Nurix Therapeutics

Blazing a New Path in Medicine

First Demonstration of Targeted Protein Degradation of BTK in Hematologic Malignancies: Initial NX-2127 Phase 1a PK/PD Data

4th Annual Targeted Protein Degradation (TPD) Summit
October 27, 2021

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Arthur T. Sands, M.D., Ph.D.

Chief Executive Officer

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Presentation Outline

Outline of key questions we plan to address:

1. What is the status of our protein modulation pipeline?
2. What levels of BTK degradation are associated with anti-tumor effects in animal models?
3. What are the initial PK/PD findings from the Phase 1a study of NX-2127 in patients with relapsed/refractory B cell malignancies?

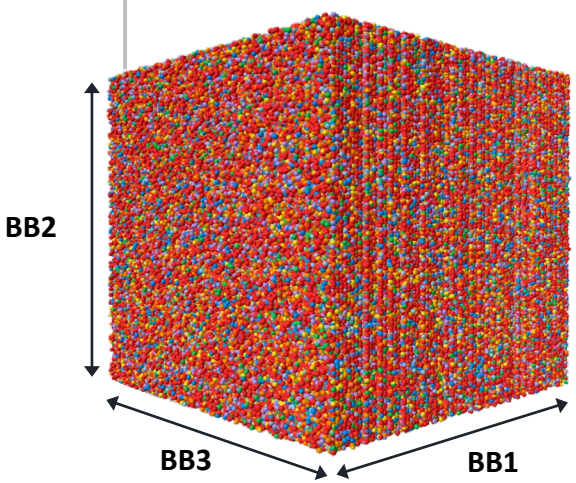
Nurix's Wholly-Owned Targeted Protein Modulation Pipeline: Both Degradation and Ligase Inhibition Programs Currently Enrolling

Drug Candidate	Target / Delivery	Therapeutic Area	Discovery	Lead Optimization	Preclinical	Phase 1	Phase 2	Phase 3
Protein Degradation Chimeric Targeting Molecule (CTM) Portfolio								
NX-2127	BTK + IMiD activity *Oral*	B-cell Malignancies				Enrolling		
NX-5948	BTK *Oral*	B-cell Malignancies and Autoimmune Diseases				Commence in H2 2021*		
KINASE-CTM3	T Cell Kinase	T-cell Malignancies and Autoimmune Diseases						
COVID-CTM	Intracellular SARs COV-2 proteins	Anti-viral						
Ligase Inhibition Portfolio								
NX-1607	CBL-B *Oral*	Immuno-oncology				Enrolling		
DeTIL-0255	CBL-B (NX-0255) *ex vivo*	Adoptive Cell Therapy (ACT)				Commence in H2 2021*		
LIGASE-INH2	Undisclosed	Immuno-oncology						

* All timing based on calendar-year periods and represents corporate goals set in January 2021

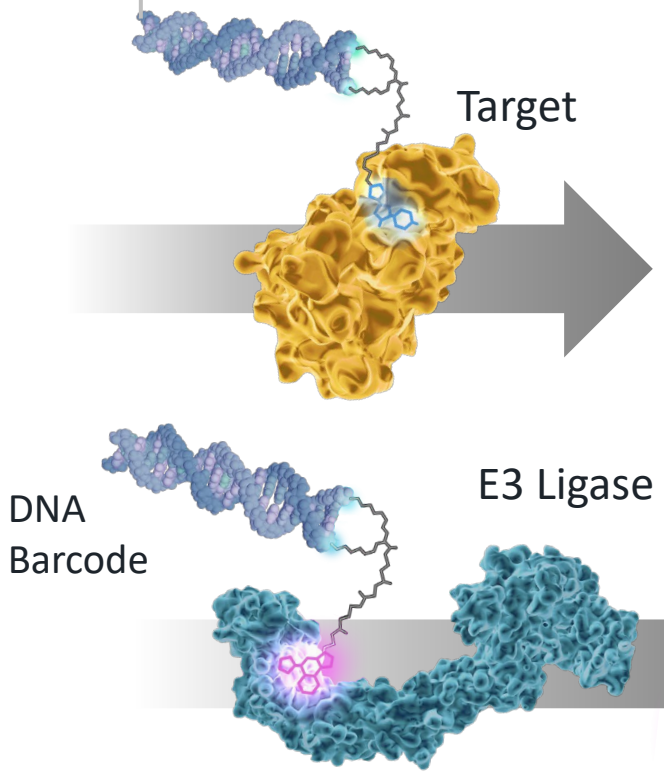
DELigase® Enables Efficient Chimeric Targeting Molecule Discovery and Design

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

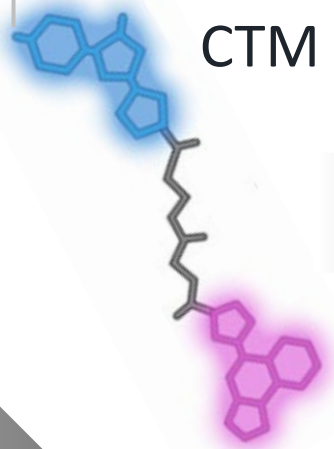


BB = Chemical Building Blocks

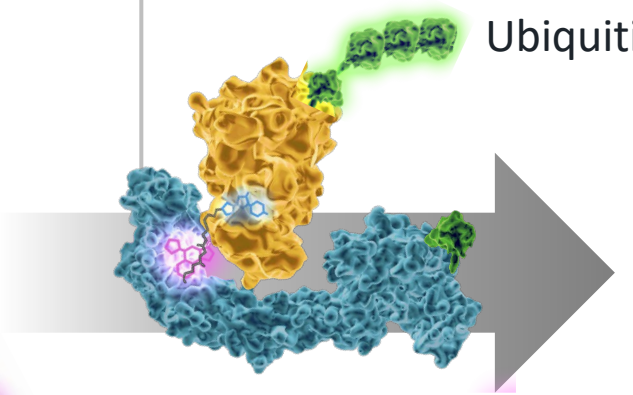
2 Target proteins and E3 ligases are screened using DEL



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

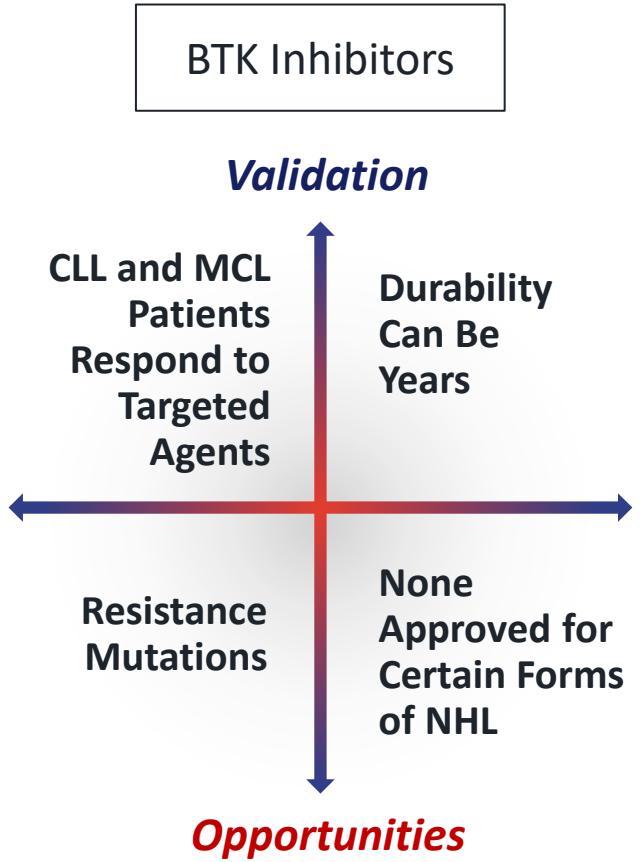


Nurix's BTK Degrader Portfolio: A Differentiated Approach to B-Cell Malignancies

- **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 sales of $7.1 billion in 2020
  - 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

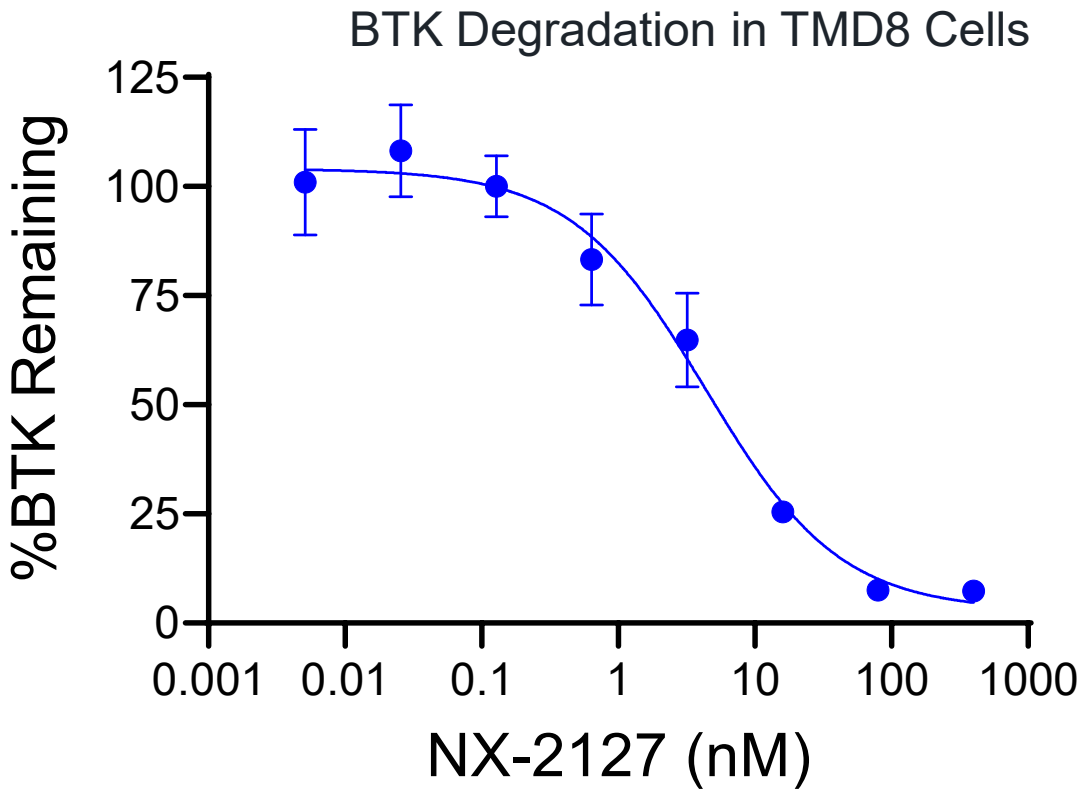
NX-2127: BTK degrader with IMiD activity. Developing across multiple B-cell malignancies (CLL, MCL, WM, MZL, DLBCL, FL)

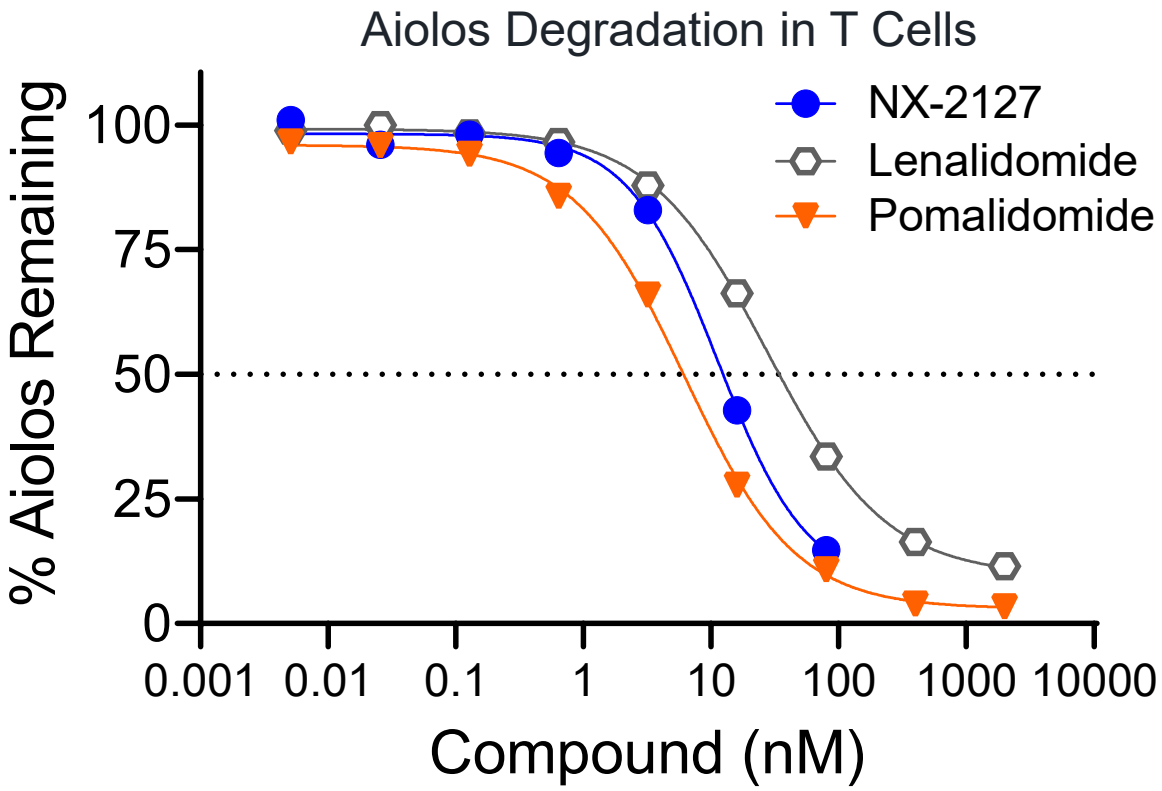
NX-5948: BTK degrader without IMiD activity. Developing for targeted B-cell malignancies and autoimmune diseases.



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

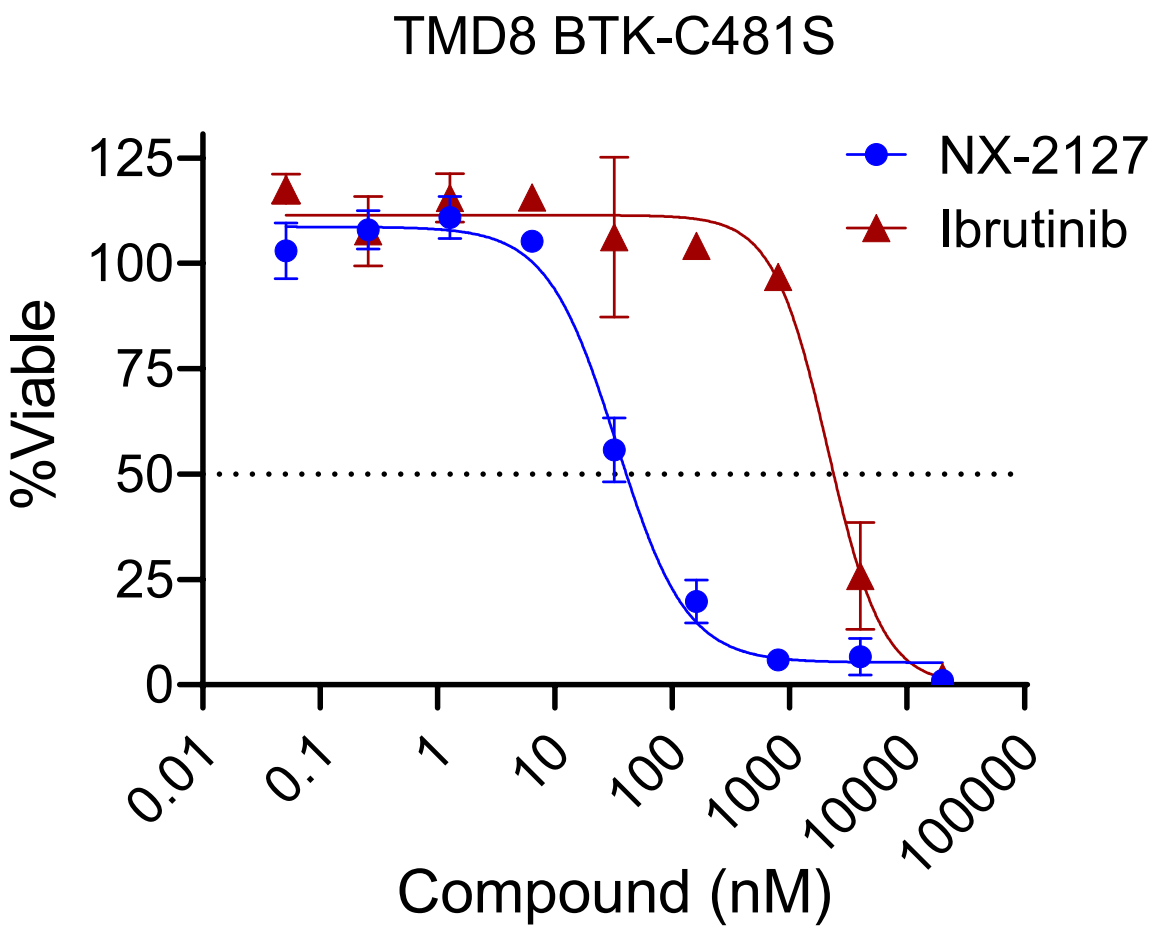




NX-2127 shows potent BTK degradation in TMD8 cells (human DLBCL cell line)

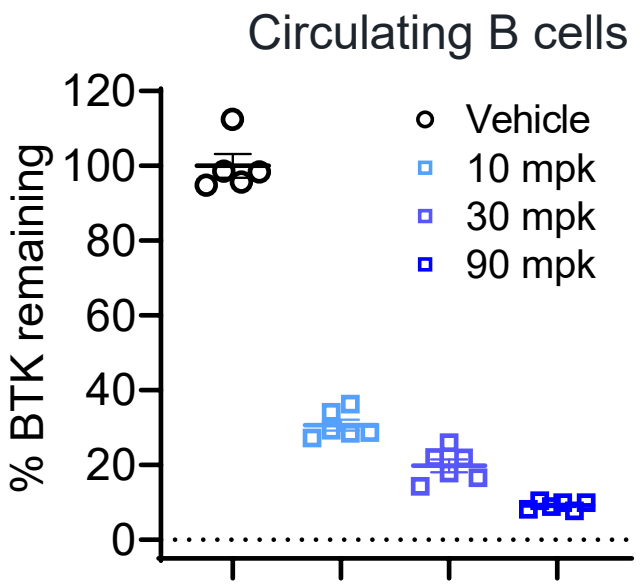
NX-2127 degradation of Aiolos in human T cells occurs at a similar potency to lenalidomide and pomalidomide

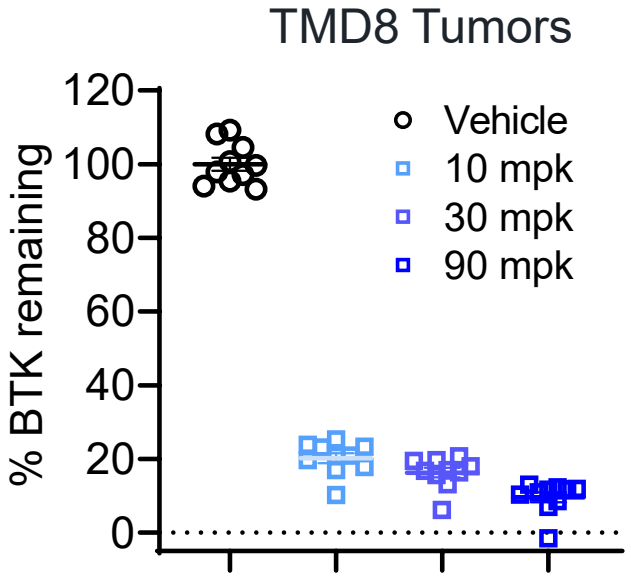
NX-2127 Potently Inhibits Growth of Ibrutinib-Resistant Tumor Cell Lines

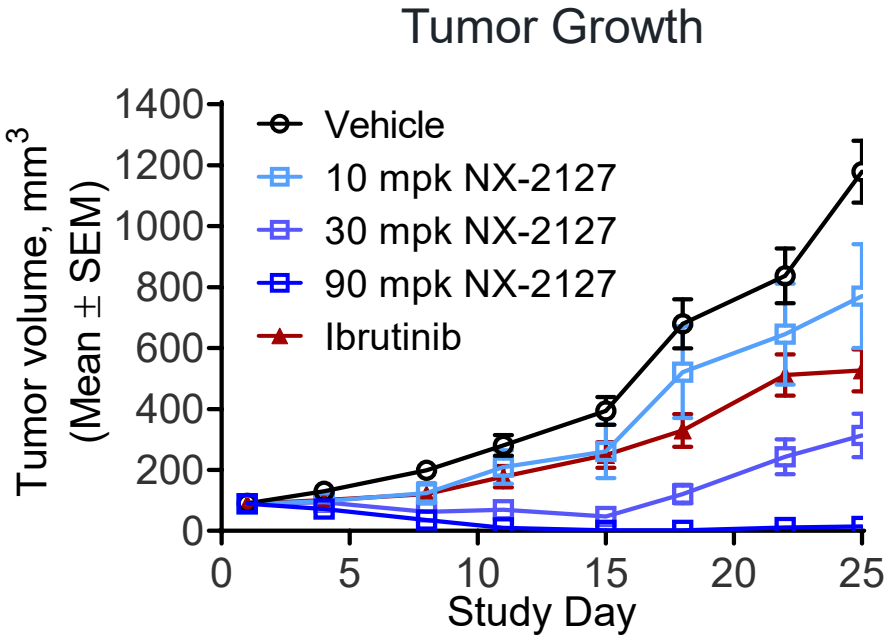


- NX-2127 retains potent growth inhibition relative to BTK inhibitors in a tumor cell line carrying the C481S mutation
- Degradation of BTK with NX-2127 may offer a therapeutic option for patients who develop resistance to BTK inhibitors
- NX-2127 also shows superior activity to BTK inhibitors in wild-type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

Increasing BTK Degradation Correlates with Significant Tumor Growth Inhibition



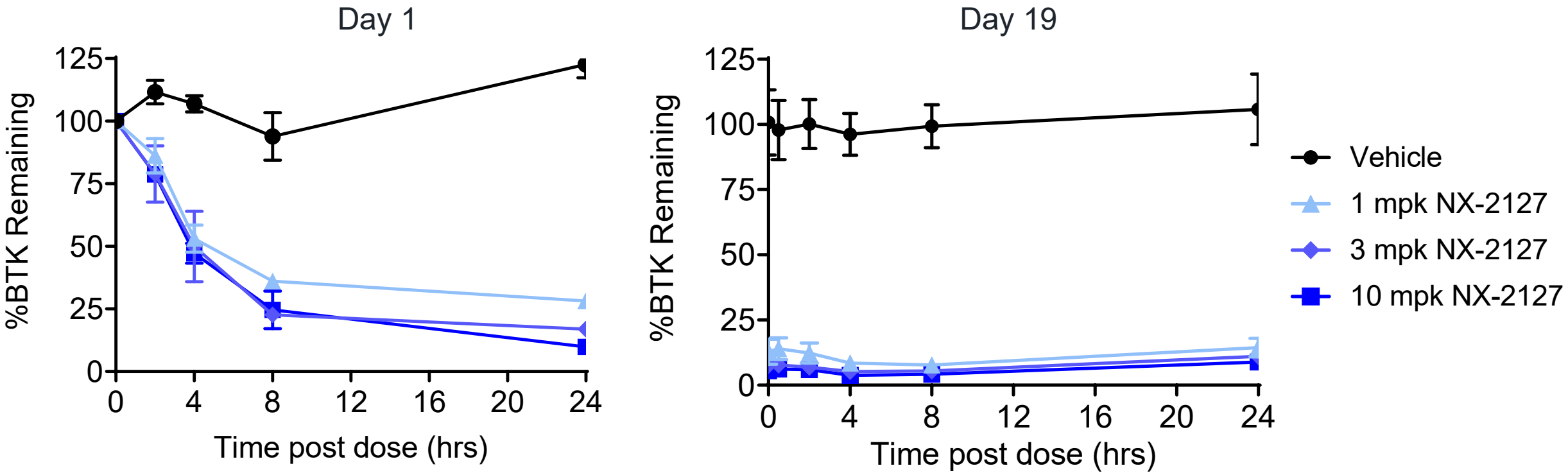




Treatment	Oral gavage dose (mg/kg)	% BTK degradation in circulating B cells	% BTK degradation in TMD8 tumor tissue	% TGI vs Vehicle (Day 24)	*P* value vs Vehicle
Vehicle	0	0.0±3.2	0.0±1.8	N/A	0
NX-2127	10	69.3±1.5	79.8±1.4	58%	0.0492
	30	80.2±1.8	83.7±1.3	74%	<0.0001
	90	90.8±0.4	90.4±1.4	100%	<0.0001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

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

BTK Degradation with Once Daily Oral Dosing of NX-2127 in Non-Human Primates



- All dose levels achieve BTK degradation consistent with anti-tumor effects in mouse model
- At steady state once daily, oral dosing of NX-2127 maintains suppression of BTK protein levels throughout the dosing period

Robert J. Brown, M.D.

SVP, Clinical Development

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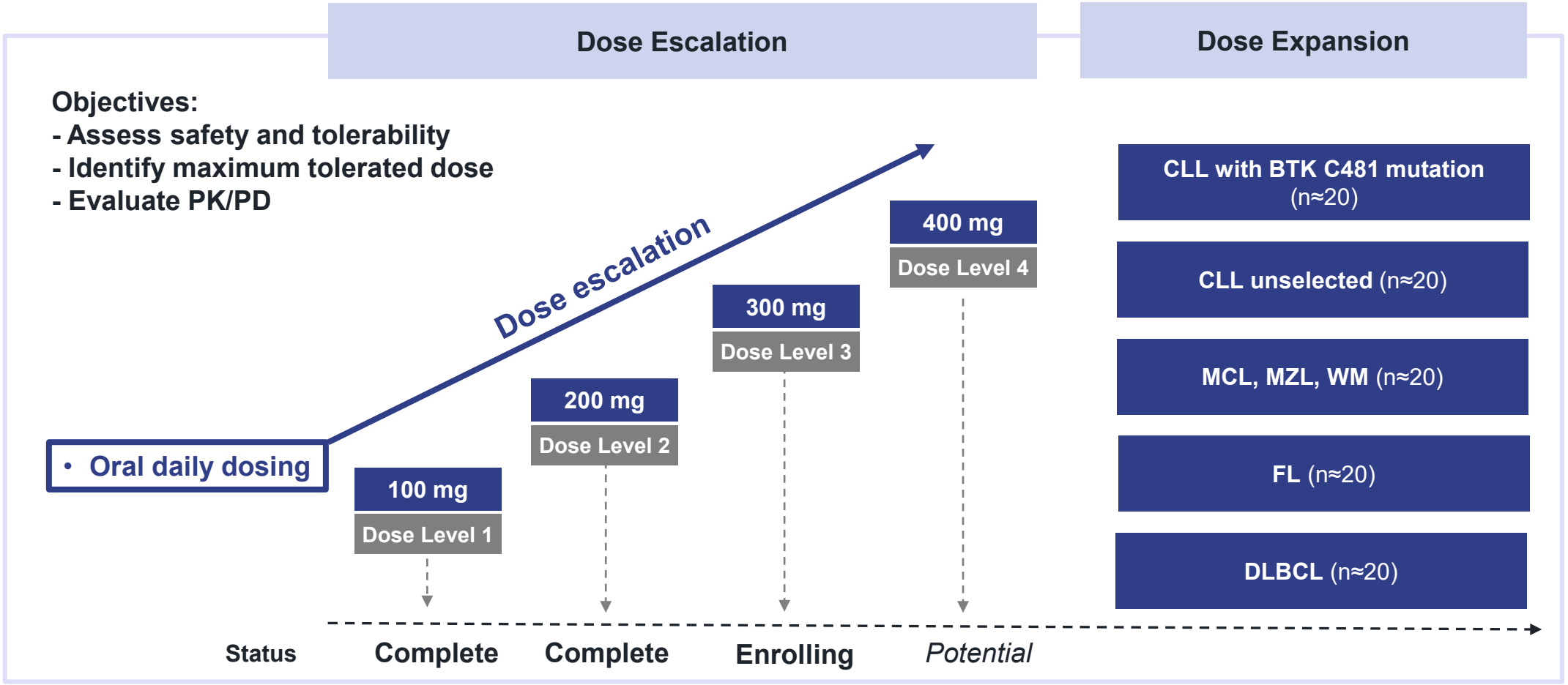
NX-2127-001: Phase 1 First-in-Human Clinical Trial Design

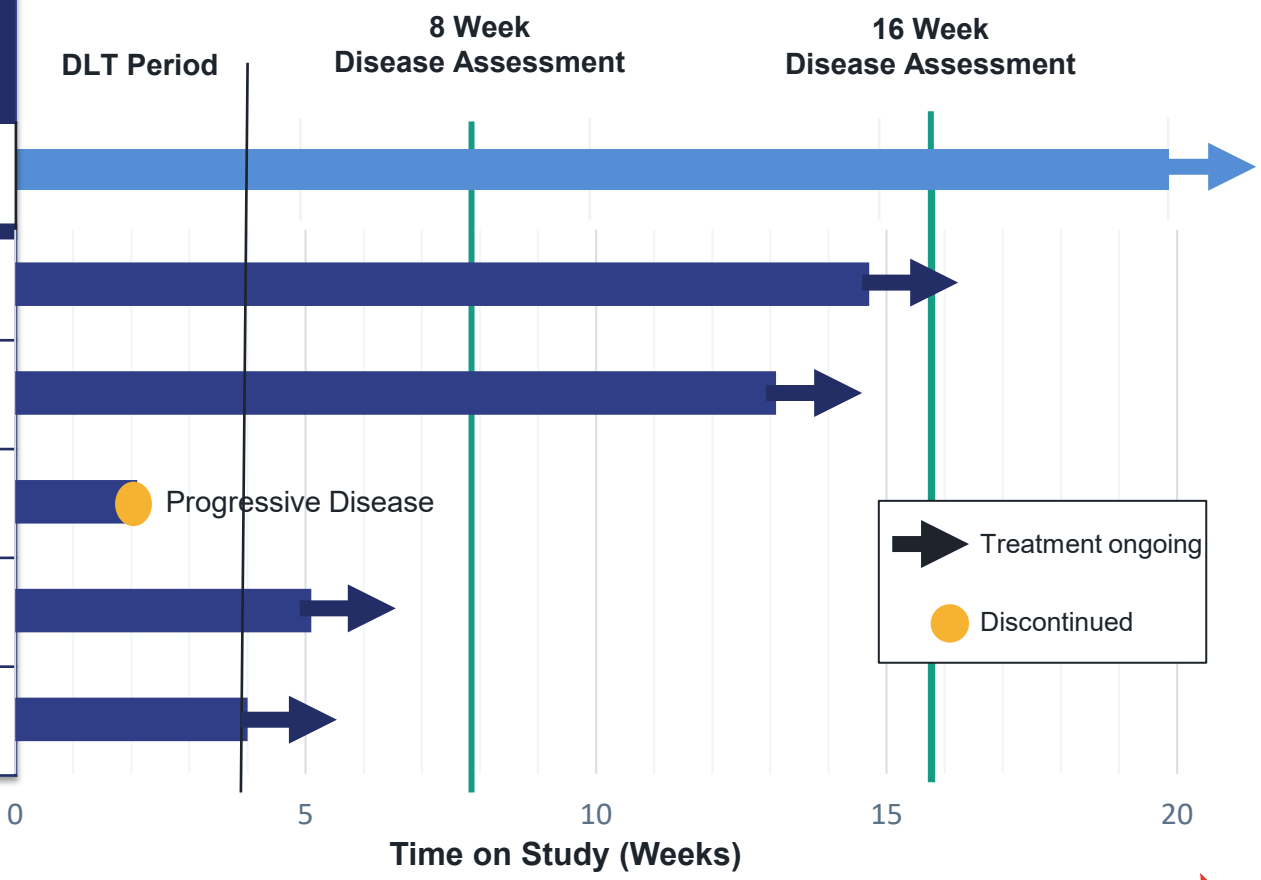
Two-Part Phase 1 Monotherapy Trial of NX-2127 in Relapsed or Refractory B-Cell Malignancies



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

Study Disposition: Five of Six Relapsed/Refractory Patients Enrolled Remain on Study with NX-2127

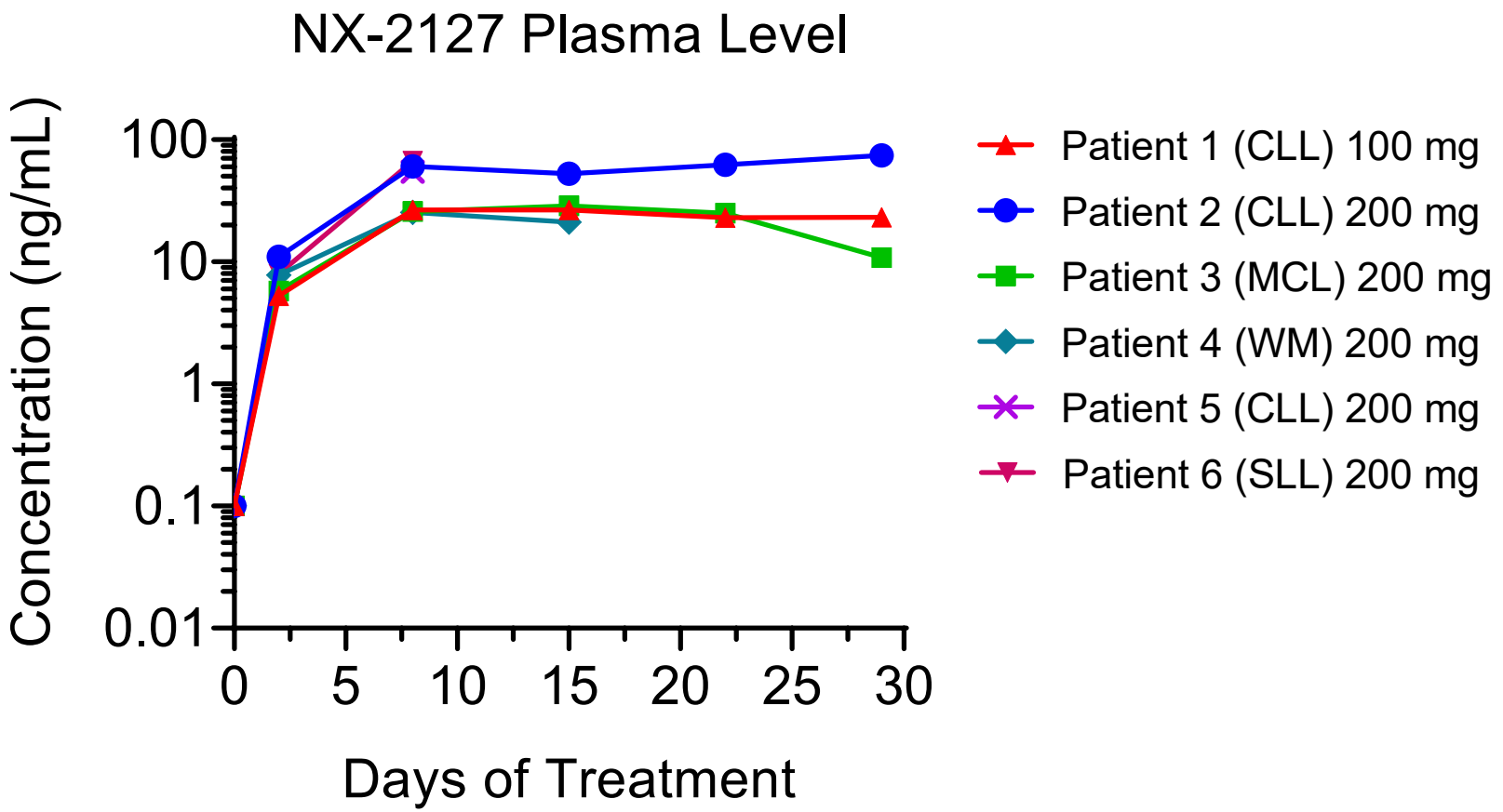
7 Patients Screened, 6 Patients enrolled				
NX-2127 Dose	**Patient**	**Disease Type**	**No. Prior Lines**	**Prior BTK-Targeted Therapy**
100 mg	1	CLL	2	Ibrutinib
200 mg	2	CLL	6	Ibrutinib
	3	MCL	4	Ibrutinib, acalabrutinib, and pirtobrutinib
	4	WM	4	Ibrutinib and pirtobrutinib
	5	CLL	3	Ibrutinib
	6	SLL	9	Ibrutinib



Data as of October 18, 2021
Time on study calculated as time from dosing start date to data extraction date

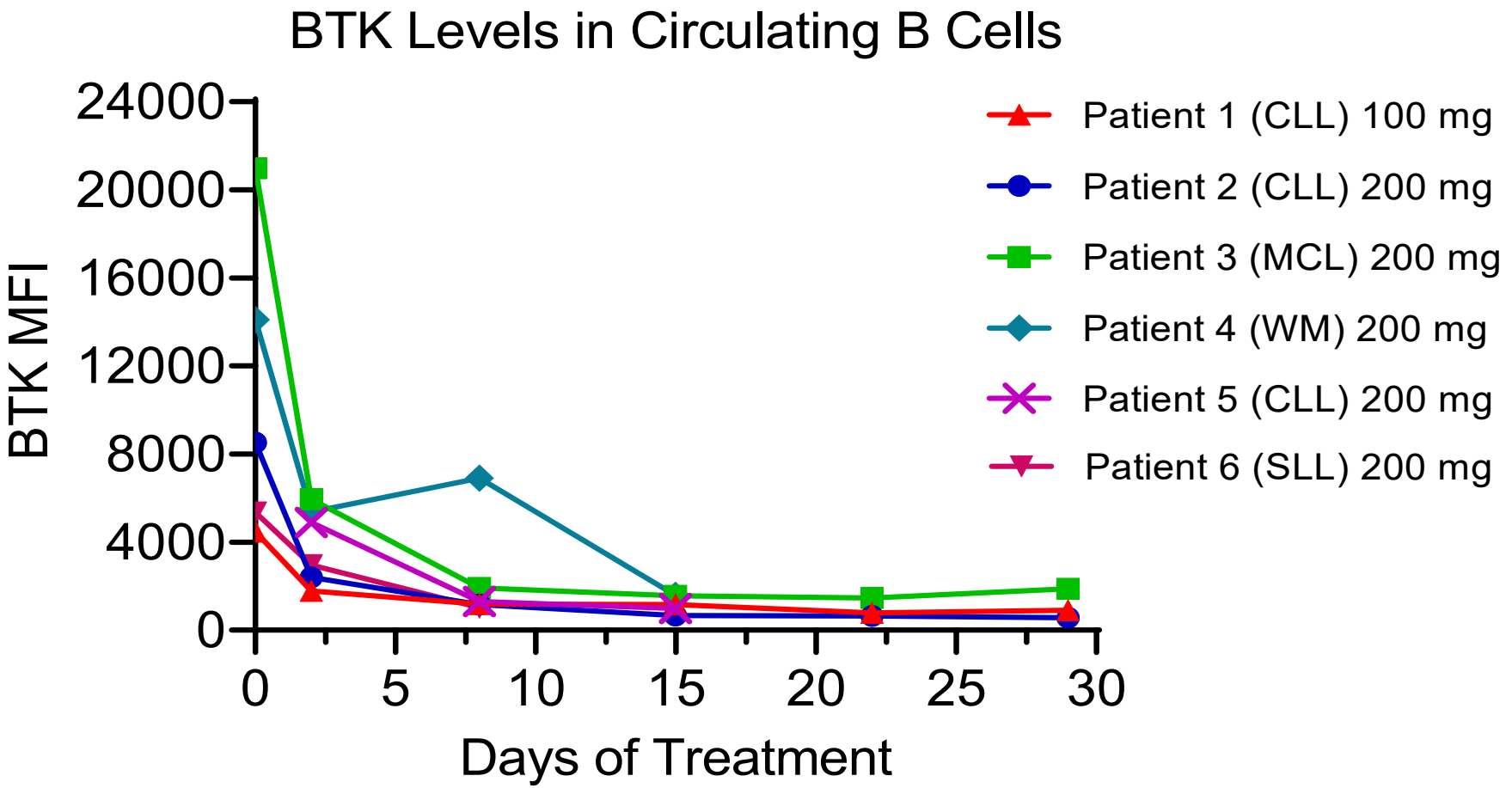
Daily Oral Dosing Achieves Steady State NX-2127 Levels by Day 8

- Oral daily doses of NX-2127 achieves steady state concentrations by Day 8
- Oral daily dosing of NX-2127 demonstrates plasma exposure similar that observed in non-human primates



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

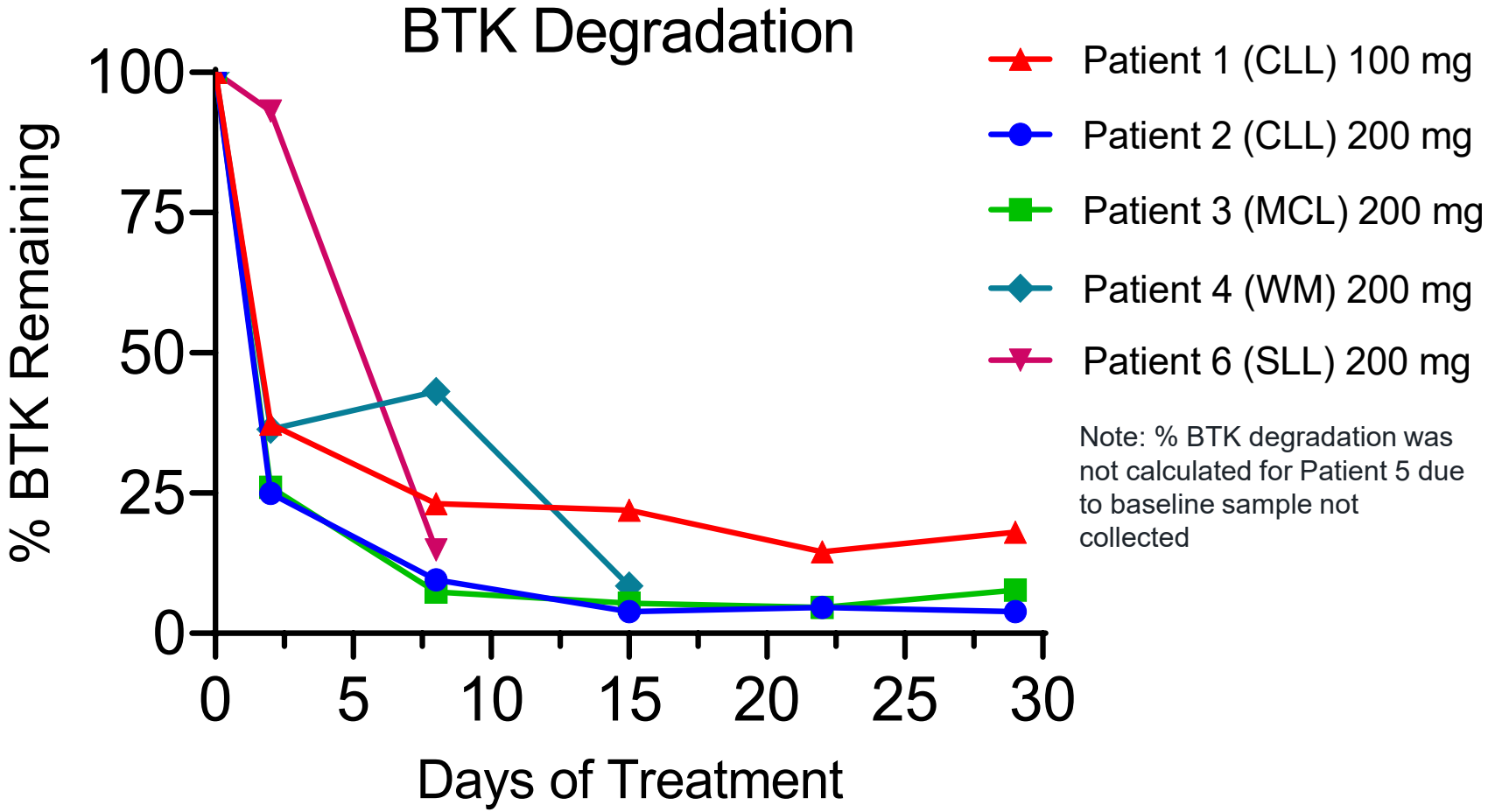
- Patients have varying levels of BTK in B cells at the start of treatment
- Oral daily treatment of NX-2127 induced a rapid and significant decrease in BTK levels that was sustained throughout dosing



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

Greater Than 90% BTK Degradation Achieved at Steady State at Second Dose Level (200 mg once daily)

- Cohort 1 patient with **>80%** BTK degradation at steady state
- Cohort 2 average **>90%** BTK degradation at steady state
- BTK degradation in patients was consistent with results from mouse and primate models
- BTK % degradation was confirmed by western blot



Note: % BTK degradation was not calculated for Patient 5 due to baseline sample not collected

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

No Dose Limiting Toxicities Observed in the First Two Cohorts

- No deaths
- No related serious adverse events

All Grade 3 or Greater Adverse Events

Preferred Term	Dose Level (mg)	Grade	Relatedness	Intervention	Disposition
Neutropenia	100	3	Yes	None	Resolved
Neutropenia	200	3	Yes	Yes	Resolved
Hypertension	200	3	Yes	No	Resolved
Dyspnea	200	3	No	No	Resolved
Pneumonia	200	3	No	Yes	Ongoing

- NX-2127 appears to be well tolerated at this early stage with a safety profile that is consistent with its known mechanisms of action
- Full safety data will be presented by our investigators at a later medical meeting

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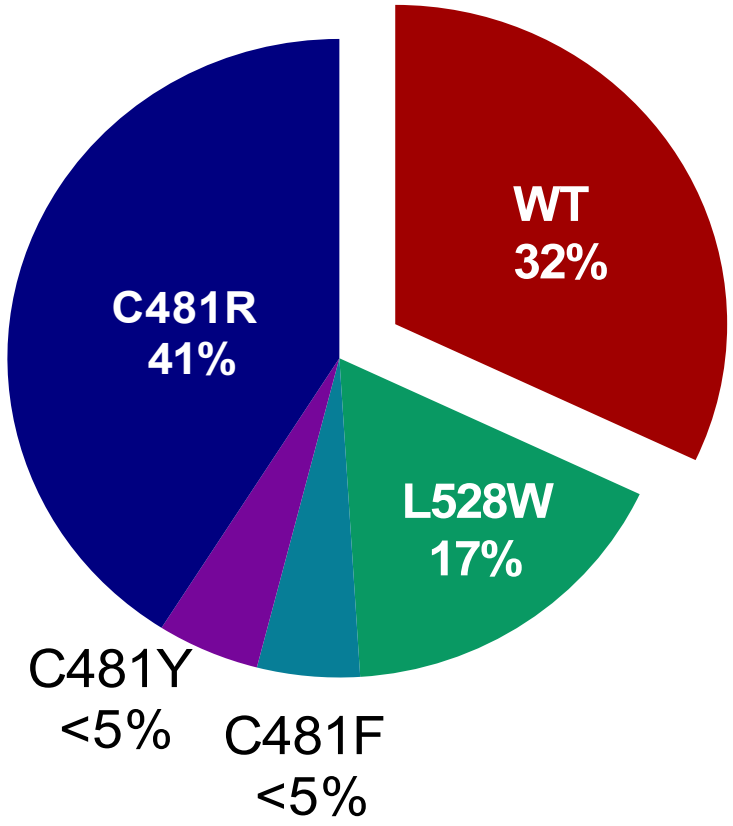
Case Study: Patient in Cohort 1

Patient History:
78 year-old male with stage IV CLL
Date of Initial Diagnosis: March 2012

Prior Treatments:
1. Rituximab (with solumedrol), 2015
2. Ibrutinib, 2015-2021

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

Up to 68% of Leukemia Cells with BTK Mutations



Clinical Response Observed in Patient 1

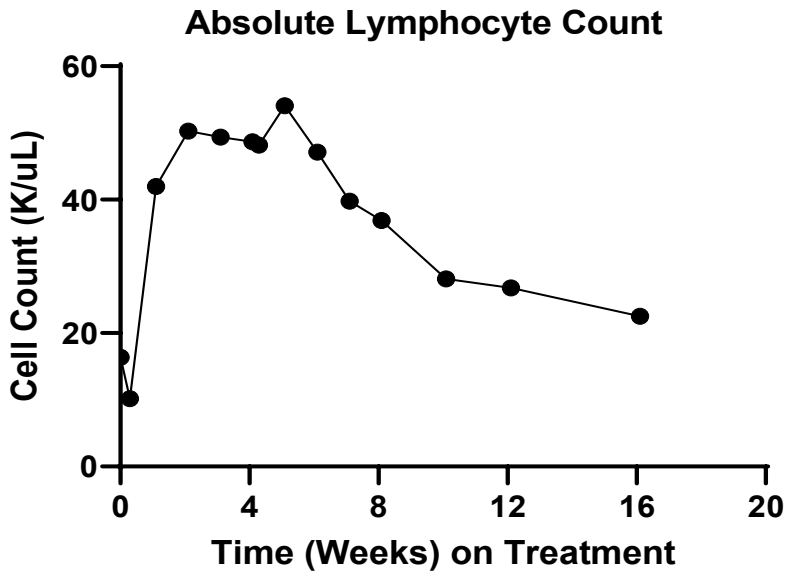
Safety

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

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



Preliminary Findings:
Robust Degradation of BTK by NX-2127 in All Patients Dosed

- NX-2127 is well-tolerated to date with no dose-limiting toxicities
  - Safety profile at this early stage is manageable and consistent with mechanisms of action
  - 5 of 6 patients remain on study
  - Dose escalation has advanced to Cohort 3 at 300 mg once daily

- First demonstration of TPD of BTK in hematologic malignancies
  - Greater than 90% BTK degradation observed in all patients at steady state in Cohort 2 (200 mg)
  - PK/PD was consistent with modeling and preclinical animal studies

- Clinical response observed in Patient 1 at first dose level of 100 mg once daily
  - BTK degradation exceeded 80% at steady state
  - Patient's disease expressed 68% mutated BTK, including approximately 50% C481 mutations

Conclusions

1. Nurix protein modulation pipeline now has two programs in clinical development: NX-2127 (TPD) and NX-1607 (ligase inhibition) with two more programs advancing

2. Robust BTK degradation demonstrated by NX-2127 in patients validates Nurix's BTK portfolio approach in targeted protein degradation

   a) Preclinical models of PK and BTK degradation have been reliable predictors of degradation mechanism of action in humans

   b) Human data from NX-2127 informs future dose selection for NX-5948, Nurix's BTK degrader that lacks IMiD activity and crosses the blood brain barrier in preclinical studies

3. Nurix anticipates advancing NX-2127 to Phase 1b dose expansion in H1 2022

4. These initial data support the concept of targeted protein degradation as a potential therapeutic approach in hematologic malignancies

Questions and Answers