nurix

Leader in Targeted Protein Modulation

NX-2127: A Degrader of BTK and IKZF1/3

Davorka Messmer, Ph.D.

Discovery on Target: Targeting Transcription Factors

Boston, MA

September 28th, 2023

Important Notice and Disclaimers

This presentation contains statements that relate to future events and expectations and as such constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. When or if used in this presentation, the words “anticipate,” “believe,” “could,” “estimate,” “expect,” “intend,” “may,” “outlook,” “plan,” “predict,” “should,” “will,” and similar expressions and their variants, as they relate to Nurix Therapeutics, Inc. (“Nurix”, the “Company,” “we,” “us” or “our”), may identify forward-looking statements. All statements that reflect Nurix’s expectations, assumptions or projections about the future, other than statements of historical fact, are forward-looking statements, including, without limitation, statements regarding our future financial or business plans; our future performance, prospects and strategies; future conditions, trends, and other financial and business matters; our current and prospective drug candidates; the planned timing and conduct of the clinical trial programs for our drug candidates; the planned timing for the provision of clinical updates and initial findings from our clinical studies; the potential advantages of our DELigase™ platform and drug candidates; the extent to which our scientific approach and DELigase™ platform may potentially address a broad range of diseases; the extent animal model data predicts human efficacy; and the timing and success of the development and commercialization of our current and anticipated drug candidates. Forward-looking statements reflect Nurix’s current beliefs, expectations, and assumptions. Although Nurix believes the expectations and assumptions reflected in such forward-looking statements are reasonable, Nurix can give no assurance that they will prove to be correct. Forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and changes in circumstances that are difficult to predict, which could cause Nurix’s actual activities and results to differ materially from those expressed in any forward-looking statement. Such risks and uncertainties include, but are not limited to: (i) risks and uncertainties related to Nurix’s ability to advance its drug candidates, obtain regulatory approval of and ultimately commercialize its drug candidates; (ii) the timing and results of clinical trials; (iii) Nurix’s ability to fund development activities and achieve development goals; (iv) the impact of macroeconomic conditions, including inflation, increasing interest rates and volatile market conditions, and global events, on Nurix’s clinical trials and operations; (v) Nurix’s ability to protect intellectual property and (vi) other risks and uncertainties described under the heading “Risk Factors” in Nurix’s Quarterly Report on Form 10-Q for the fiscal quarter ended May 31, 2023, and other SEC filings. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. The statements in this presentation speak only as of the date of this presentation, even if subsequently made available by Nurix on its website or otherwise. Nurix disclaims any intention or obligation to update publicly any forward-looking statements, whether in response to new information, future events, or otherwise, except as required by applicable law.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company’s own internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal estimates and research are reliable, such estimates and research have not been verified by any independent source.

Nurix Drugs Engage Ligases for the Treatment of Cancer

Targeted Protein Modulation: TPM = TPD + TPE

A Powerful Cellular System

Targeted Protein Elevation (TPE)

Inhibit ligases to increase specific protein levels

Harness ligases to decrease specific protein levels

Targeted Protein Degradation (TPD)

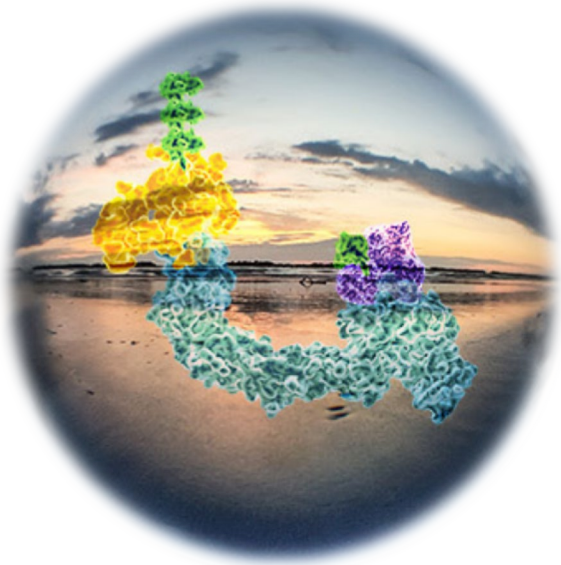
Ubiquitin is ligated to target proteins to tag them for degradation by the proteasome

A First-In-Class Franchise of BTK Degraders:
NX-5948 & NX-2127

NX-5948

BTK DEGRADATION

- Clinical evidence of potent BTK degradation in all patients tested
- Active against BTK inhibitor-resistant mutations in vitro
- Crosses blood brain barrier and degrades BTK in microglia and brain-resident lymphoma cells preclinically
- Activity in multiple models of autoimmune disease
- Phase 1a dose escalation trial ongoing in U.K. and U.S.



NX-2127

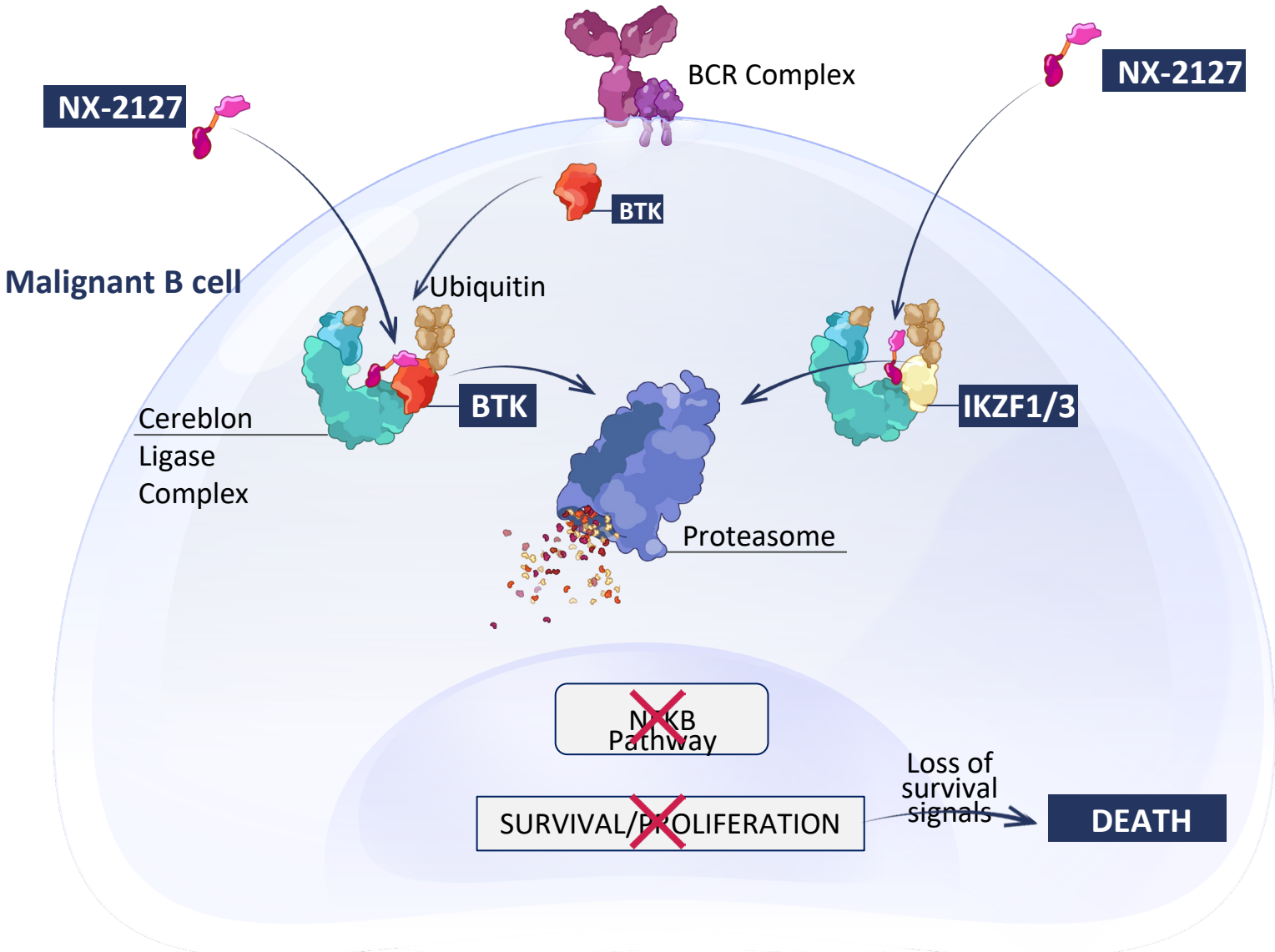
BTK DEGRADATION & IMMUNOMODULATION

- Positive clinical activity in CLL patients, including responses in patients with BTK or BCL2 mutations
- Active in the clinic against BTK inhibitor-resistant mutations
- Complete response observed in a patient with DLBCL
- Phase 1b cohort expansion for CLL, DLBCL, and MCL patients are ongoing
- Dose exploration is ongoing for patients with NHL

BTK, Bruton's tyrosine kinase

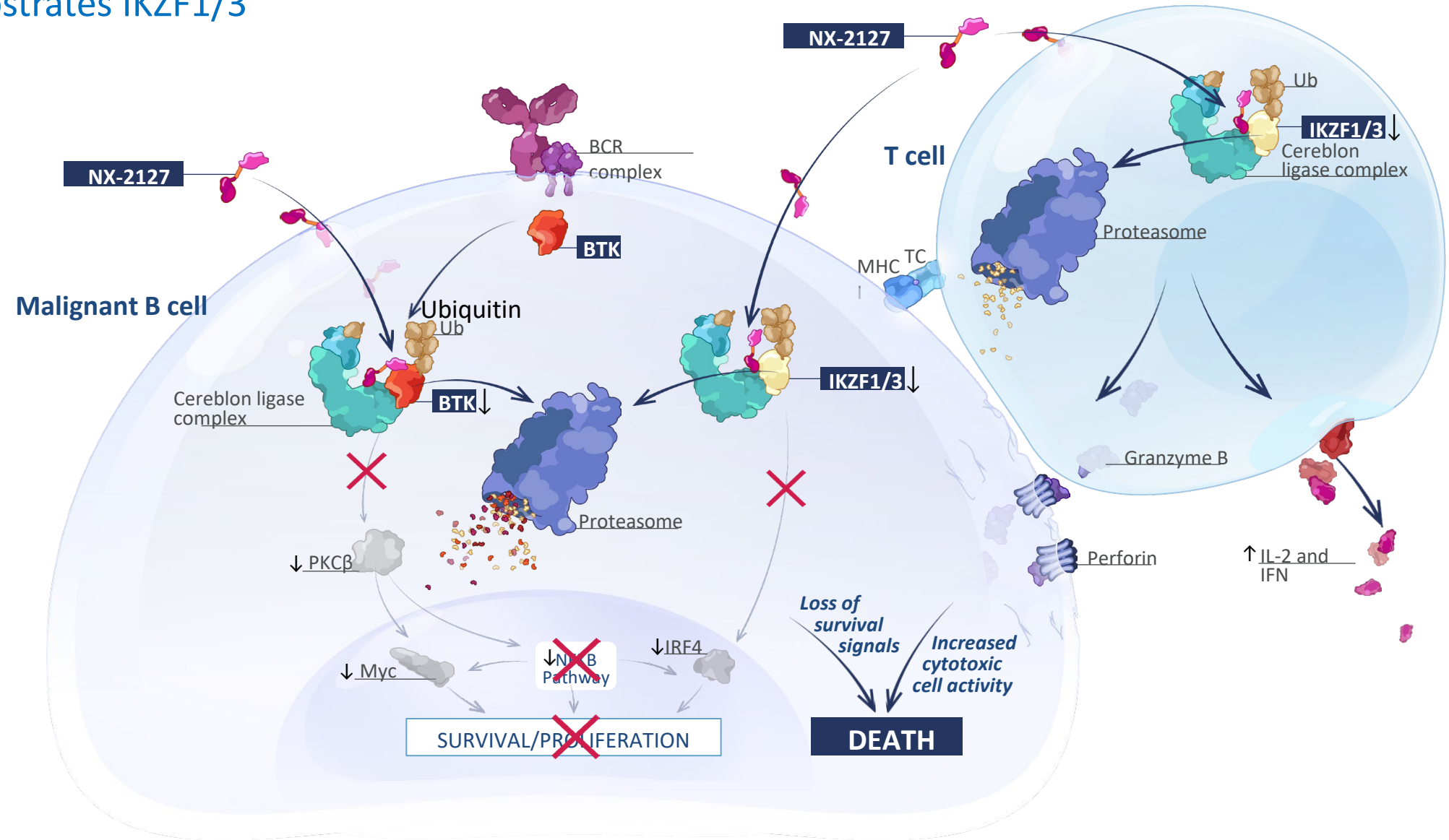
NX-2127 Dual Mechanism of Action

Targeted Degradation of BTK and CRBN Immunomodulatory Substrates IKZF1/3



NX-2127 Dual Mechanism of Action

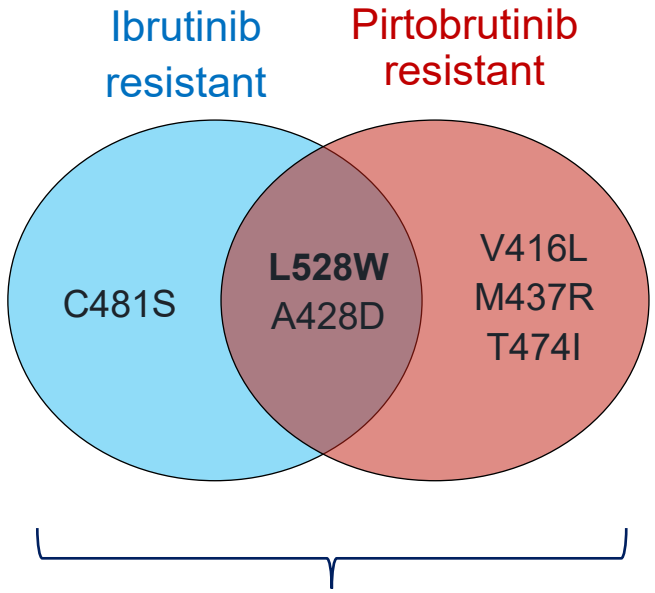
Targeted Degradation of BTK and CRBN Immunomodulatory Substrates IKZF1/3



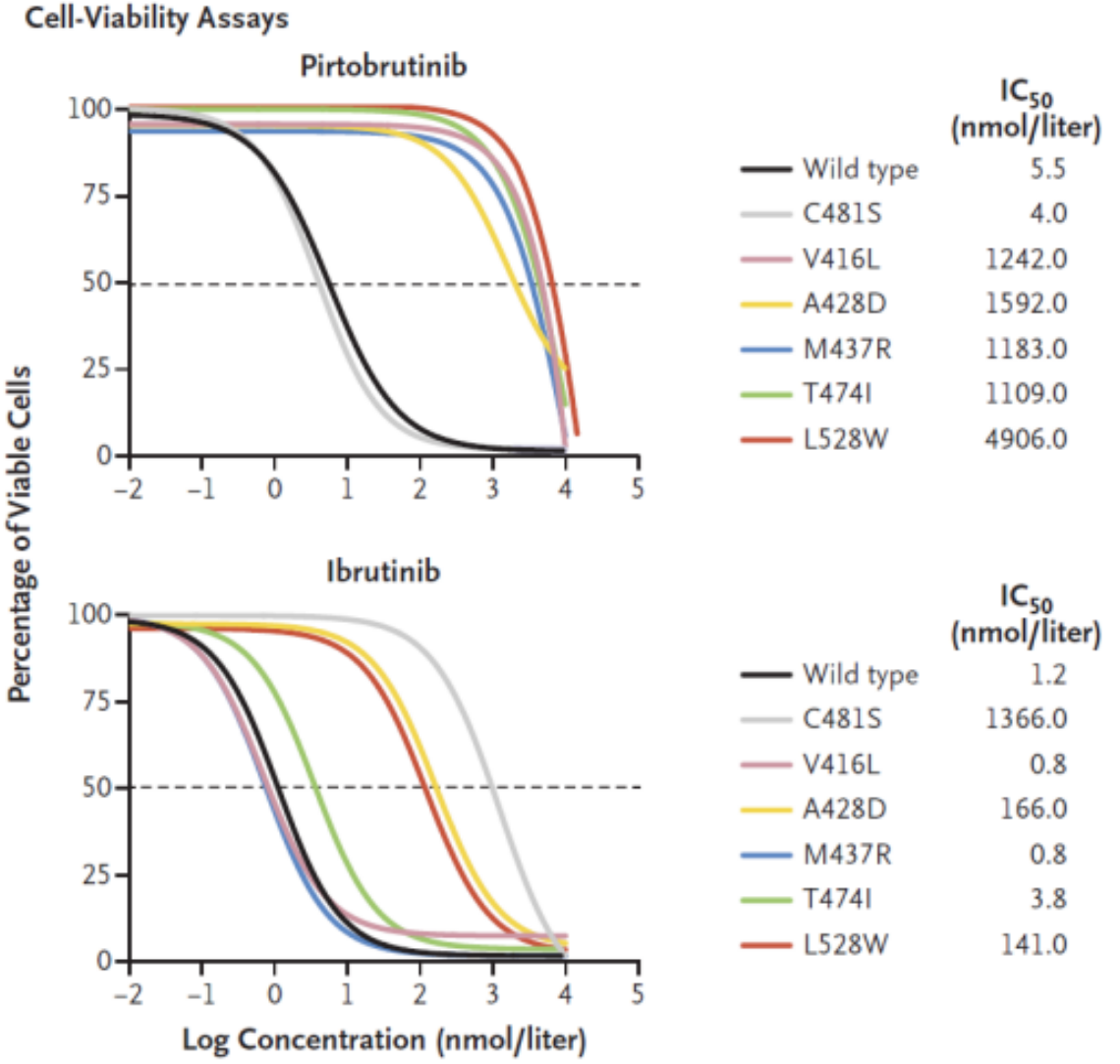
Emerging BTK Mutations Confer Resistance to Covalent and Non-Covalent BTK Inhibitors

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."

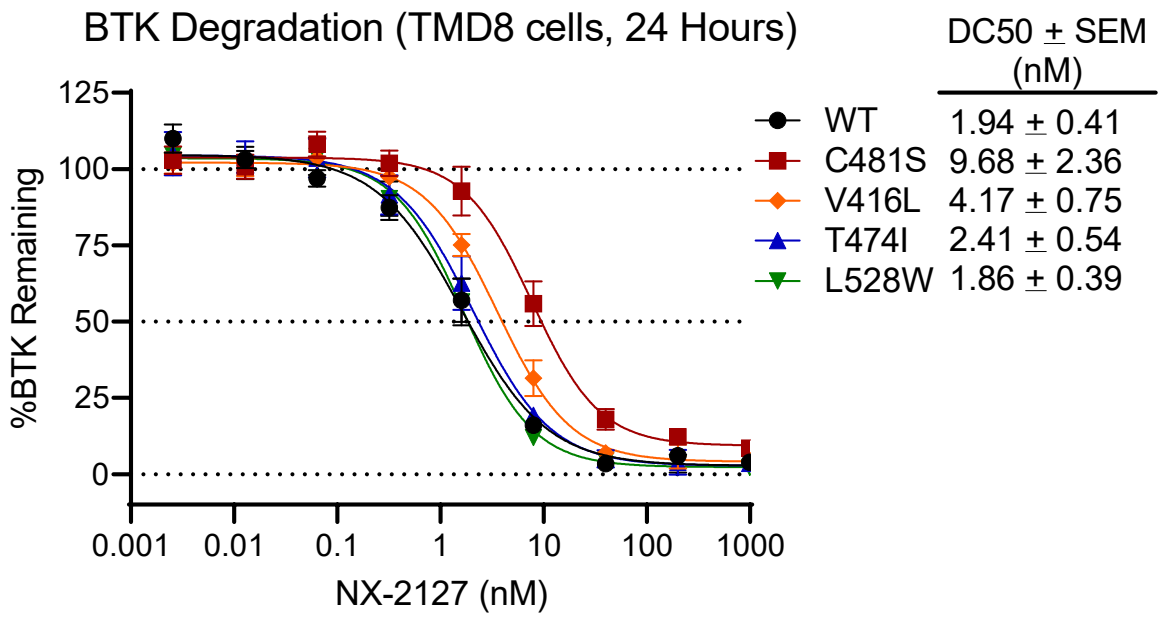


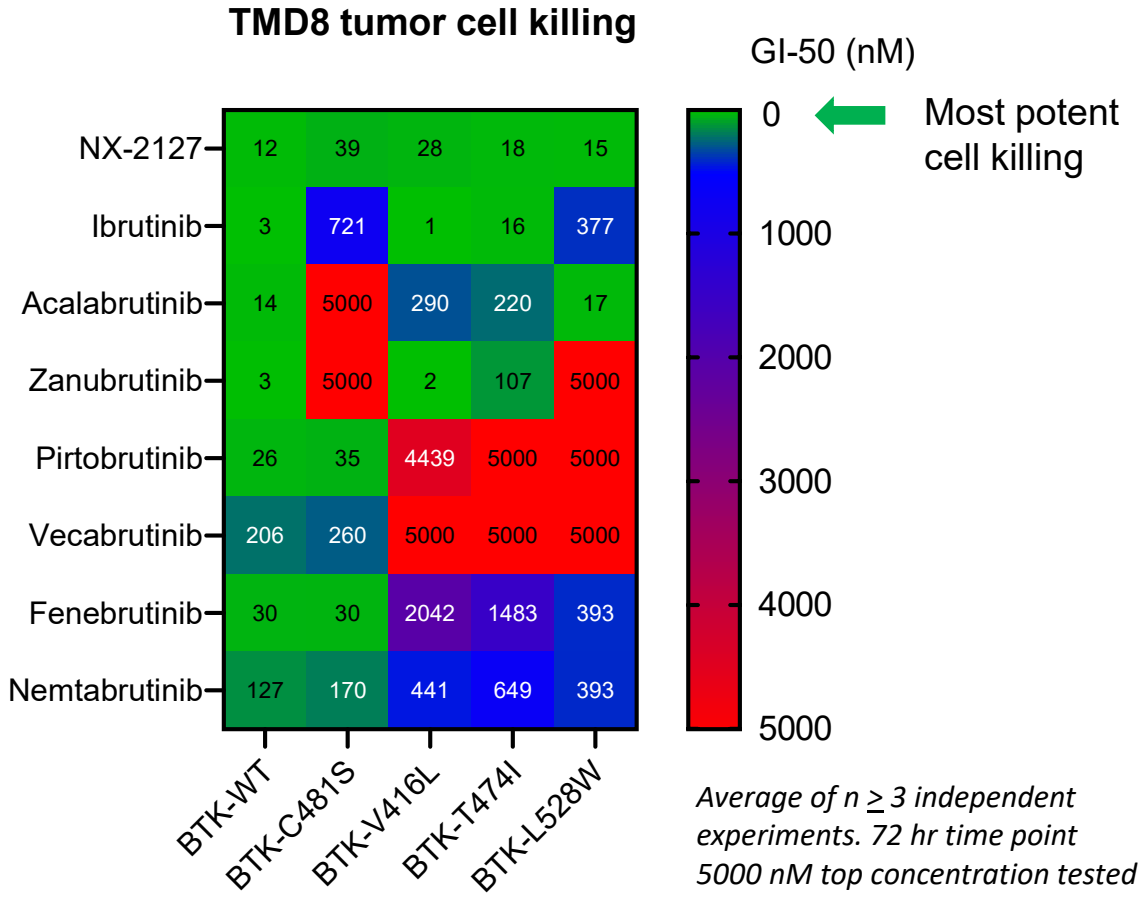
Opportunity for BTK degrader?



Wang E, et al. NEJM 2022

NX-2127 is Potent and More Broadly Active Than All BTK Inhibitors Tested





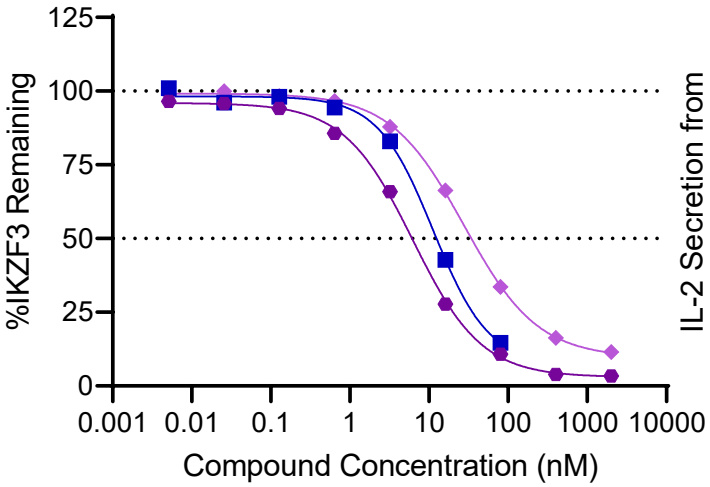
Average of n ≥ 3 independent experiments. 72 hr time point 5000 nM top concentration tested

- All inhibitors have resistance mutation liabilities
- NX-2127 displays potent BTK degradation and cell killing in the context of key resistance mutations

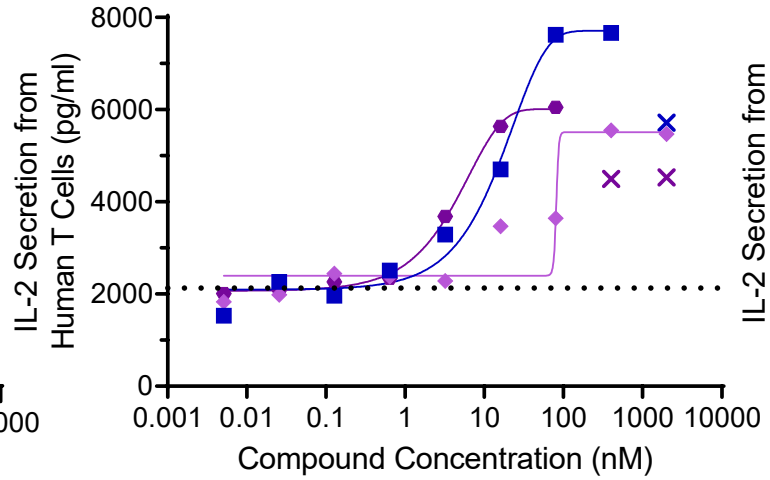
NX-2127 Degrades IKZF3 in T cells and Enhances IL-2 Secretion with Potency Similar to Immunomodulatory Drugs

Partial IKZF1/3 degradation is sufficient to enhance IL-2 secretion

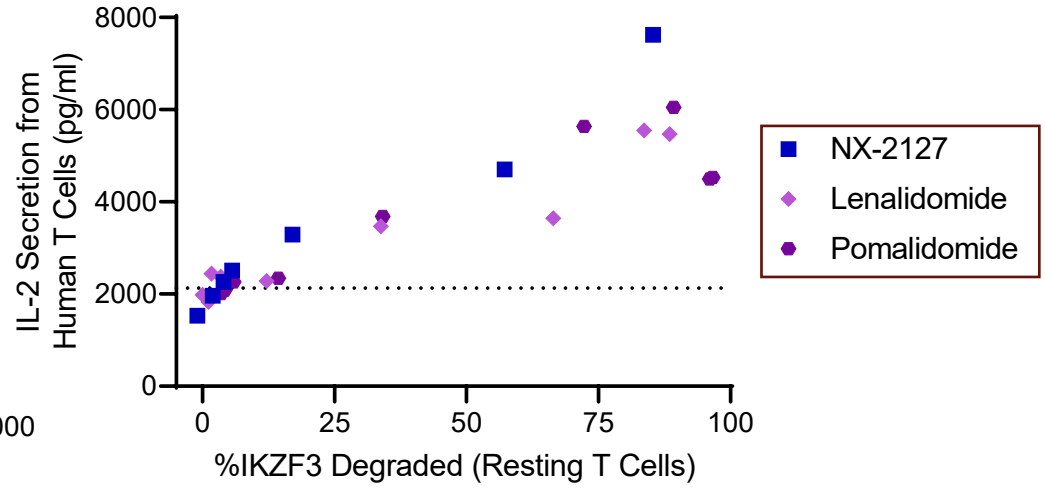
IKZF3 Degradation in Unstimulated human T Cells



Enhancement of IL-2 Secretion In TCR stimulated human T cells



Correlation of IKZF3 degradation with IL-2 Secretion



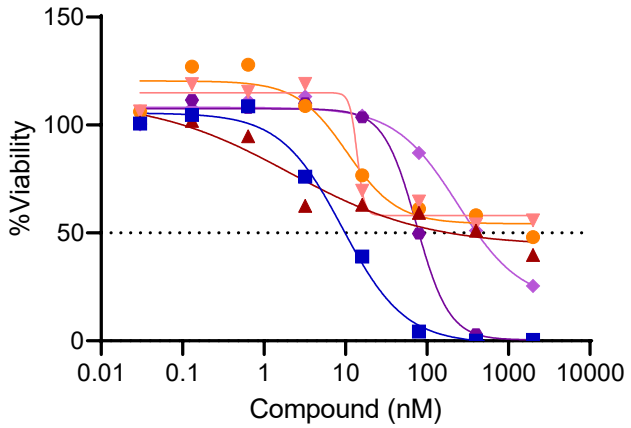
- Potency of NX-2127 falls between pomalidomide and lenalidomide in IKZF1/3 degradation and IL-2 secretion assays (IKZF1 data not shown)
- Enhancement of IL-2 secretion is observed with partial IKZF1/3 degradation

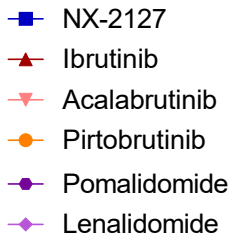
Noviski et al. AACR 2022. New Orleans, LA. Poster presentation.

NX-2127 Promotes Potent and Complete Killing of Mantle Cell Lymphoma Cells

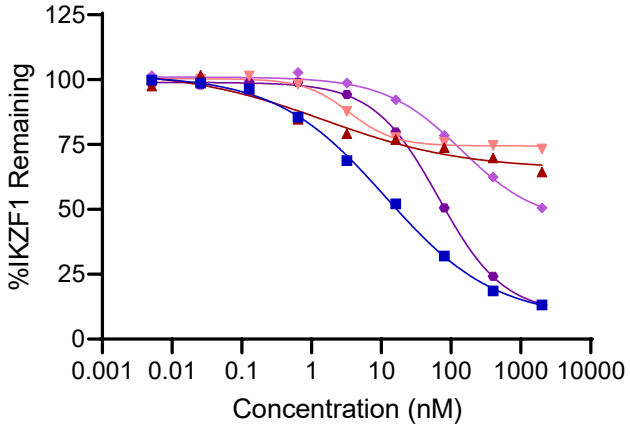
Potency and completeness are superior to BTK inhibitors and immunomodulatory drugs

REC-1 Cell Viability

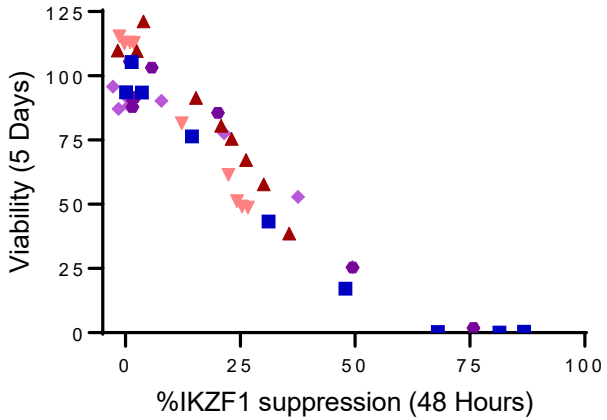


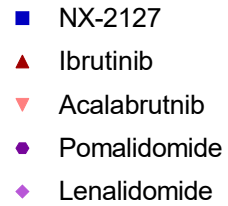


IKZF1 Suppression



Correlation between IKZF1 and Viability



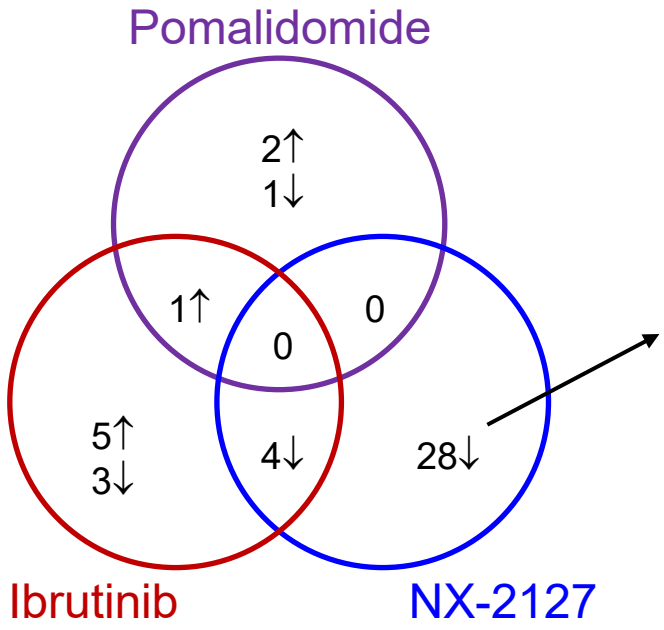


- BTK inhibitors only partially kill REC-1 cell line
- NX-2127 promotes complete killing of REC-1 cells and does so more potently than pomalidomide
- Anti-proliferative activity in REC-1 cells correlates with degradation or downregulation of IKZF1, and partial suppression of IKZF1 is sufficient to achieve maximal effect

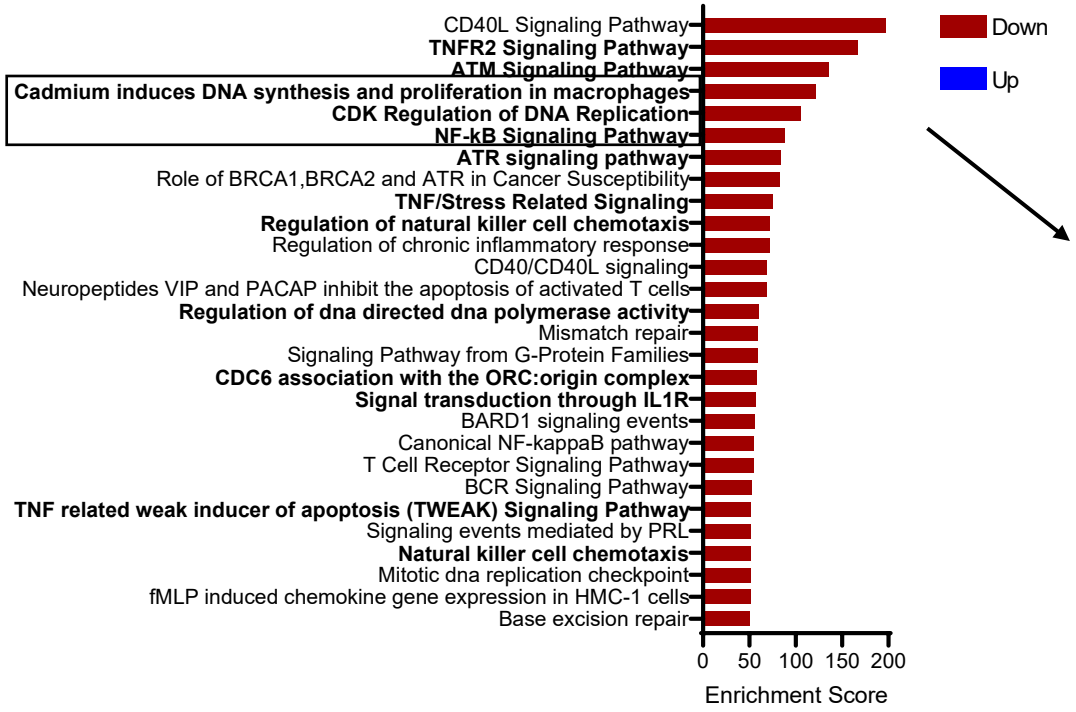
Noviski et al. AACR 2022. New Orleans, LA. Poster presentation.

Combination of BTK and Immunomodulatory Activity Downregulates Key Genes in Cell Cycle and NF-κB Pathway in REC-1 MCL Line

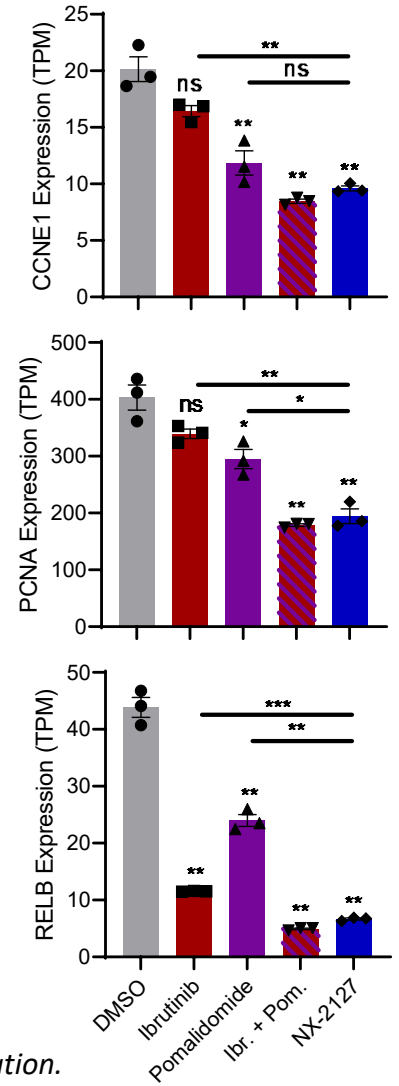
RNAseq in REC-1: Gene Set Modulation



Unique NX-2127 Gene Sets



Representative Genes



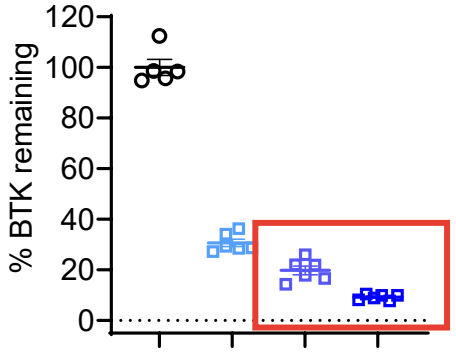
- Treatment with NX-2127 or ibrutinib + pomalidomide leads to downregulation of Cyclin E1, PCNA, and RELB in REC-1 mantle cell lymphoma line
- Combined effect is stronger than what BTK inhibition or immunomodulation achieves in isolation

Noviski et al. AACR 2022. New Orleans, LA. Poster presentation.

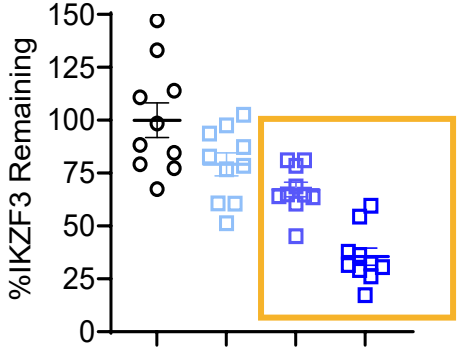
BTK Degradation of 80%+ Drives Potent Anti-tumor Activity in Preclinical Models

IKZF1 and IKZF3 degradation also achieve target range at therapeutic doses

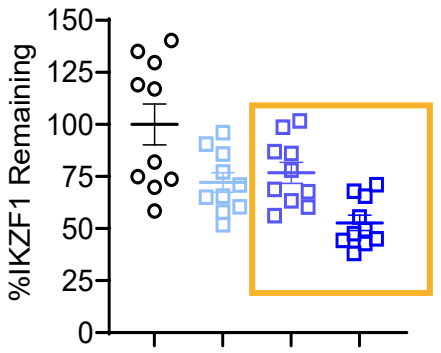
BTK Degradation in Peripheral B cells



IKZF3 Degradation in TMD8 Tumor Tissue

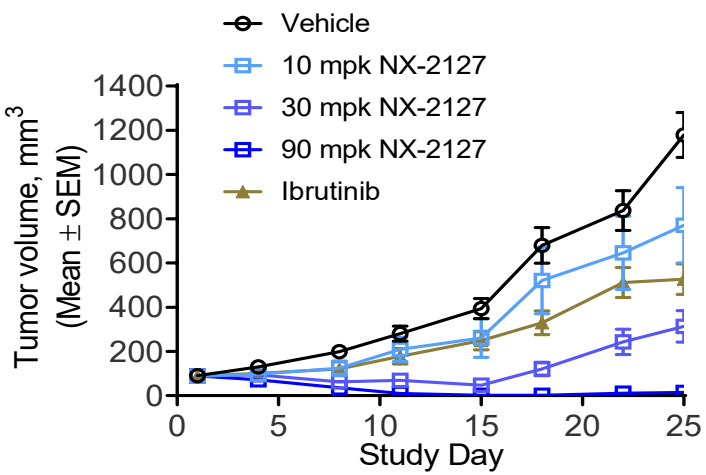


IKZF1 Degradation in TMD8 Tumor Tissue



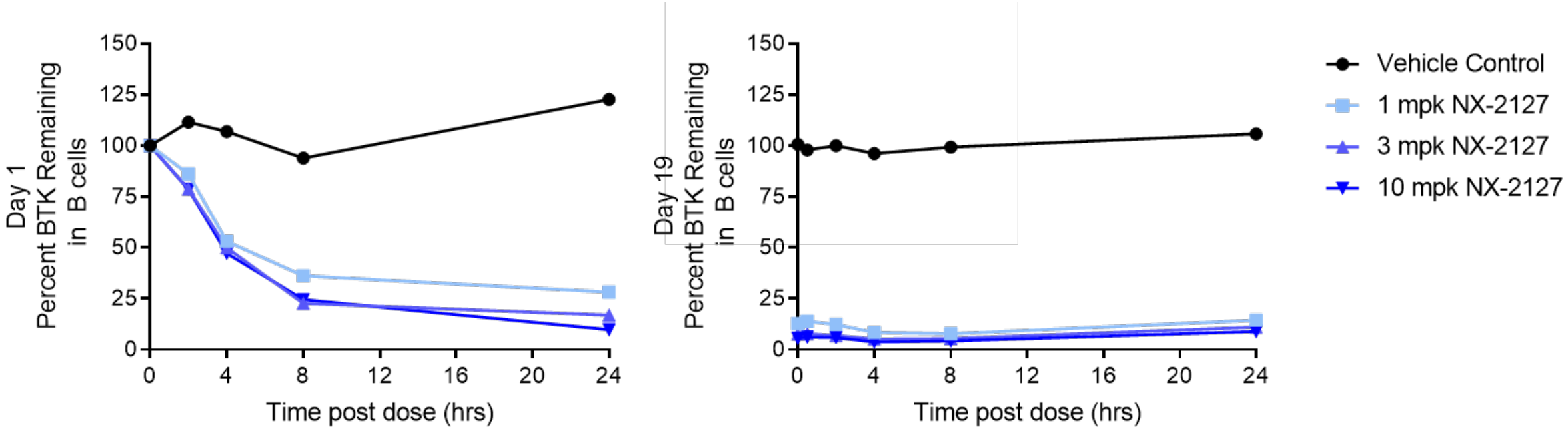
Vehicle 30 mpk
10 mpk 90 mpk

Tumor Growth



Oral dose of NX-2127 (mg/kg)	10	30	90
% BTK degradation in peripheral B cells	69%	80%	91%
% IKZF3 degradation in tumor tissue	21%	33%	64%
% IKZF1 degradation in tumor tissue	28%	23%	47%
% Tumor growth inhibition vs Vehicle(Day 24)	58%	74%	100%

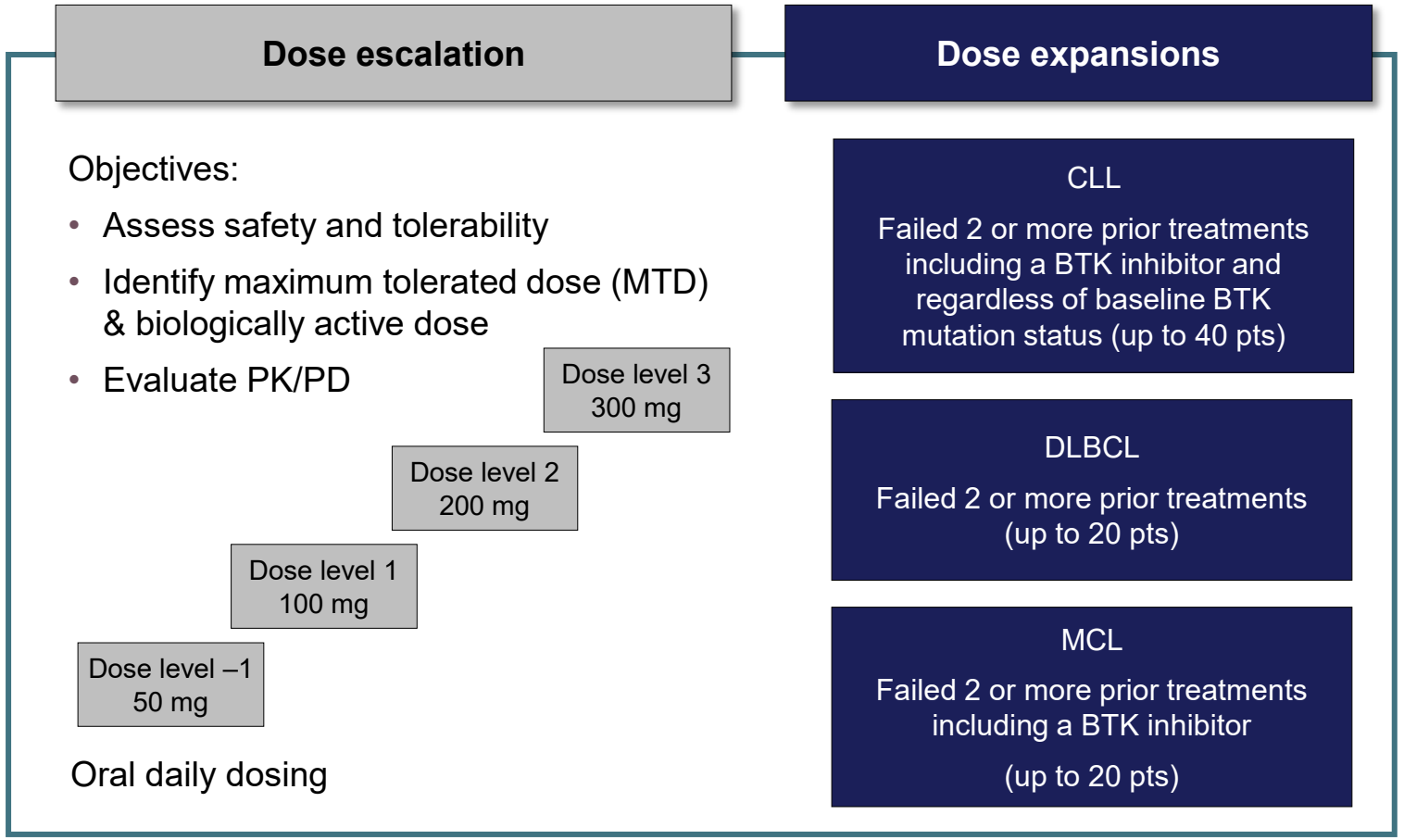
Oral Dosing of NX-2127 Degrades BTK in Non-Human Primates



- Significant degradation of BTK in 4 hours and more than 90% degradation through 24 hours post dosing at the highest dose level
- Once daily, oral dosing of NX-2127 maintains suppression of BTK protein levels throughout the 19-day duration of the study (NX-2127 PK $t_{1/2}$ = 5.4 h)

NX-2127-001: Trial Design

Phase 1 trial in adults with relapsed/refractory B-cell malignancies

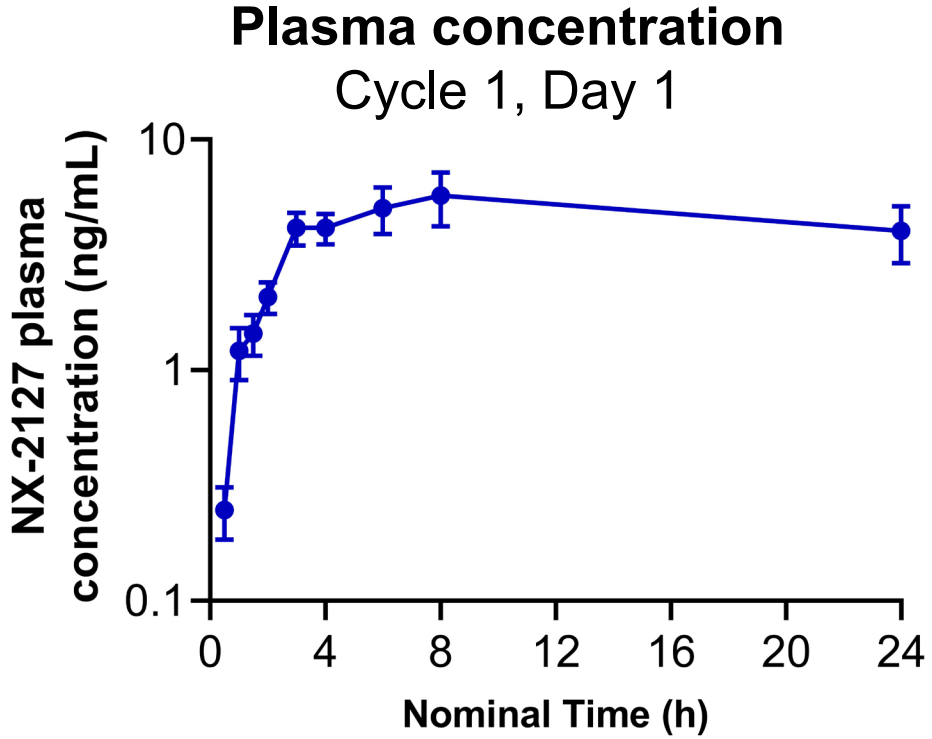


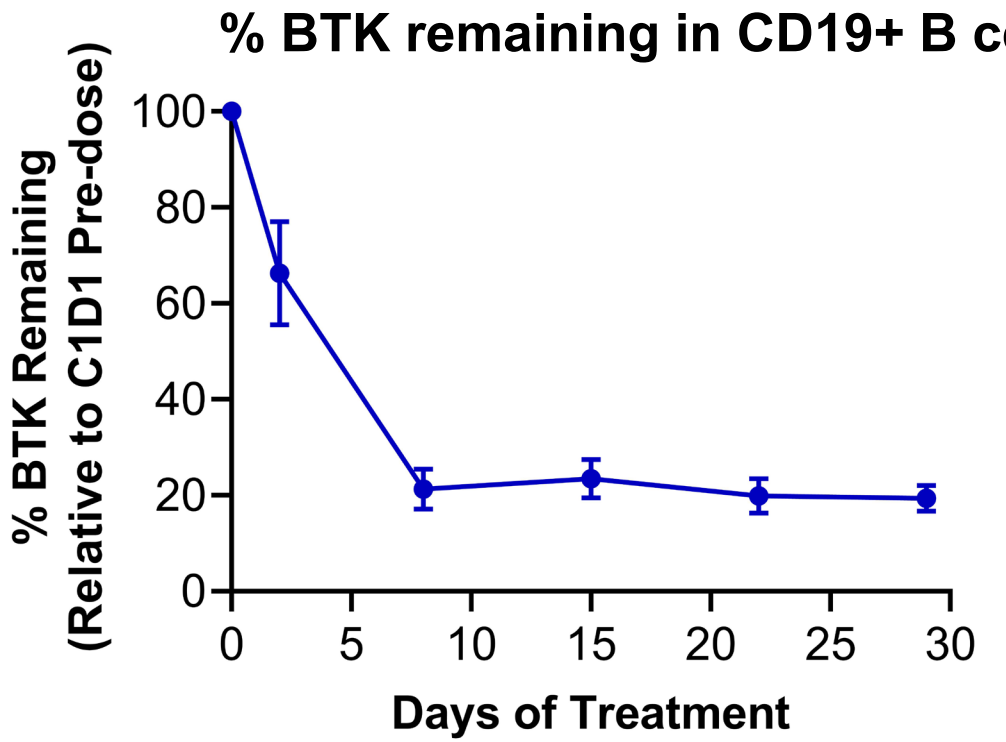
- CLL Phase 1b expansion cohort ongoing at 100 mg dose
- DLBCL Phase 1b expansion cohort ongoing at 300 mg
- MCL Phase 1b expansion cohort ongoing at 300 mg
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL

BTK, Bruton tyrosine kinase; **CLL**, chronic lymphocytic leukemia; **DLBCL**, diffuse large B-cell lymphoma; **FL**, follicular lymphoma; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **NHL**, non-Hodgkin lymphoma; **PCNSL**, primary CNS lymphoma; **PD,** pharmacodynamics; **PK,** pharmacokinetics; **WM**, Waldenstrom's macroglobulinemia

NX-2127 Leads to Robust BTK Degradation in Phase 1 Patients

Cohort 1 - 100 mg N = 14



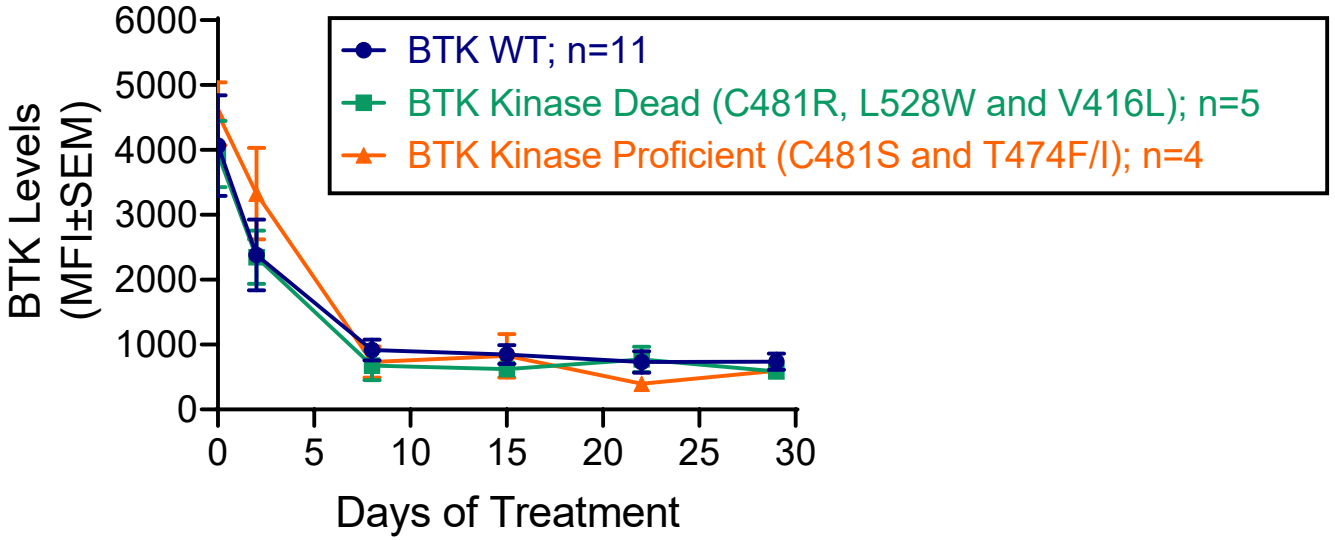


- Daily treatment with NX-2127 resulted in a rapid and sustained suppression of BTK (CD19+) as measured in patient whole blood using a flow cytometry assay.

Treatment with NX-2127 Leads to BTK Degradation and Clinical Response in CLL Patients Irrespective of Mutation Status

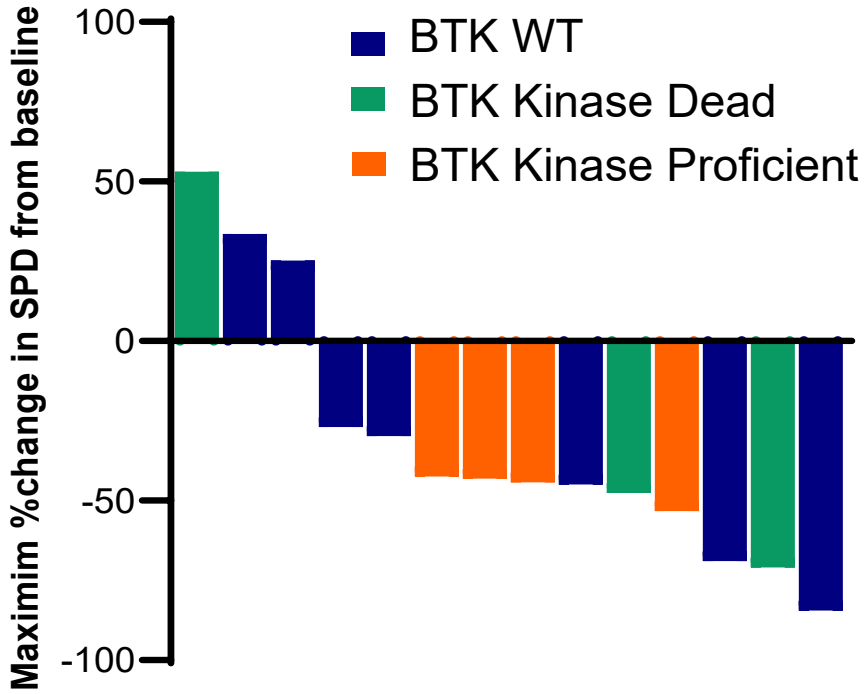
NX-2127 Preliminary Efficacy in Patients with CLL

BTK degradation in CLL patients with known BTK mutation status



Patients with kinase dead mutations are classified as kinase dead regardless of co-occurrence of kinase proficient mutations

Disease-evaluable patients



- BTK degradation of 80% achieved in CLL patients including those harboring BTK C481, T474, L528, and V416 resistance mutations

Data Cut-off Date: September 21, 2022

Montoya et al. ASH 2022. New Orleans, LA.

Mechanistic Rationale for Dual Degrader in DLBCL

CLINICAL TRIALS AND OBSERVATIONS

Comment on Goy et al, page 1024

Ibrutinib and lenalidomide: when 1+1 = >2

Jason Westin | MD Anderson Cancer Center

Hyper-activated BCR (CD79b-mut) and TLR (MyD88-mut) signaling are hallmarks of non-GCB DLBCL:

- NX-2127 targets both BCR and TLR signaling through BTK degradation
- NX-2127 targets non-BTK dependent TLR signaling through its immunomodulatory activity

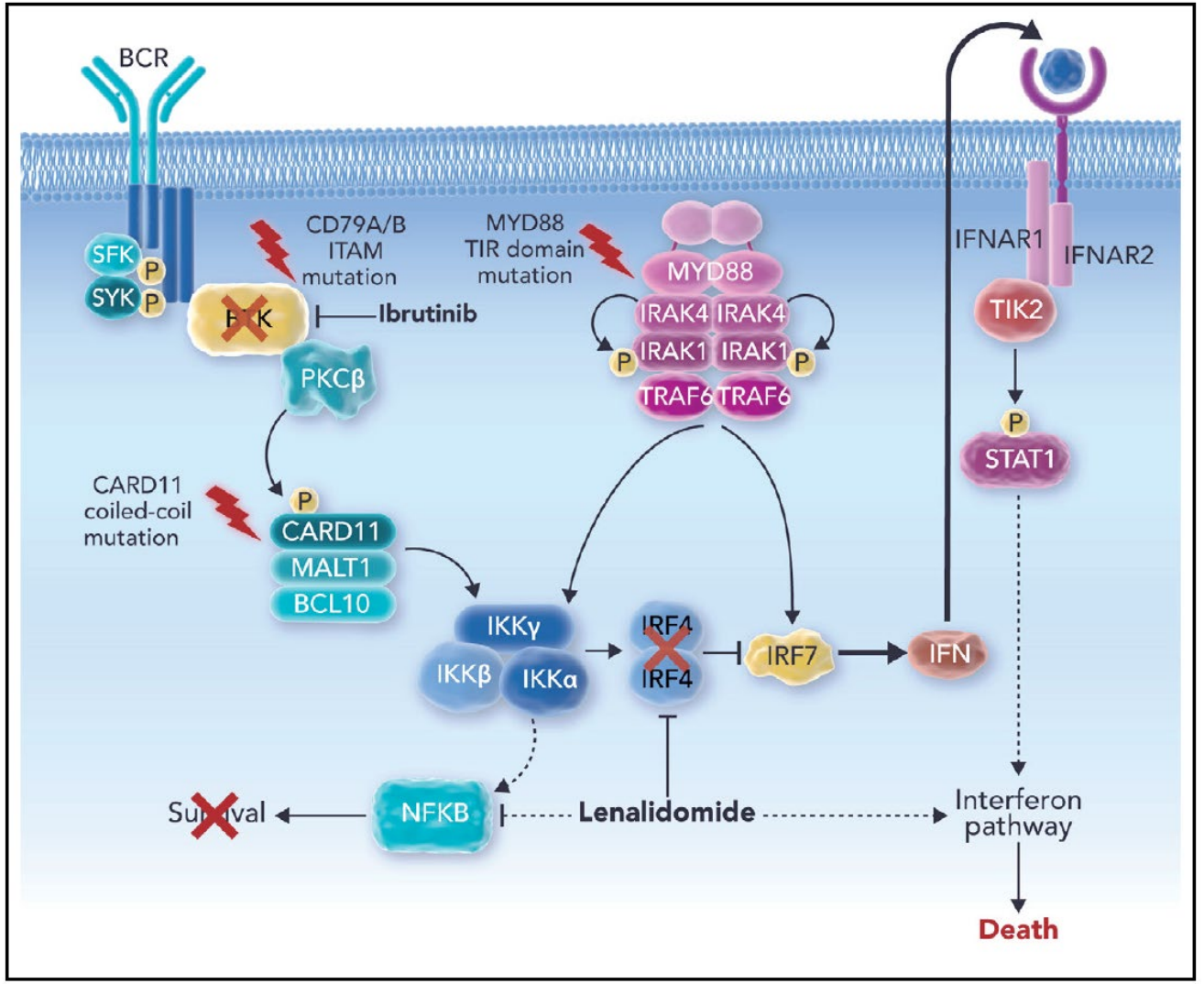
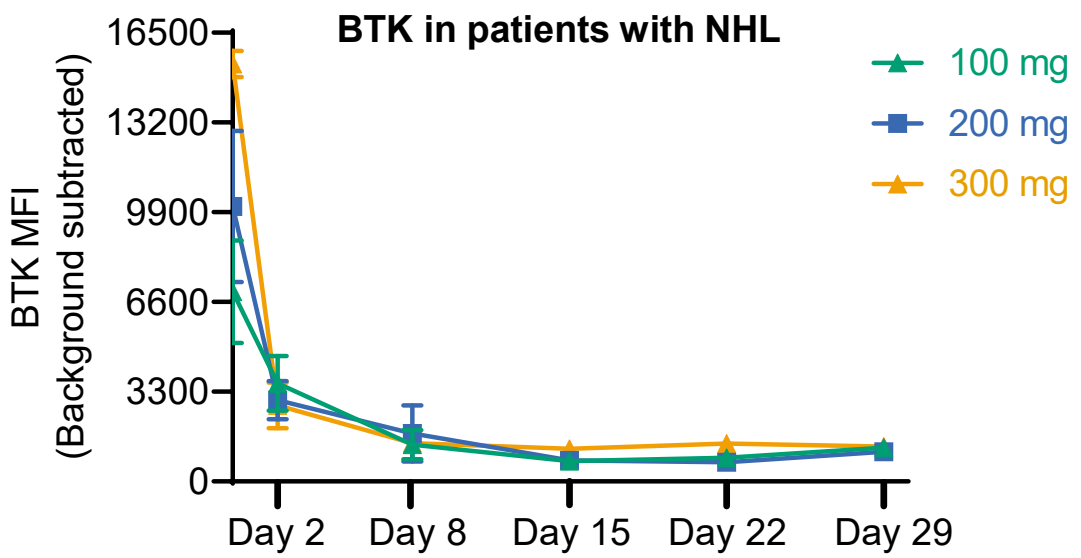


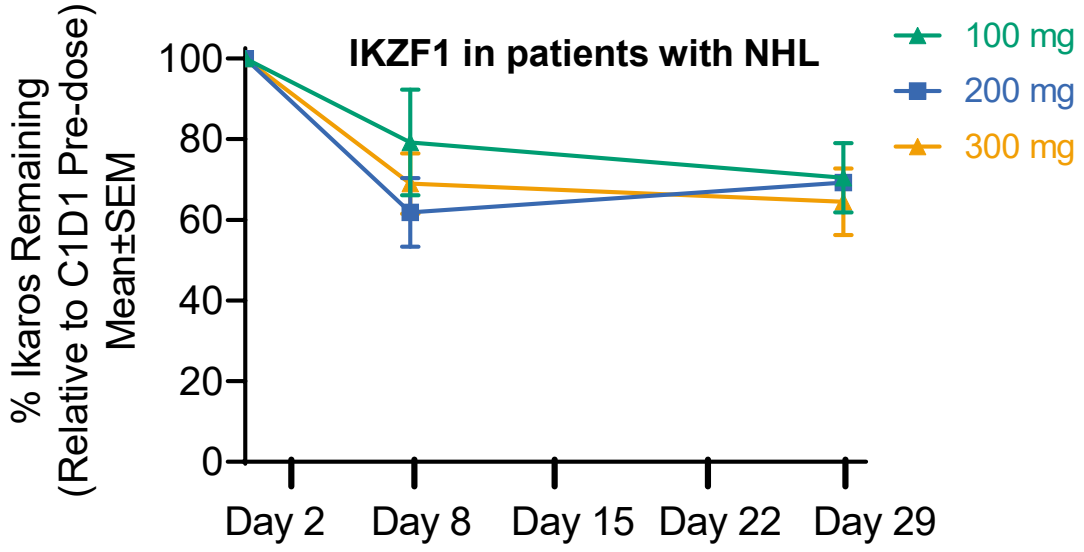
Figure from Westin J. Blood 2019;134:996–8

NX-2127 leads to BTK and IKZF1 degradation in NHL patients across dose levels

- NX-2127 led to robust BTK degradation of >85% (89%±2) at Cycle 2 Day 1 across dose levels in NHL patients
- NX-2127 promoted IKZF1 degradation in all patients at all dose levels



BTK measured by flow cytometry in circulating B cells in all patients
Data normalized to each patient's baseline; Error bars represent mean +/- SEM



IKZF1 measured by flow cytometry in circulating T cells in all patients
Data normalized to each patient's baseline IKZF1 levels; Error bars represent mean +/- SEM

BTK, Bruton's tyrosine kinase

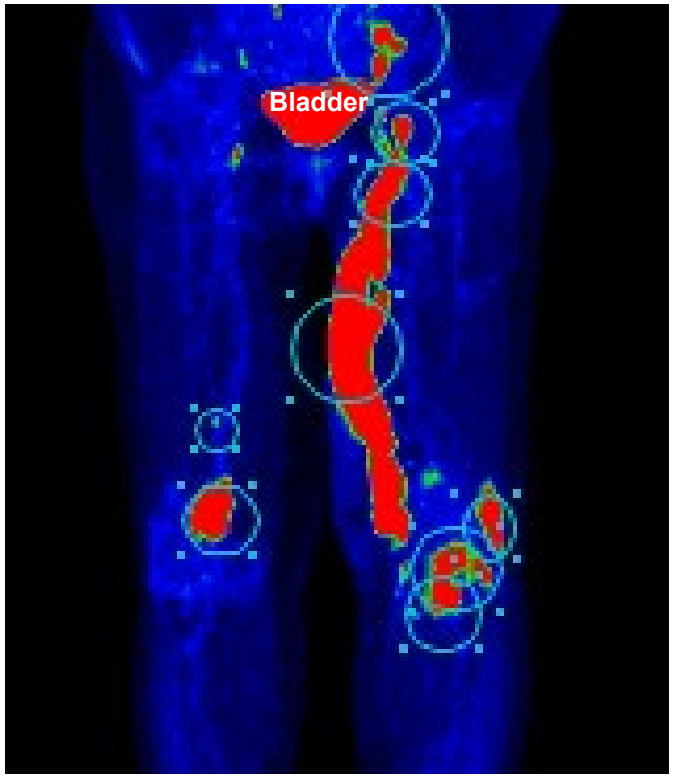
Data cutoff: January 14, 2023

First Confirmed Complete Response in Diffuse Large B Cell Lymphoma with a BTK Degrader

Diagnosis	1988: Waldenstrom's 2015: DLBCL (ABC subtype)
Disease characteristics	Stage IV MYD88 and CXCR4 mutated
Age and history	84 years old Aortic regurgitation, diastolic dysfunction, aspergillosis sinus infection
Dose	300 mg
Prior treatments (4)	2015: Rituximab + CHOP followed by focal axillary irradiation 2017: Rituximab + ICE 2018: Rituximab, mogamulizumab (anti-CCR4), and magrolimab (anti-CD47) 2019: Rituximab, ibrutinib, and lenalidomide (RIL)

FDG-PET CT Scan Disease Assessment

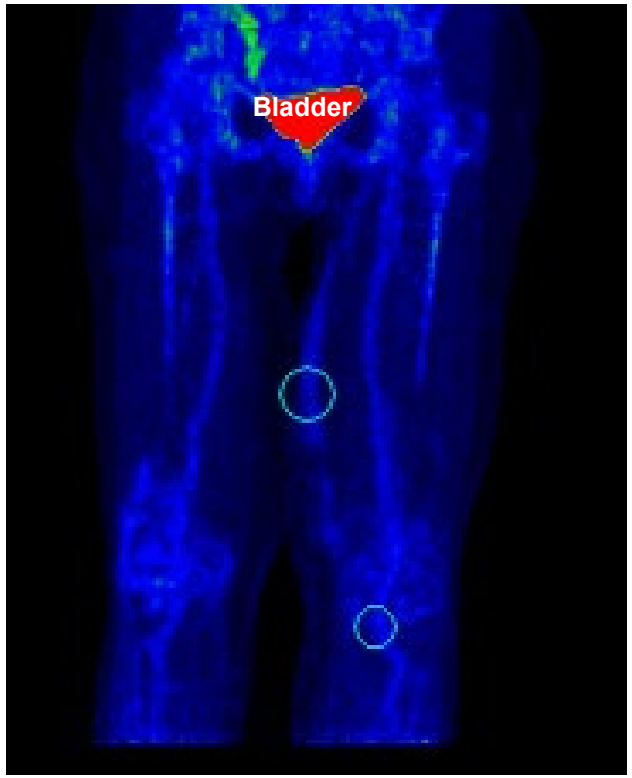
Baseline



Max SUV: 17.6
Deauville 5PS: 5

SUV: Standard Uptake Value

Week 16



Max SUV: 2.5
Deauville 5PS: 2

Normal SUV

- Complete response at first assessment (Week 8) and confirmed at subsequent assessment (Week 16)
- Safety: No DLT or SAE. Grade 3 neutropenia without infection, resolved with G-CSF. No Rx interruptions.

nurix

Data Cut-off Date: September 21, 2022

Summary

- NX-2127 is an orally bioavailable dual degrader. In addition to BTK it degrades IKZF1 and 3 and enhances IL-2 secretion in T cells with potency similar to immunomodulatory drugs.
- NX-2127 displays potent BTK degradation and cell killing in the context of key resistance mutations identified in CLL patients.
- BTK Degradation of 80%+ drives potent anti-tumor activity in preclinical models.
- Treatment with NX-2127 leads to BTK degradation and clinical response in CLL patients irrespective of mutation status.
- NX-2127 is the first BTK degrader to show complete response in Diffuse Large B Cell Lymphoma.

Thank you

nurix