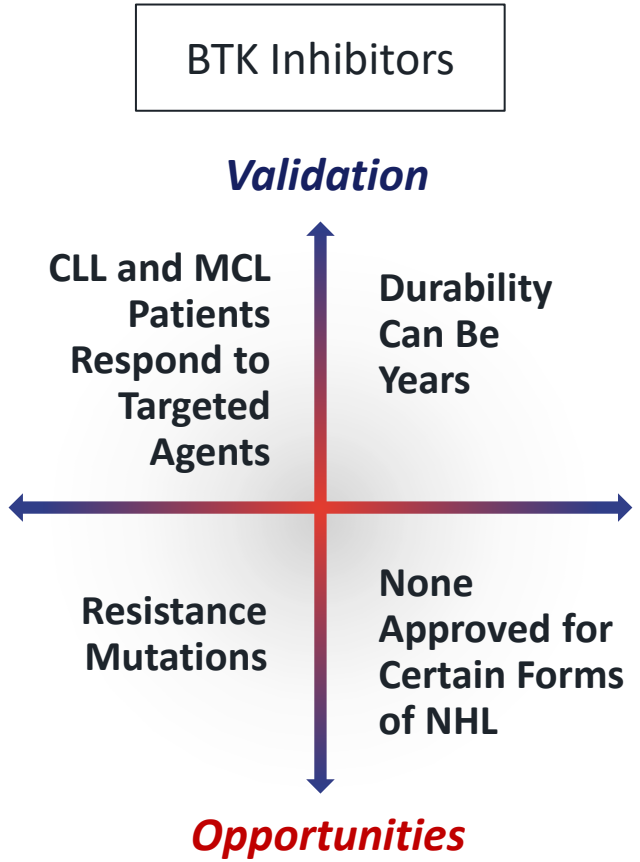
Nurix's BTK Degrader Portfolio: A Differentiated Approach to B-Cell Malignancies

- **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 estimated 2021 sales ~ $8.5 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
  - Unique dual activity: NX-2127 combines the activities of BTK degradation and IMiDs which may be beneficial across a range of hematologic malignancies, particularly in NHL / DLBCL

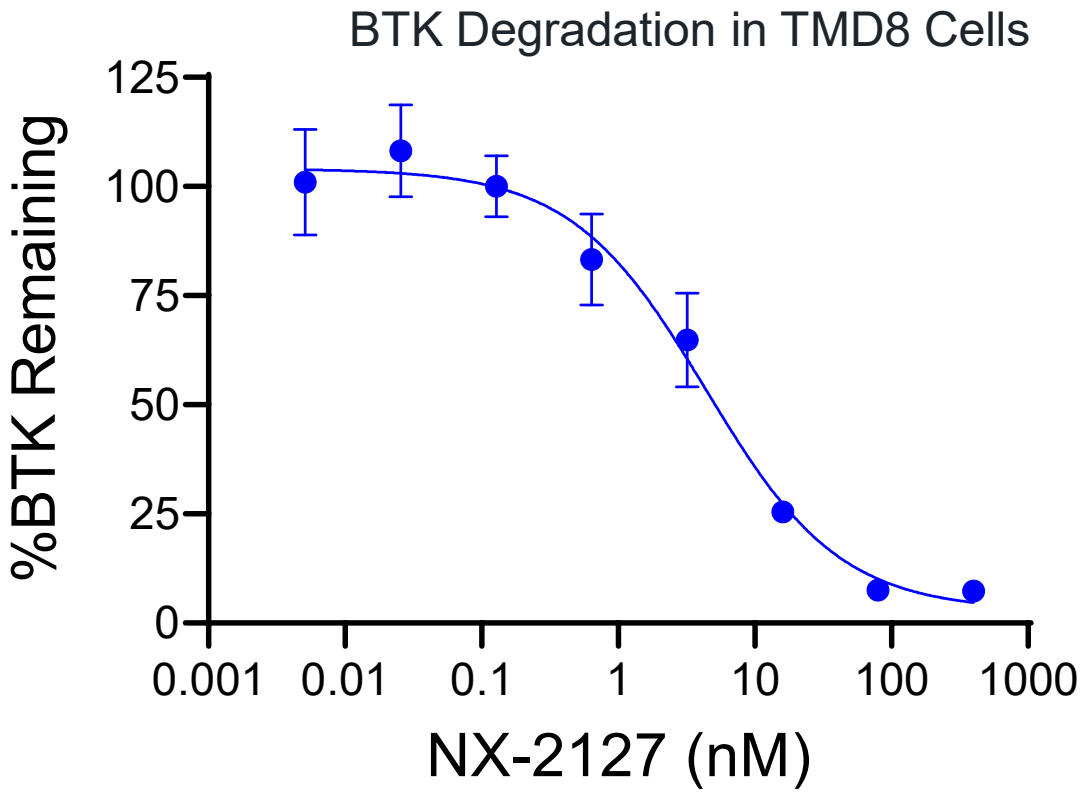
NX-2127: BTK degrader with IMiD activity. Developing across multiple B-cell malignancies (CLL, MCL, WM, MZL, DLBCL, FL)

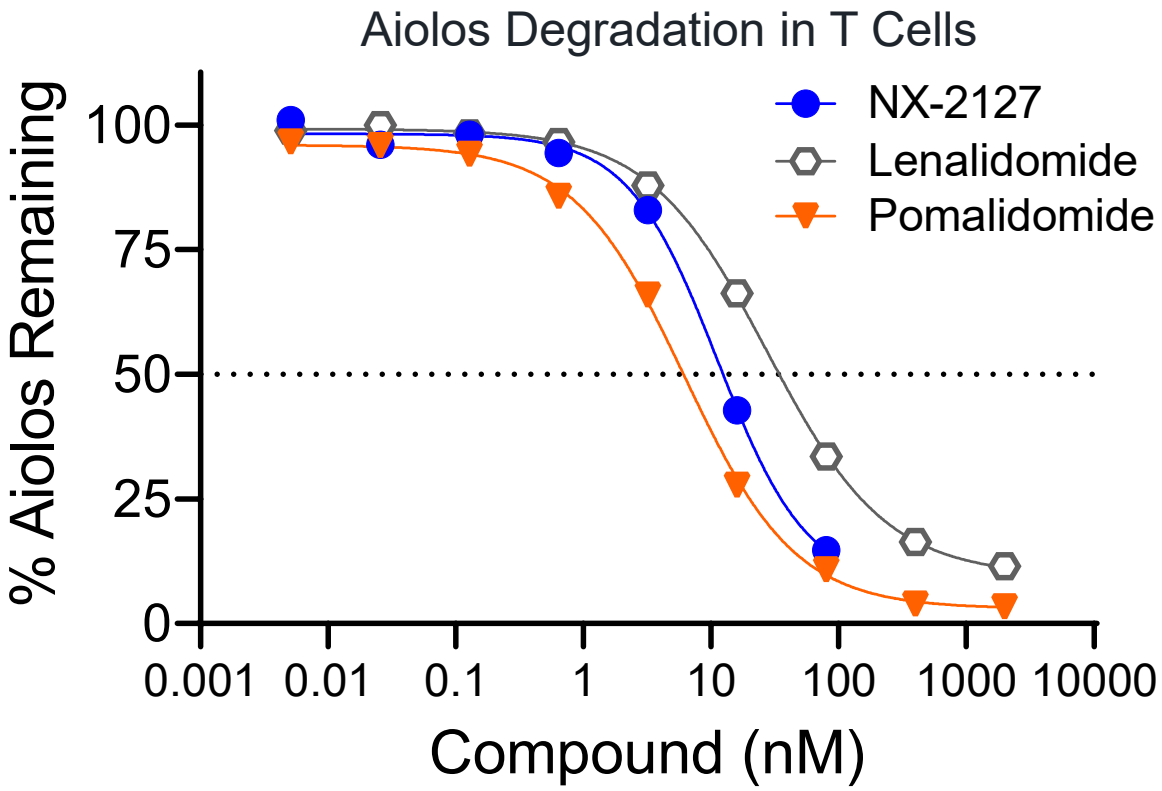
NX-5948: BTK degrader without IMiD activity. Developing for targeted B-cell malignancies and autoimmune diseases



BTK, Bruton tyrosine kinase; IMiD, Immunomodulatory imide drugs; 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 IMiD Neosubstrate Aiolos

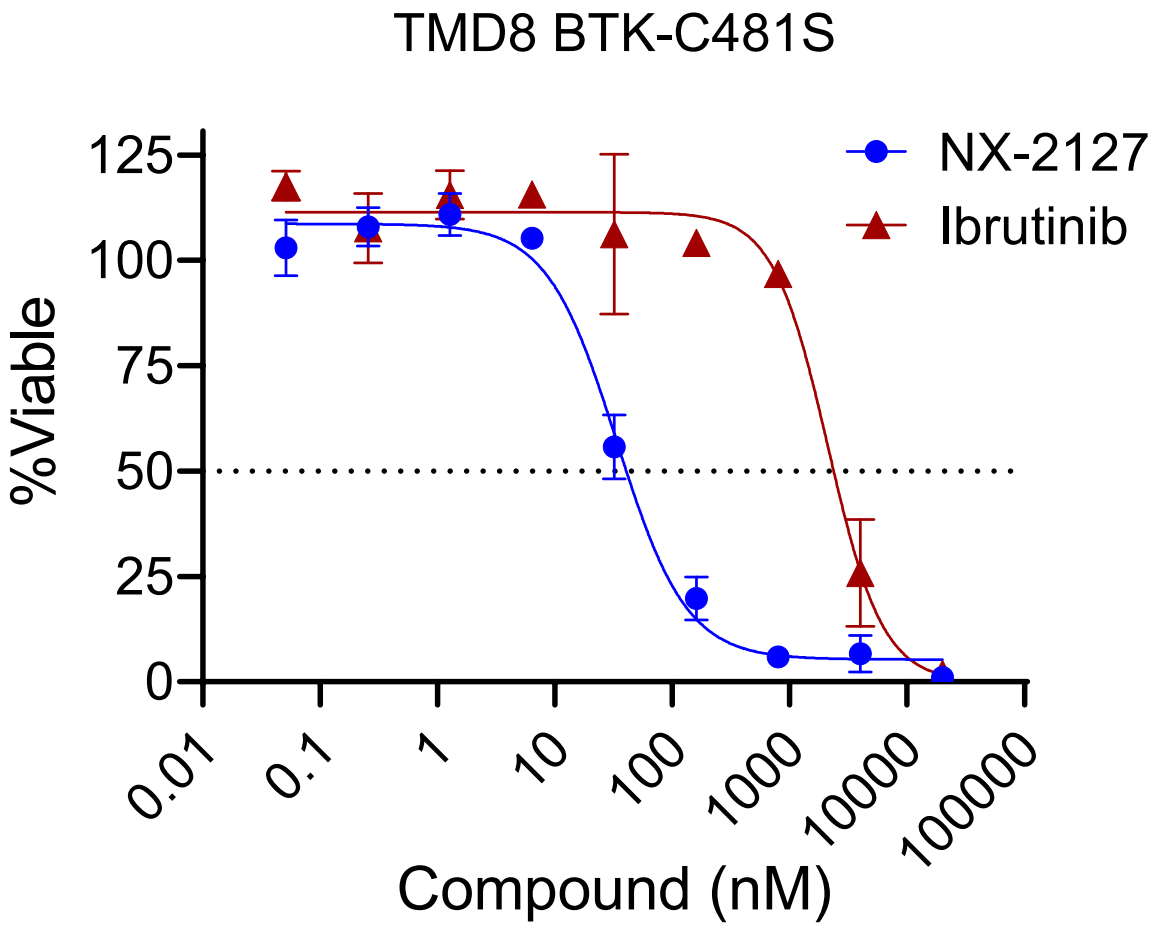




NX-2127 shows potent BTK degradation in TMD8 cells (human DLBCL cell line)

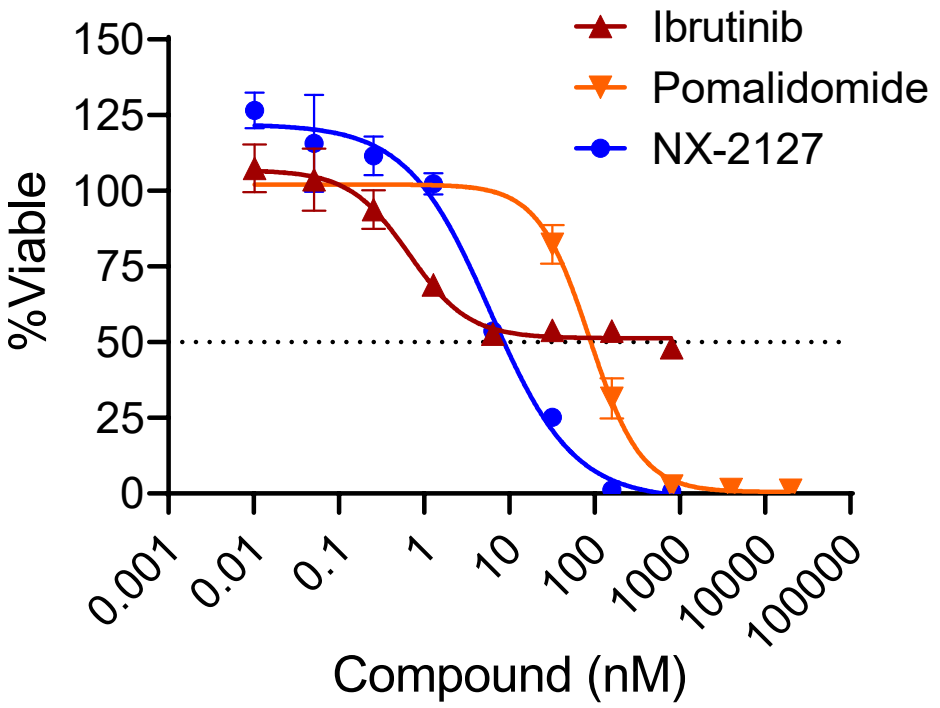
NX-2127 degradation of Aiolos in human T cells occurs at a similar potency to lenalidomide and pomalidomide

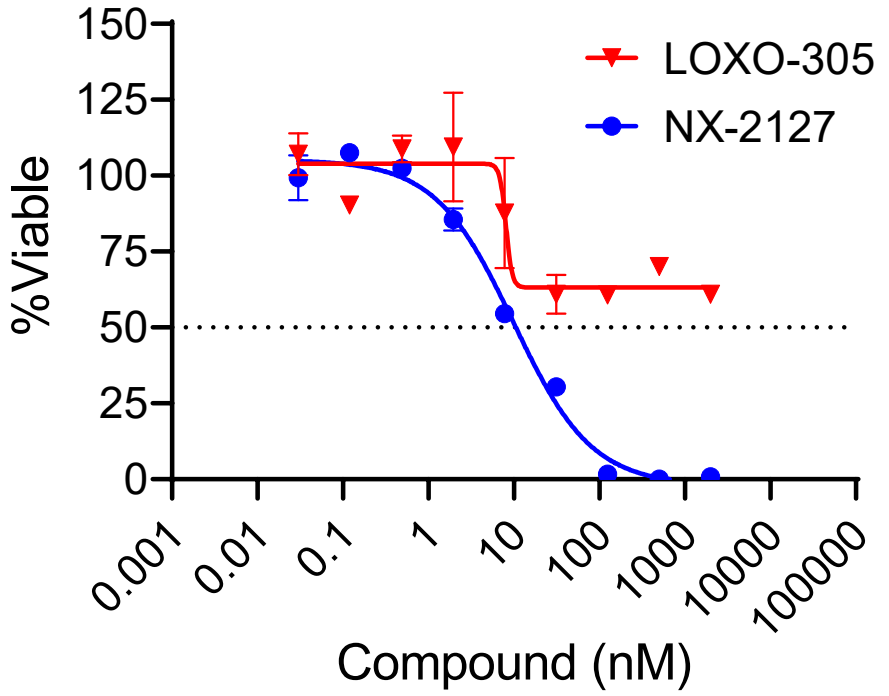
NX-2127 Potently Inhibits Growth of Ibrutinib-Resistant Tumor Cell Lines



- 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 IMiD Activity Plus BTK Degradation in REC-1 Mantle Cell Lymphoma Cells: Complete Cell Killing by NX-2127

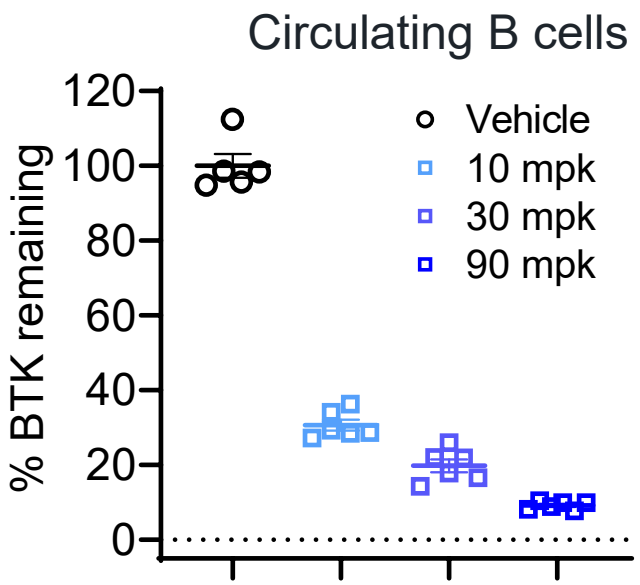


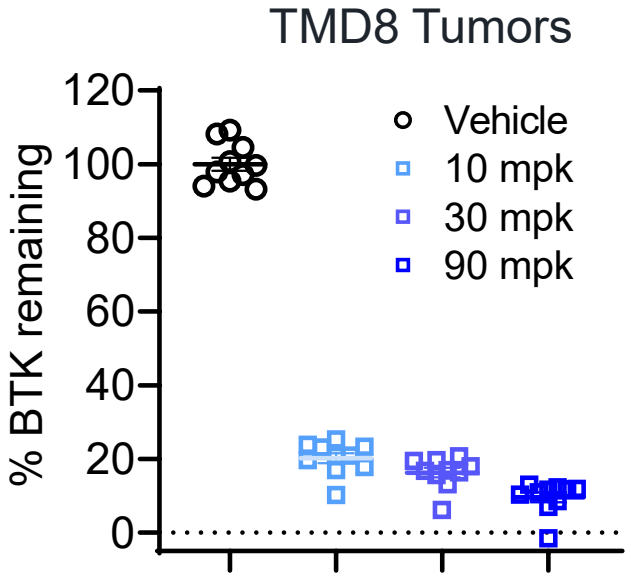


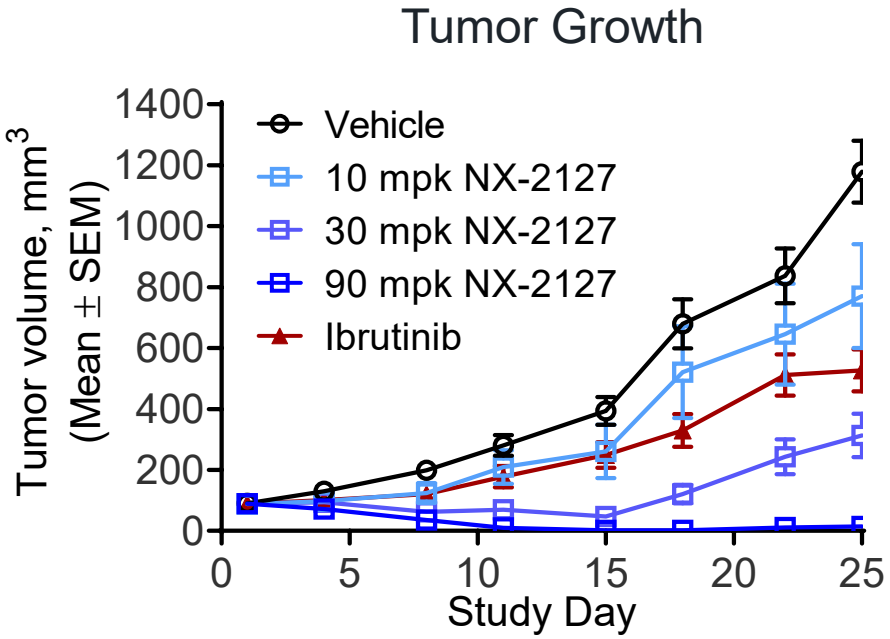
- Compounds active against BTK reduce cell viability at low doses, but this effect plateaus
- IMiDs promote more complete killing but require higher doses to reduce cell viability
- The combined BTK and IMiD activities of NX-2127 allow it to potently and completely kill REC-1 cells

- 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





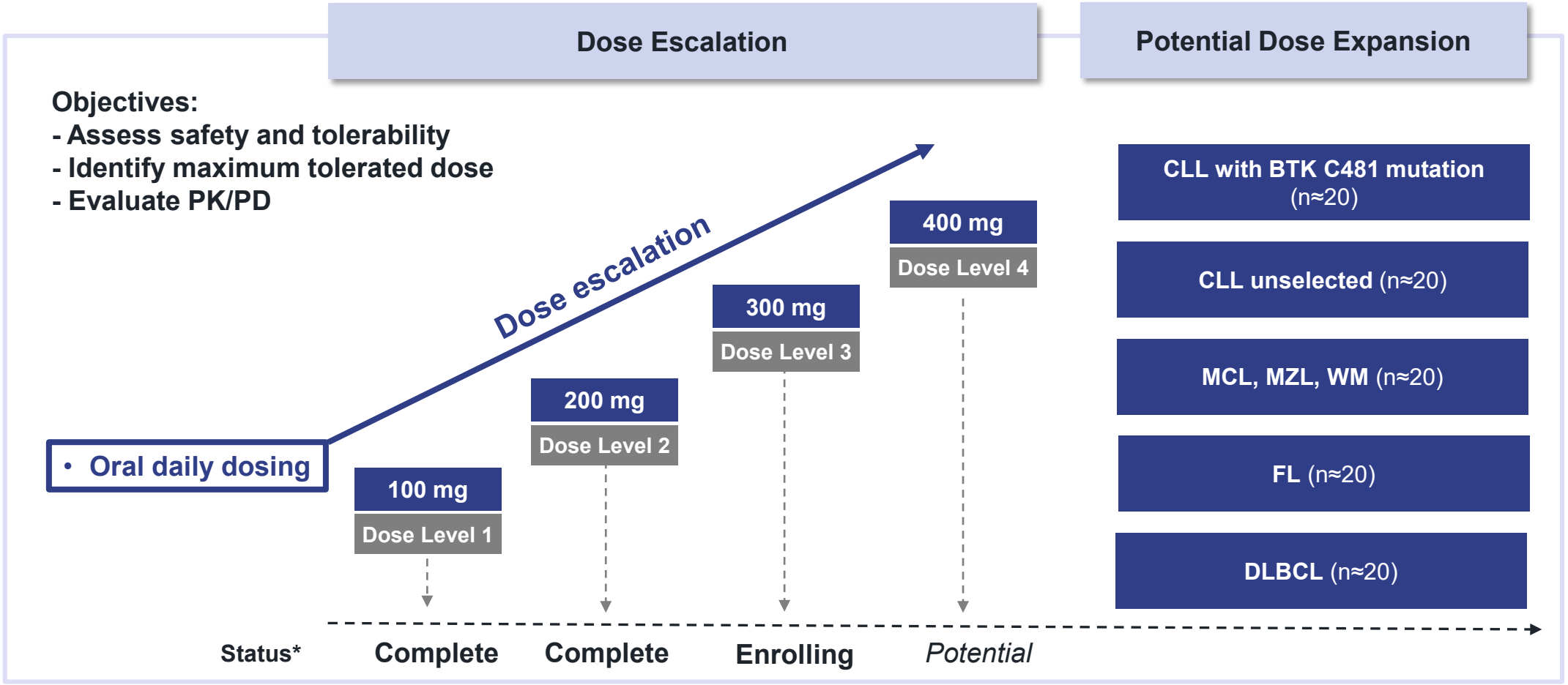


Treatment	Oral gavage dose (mg/kg)	% BTK degradation in circulating B cells	% BTK degradation in TMD8 tumor tissue	% TGI vs Vehicle (Day 24)	*P* value vs Vehicle
Vehicle	0	0.0±3.2	0.0±1.8	N/A	0
NX-2127	10	69.3±1.5	79.8±1.4	58%	0.0492
	30	80.2±1.8	83.7±1.3	74%	<0.0001
	90	90.8±0.4	90.4±1.4	100%	<0.0001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

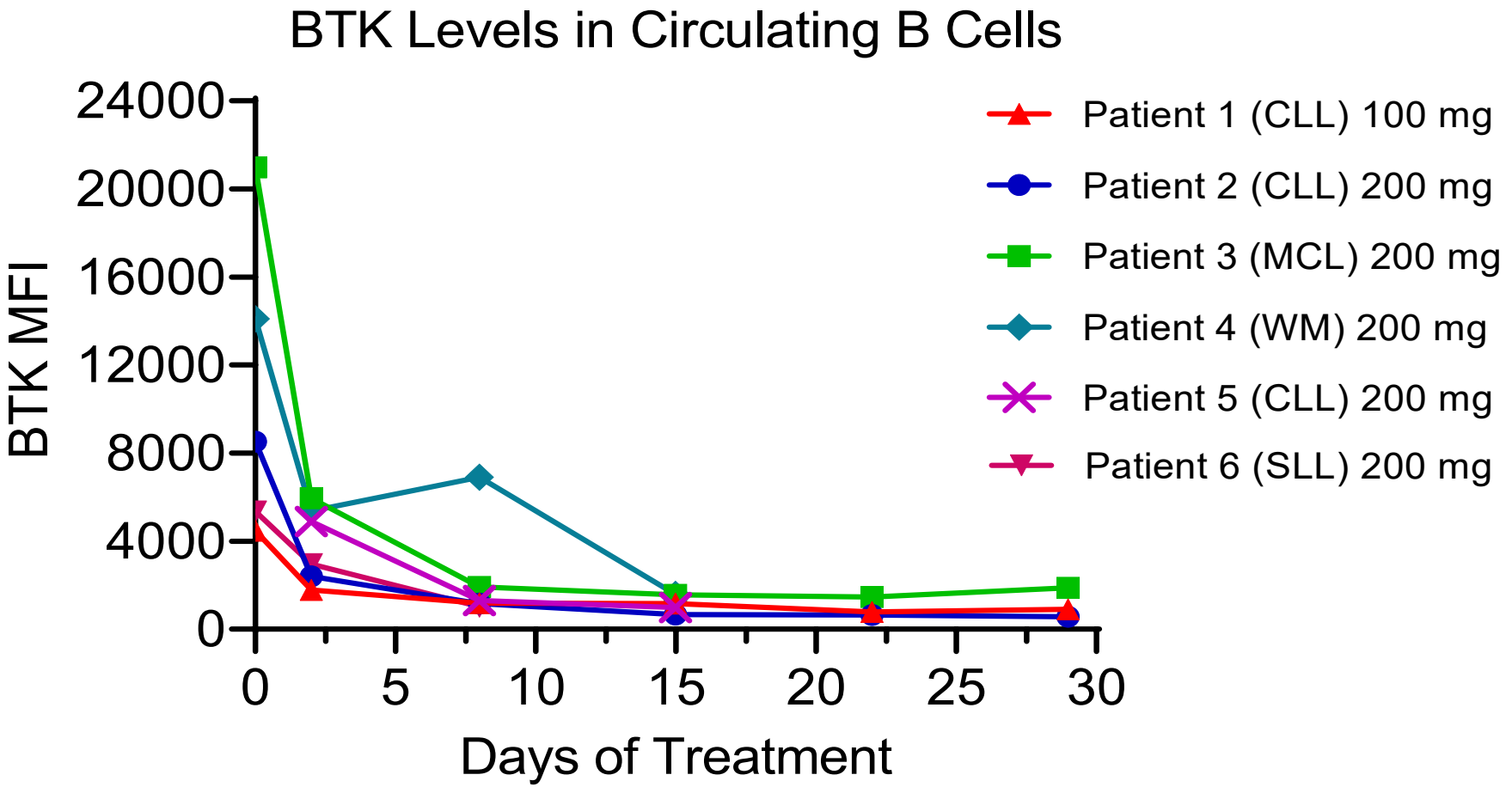


CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenstrom's macroglobulinemia.

*** Status as of October data presentation**

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

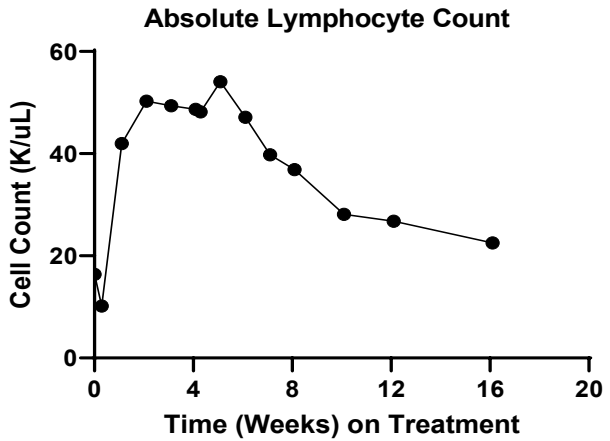
Clinical Response Observed in Patient 1

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

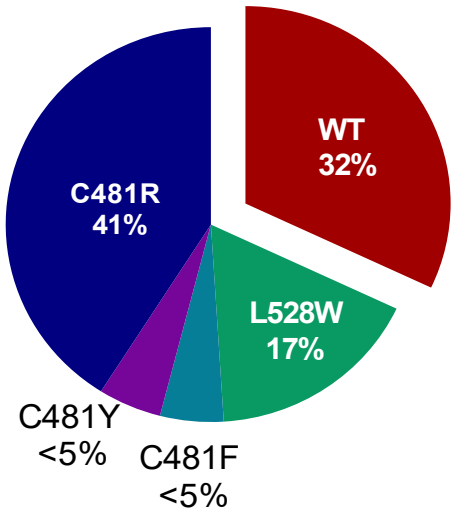
Prior Treatments:
1. Rituximab, 2015
2. Ibrutinib, 2015-2021

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

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

Differentiated profile

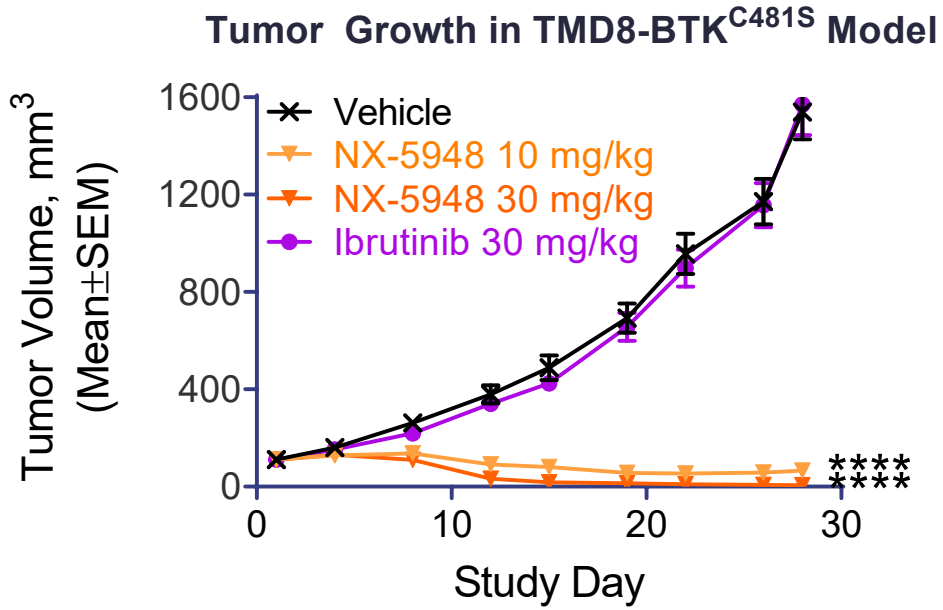
- NX-5948 retains potent activity against both wild type and mutant BTK
- NX-5948 spares IMiD activity, unlike NX-2127
- NX-5948 crosses the blood brain barrier in animal models and degrades BTK in both brain-resident lymphoma cells and microglia

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

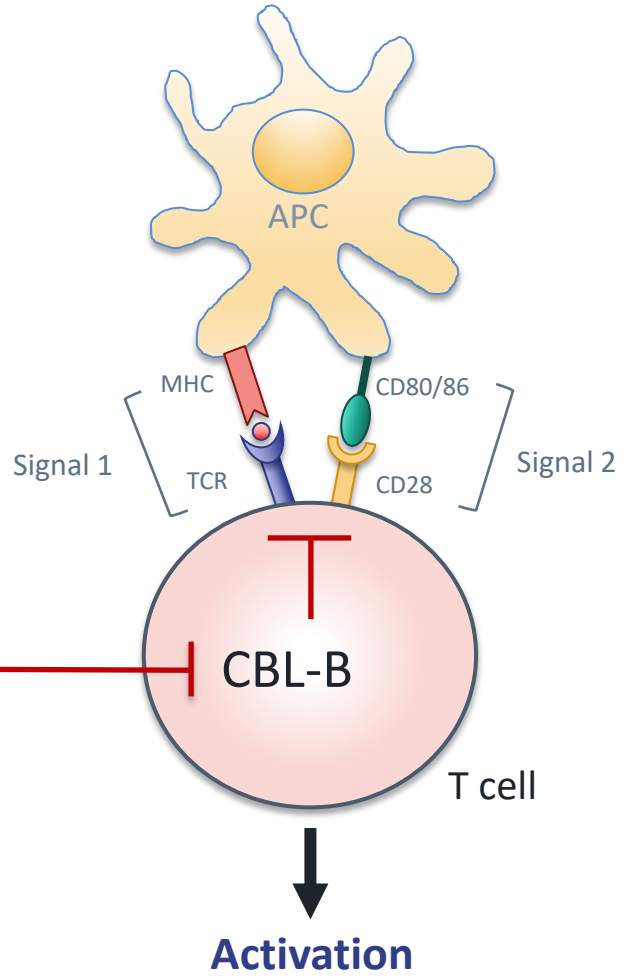


CBL-B: A Modulator of T Cell Activation and a Novel Target for Immuno-oncology

- 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
- 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

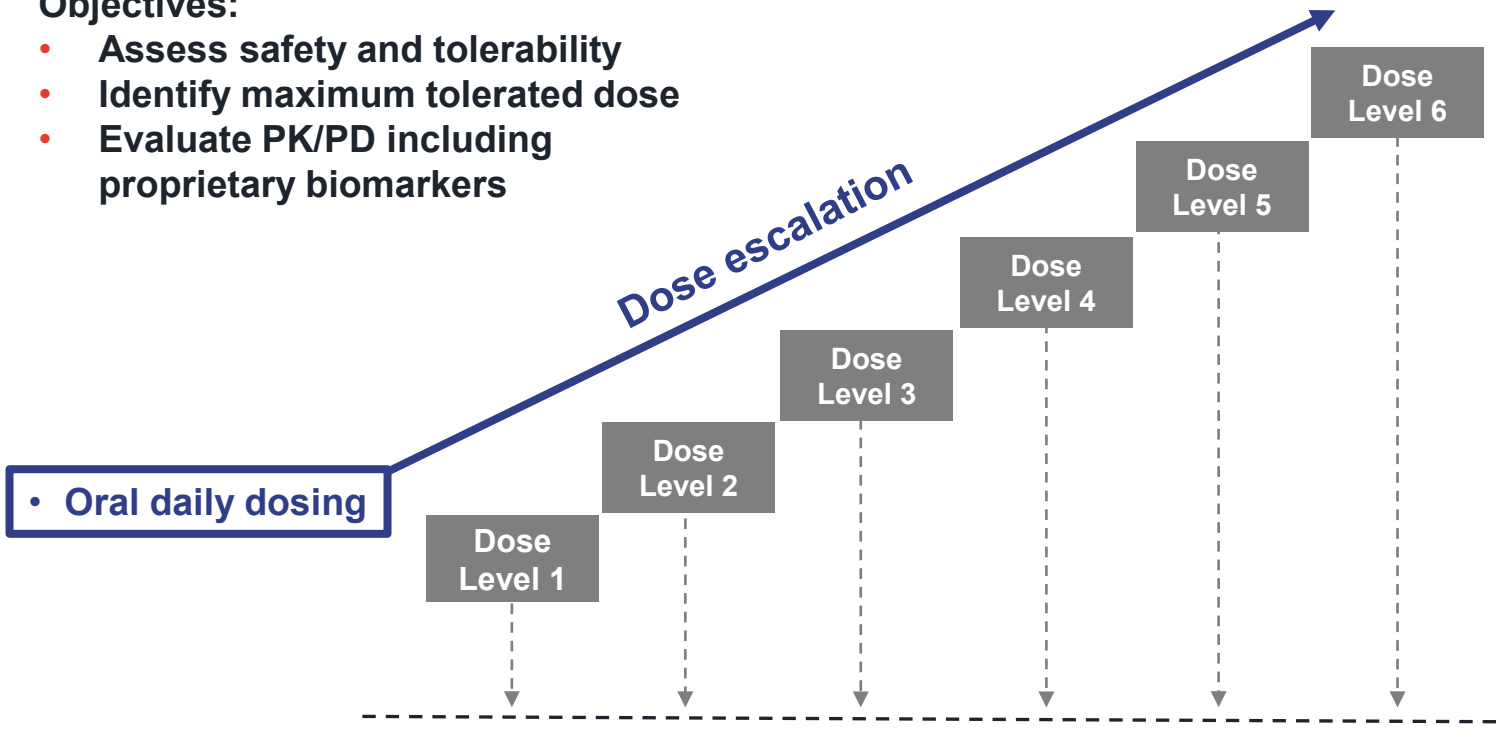
NX-1607-101: Phase 1 First-in-Human Clinical Trial Design

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

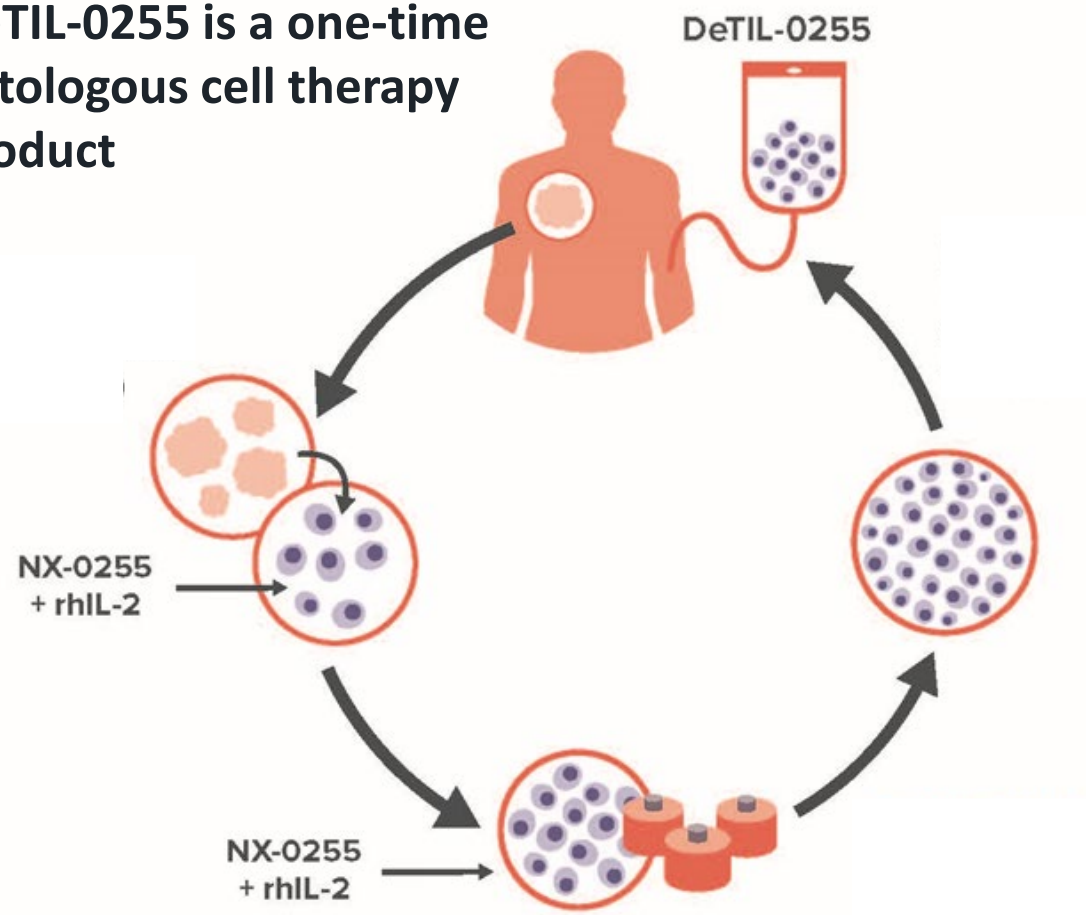
Tumor **I**nfiltrating **L**ymphocytes

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



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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

- $465 million in cash as of August 31, 2021
- $518 million raised in equity financings in 2020-2021
- $276 million to date from partnership upfront payments
- $19.5 million to date in partnership progress 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

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

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

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

Thank you

Nurix Therapeutics