nurix

Leader in Targeted Protein Modulation

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

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Drug Discovery Chemistry

San Diego, CA

April 12th, 2023

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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)

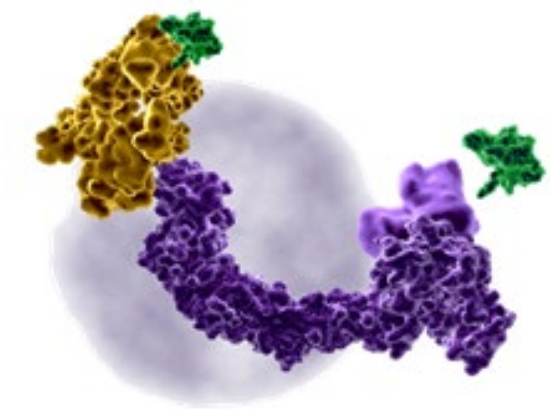
Ubiquitin is ligated to target proteins to tag them for degradation by the proteasome

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

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 multiple BTK inhibitor-resistant mutations
- Complete response observed in a patient with DLBCL
- Phase 1b cohort expansion for CLL patients is ongoing
- Dose exploration is ongoing for patients with NHL



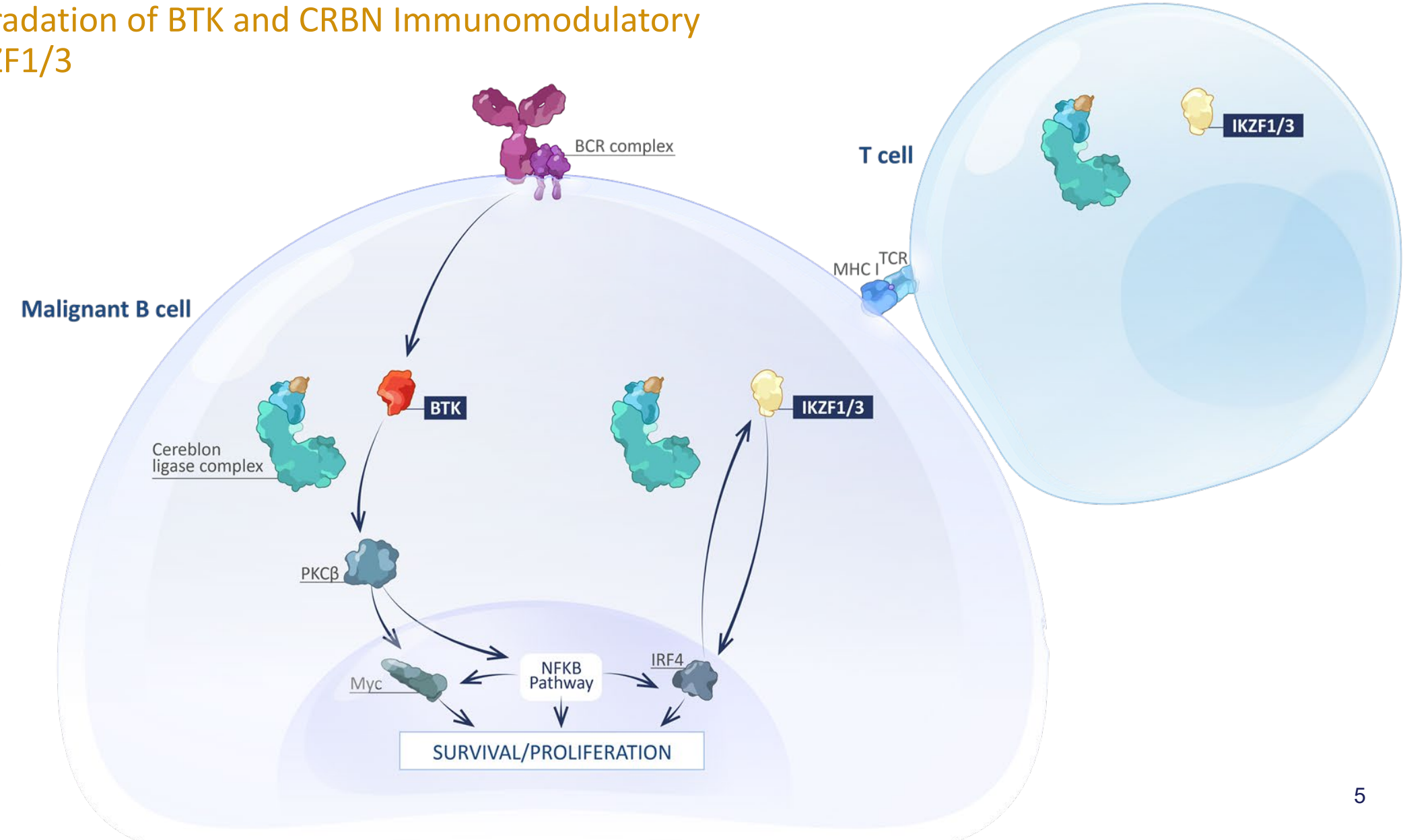
NX-5948

BTK DEGRADATION

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

NX-2127 Dual Mechanism of Action

Targeted Degradation of BTK and CRBN Immunomodulatory Substrates IKZF1/3



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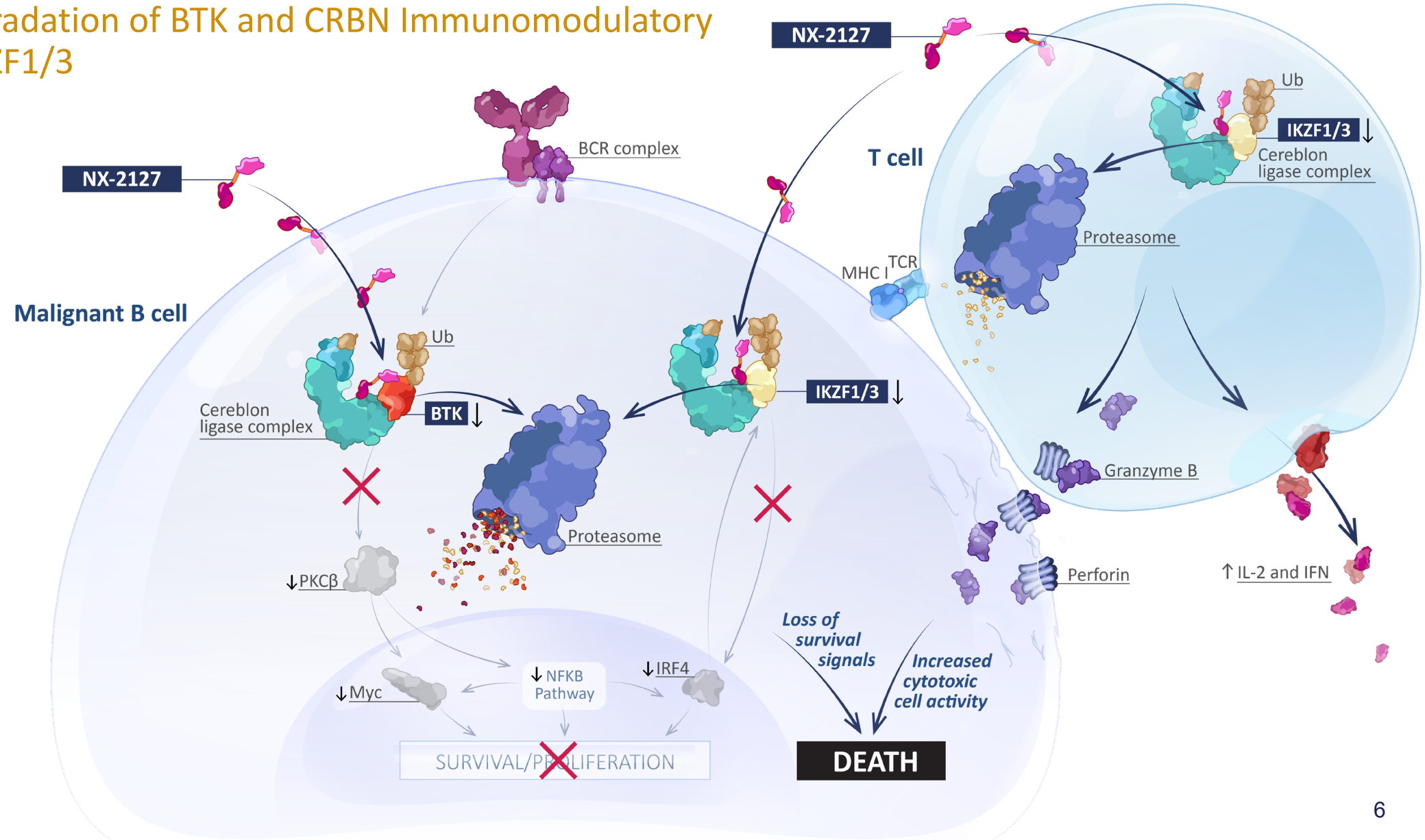
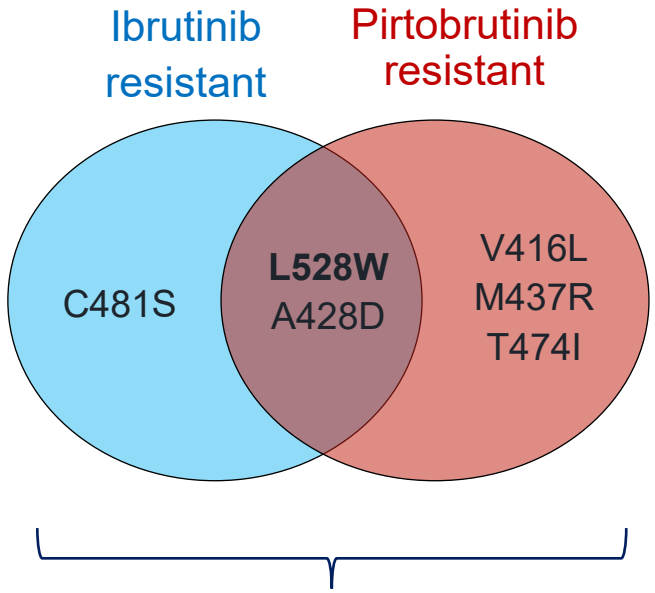


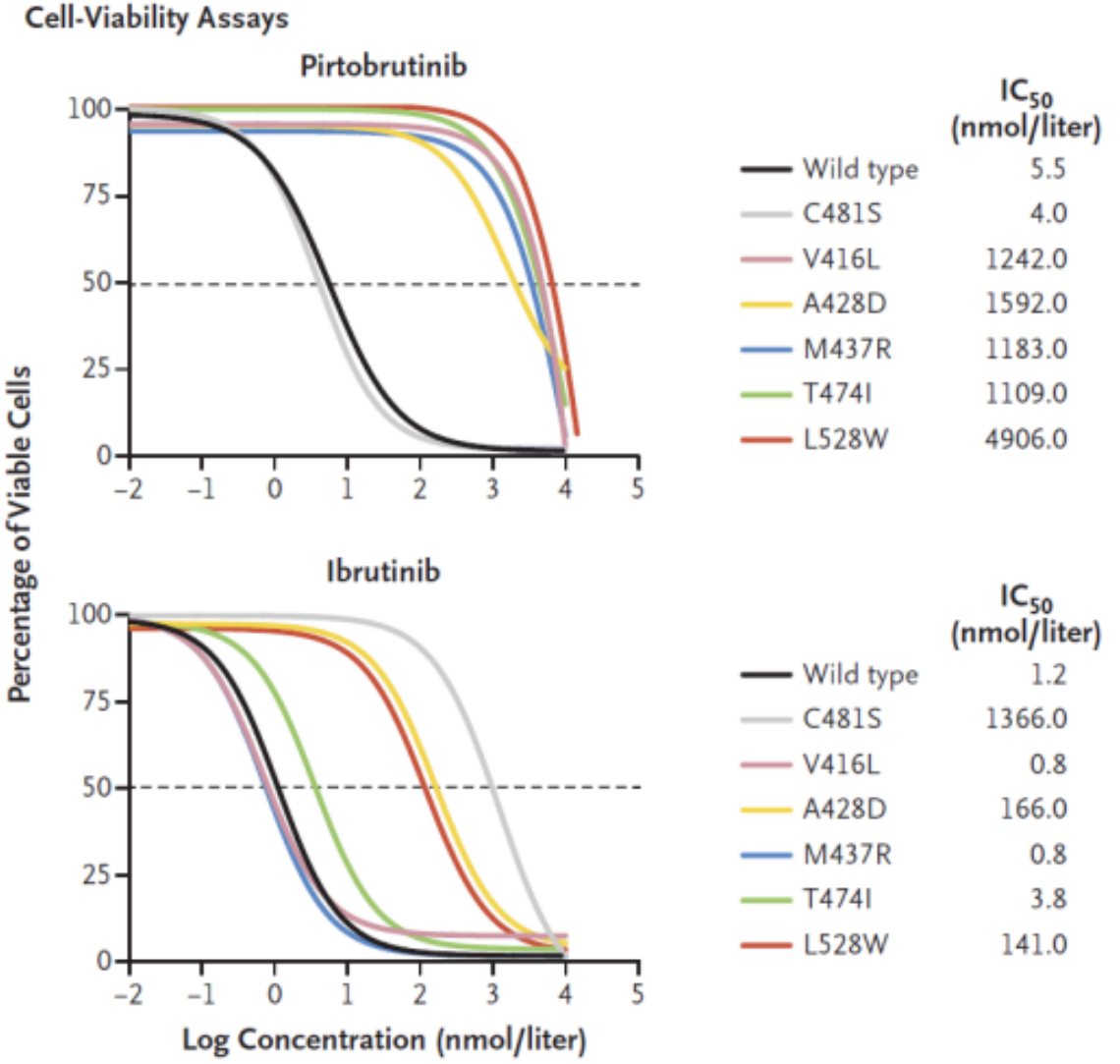
Emerging BTK Mutations Confer Resistance to Covalent and Non-Covalent BTK Inhibitors

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."



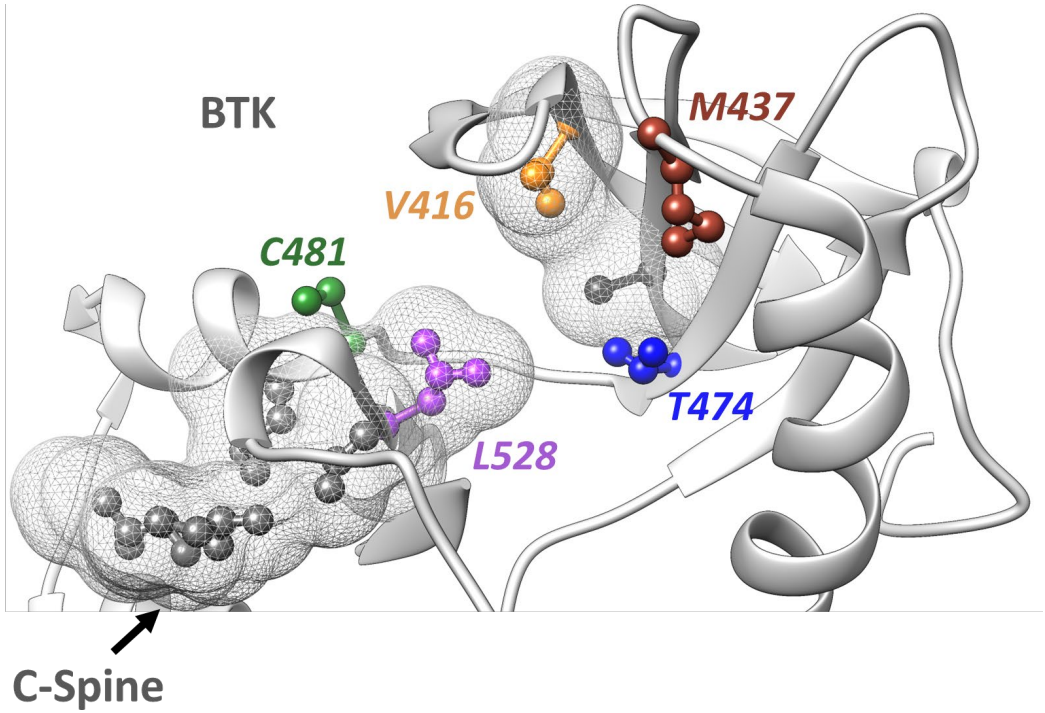
Opportunity for BTK degrader?



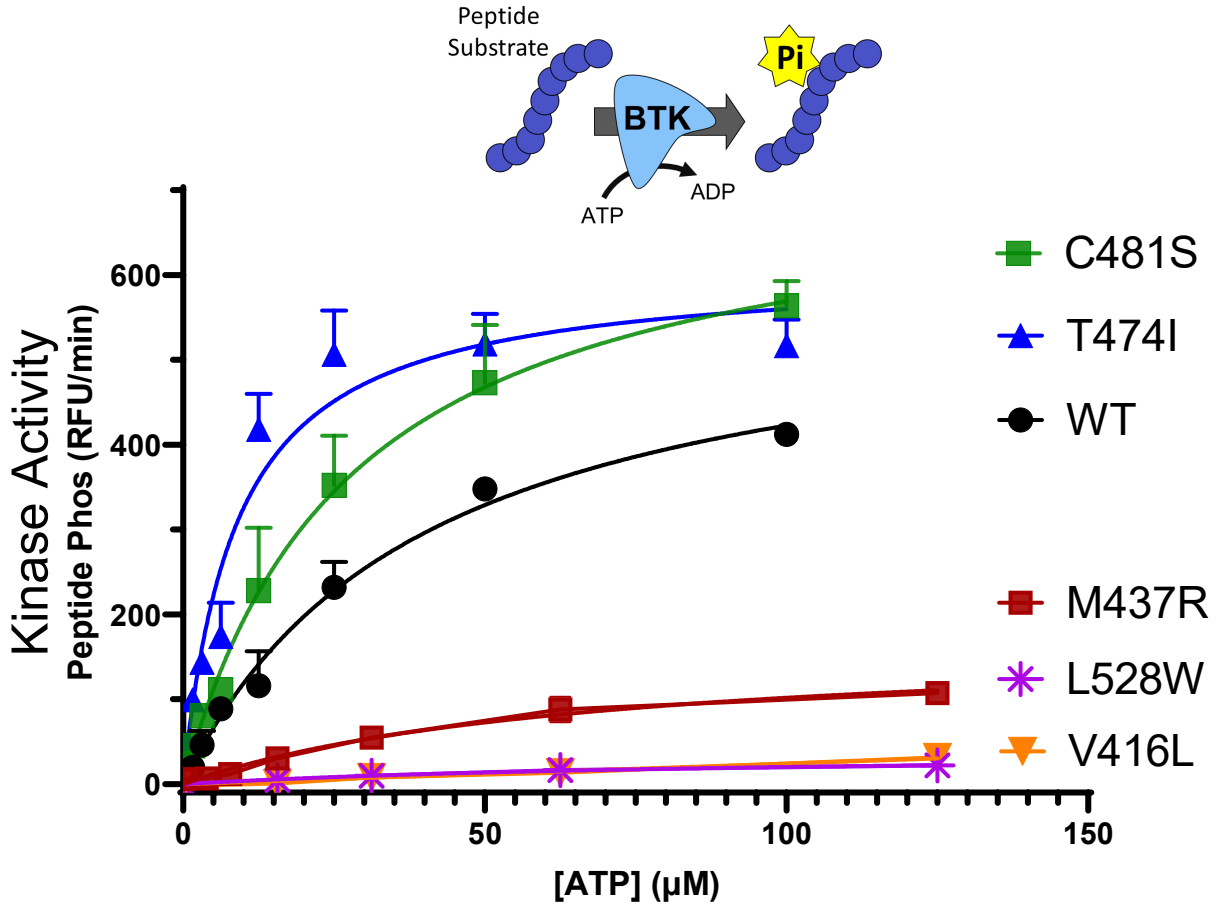
Wang E, et al. NEJM 2022

Emerging Resistance Mutations and BTK Scaffolding Activity

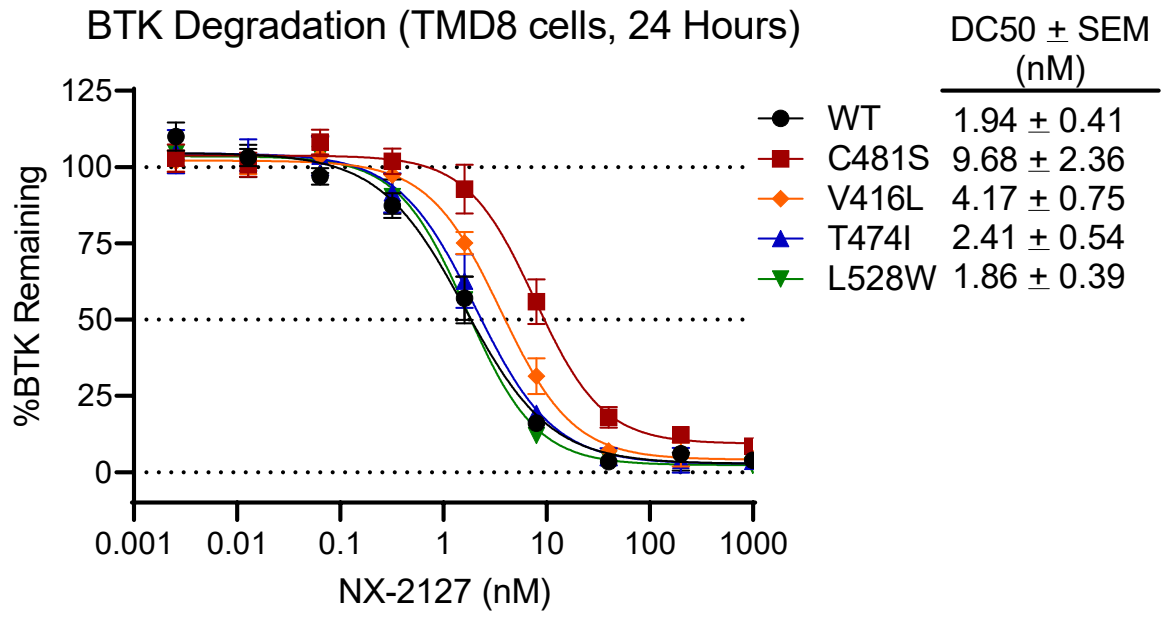
Treatment with non-covalent BTK inhibitors are changing the resistance landscape

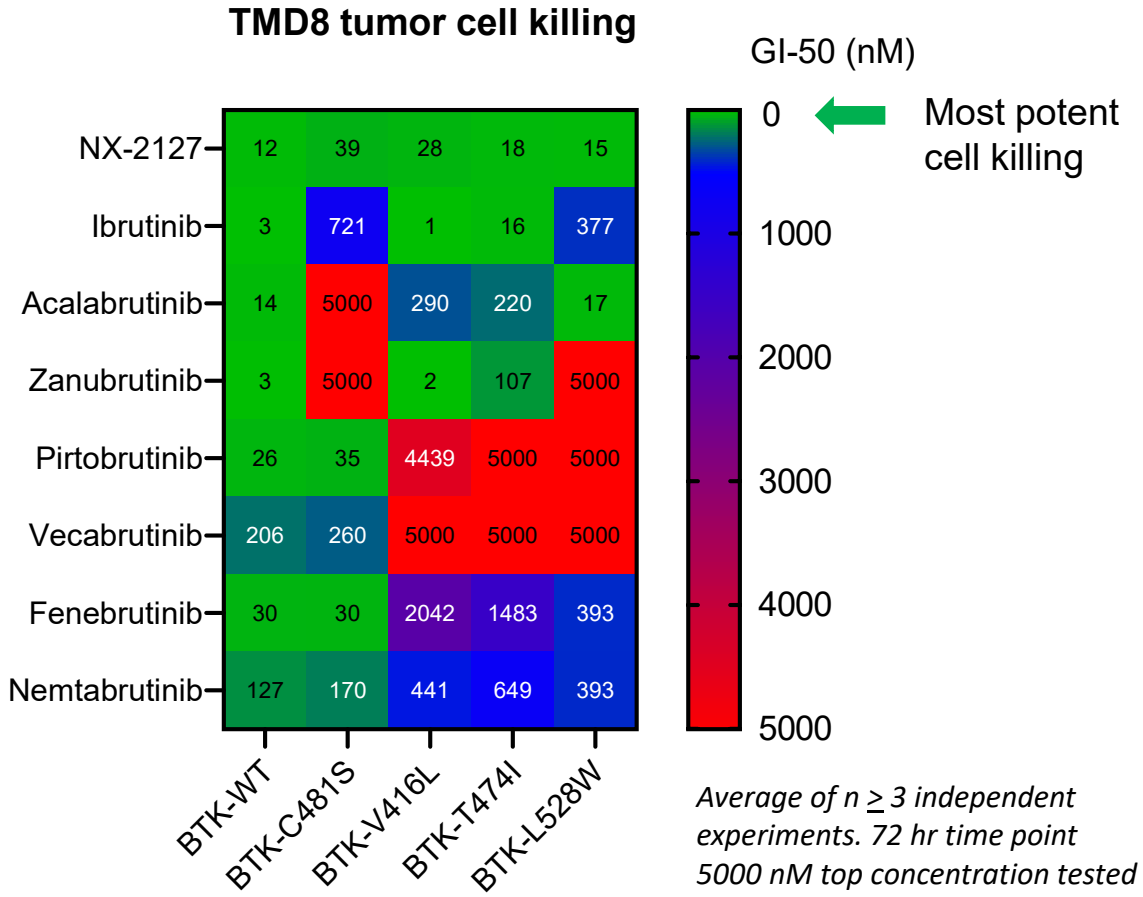


Many of the mutations that confer resistance to BTK inhibitors lack kinase activity



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



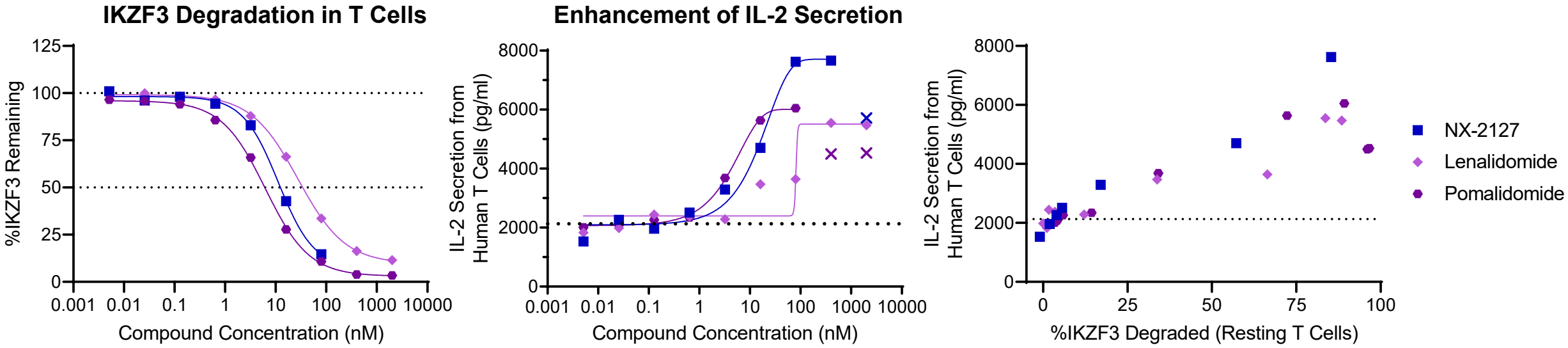


Average of n ≥ 3 independent experiments. 72 hr time point 5000 nM top concentration tested

- 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

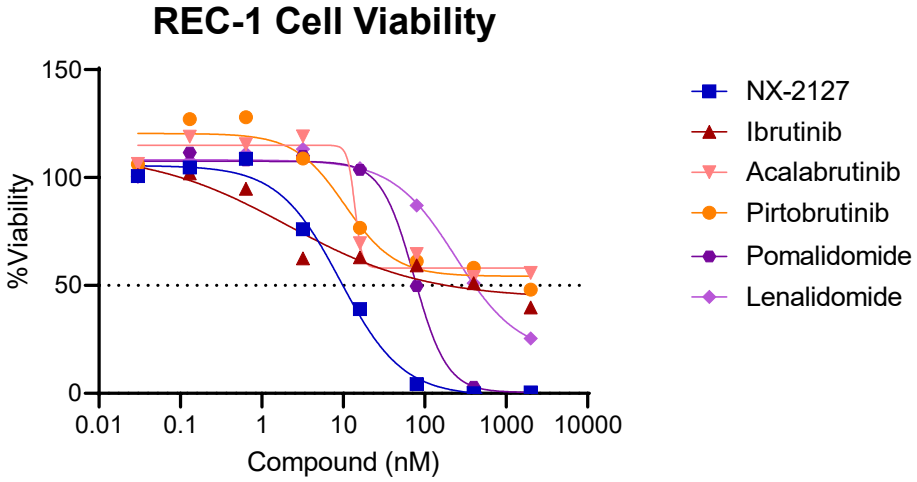
Partial IKZF1/3 degradation is sufficient to enhance IL-2 secretion

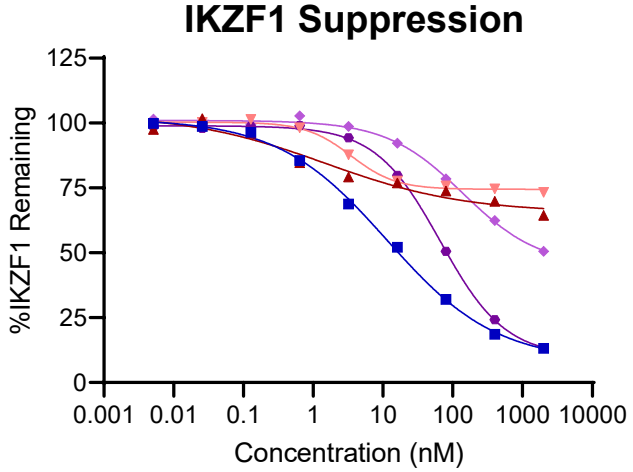


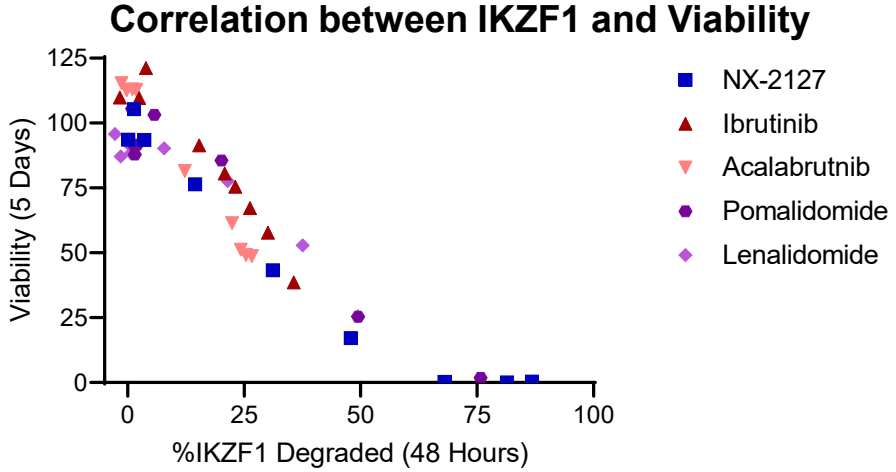
- Potency of NX-2127 falls between pomalidomide and lenalidomide in IKZF1/3 degradation and IL-2 secretion assays (IKZF1 data not shown)
- Enhancement of IL-2 secretion is observed with partial IKZF1/3 degradation

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

Potency and completeness are superior to BTK inhibitors and immunomodulatory drugs





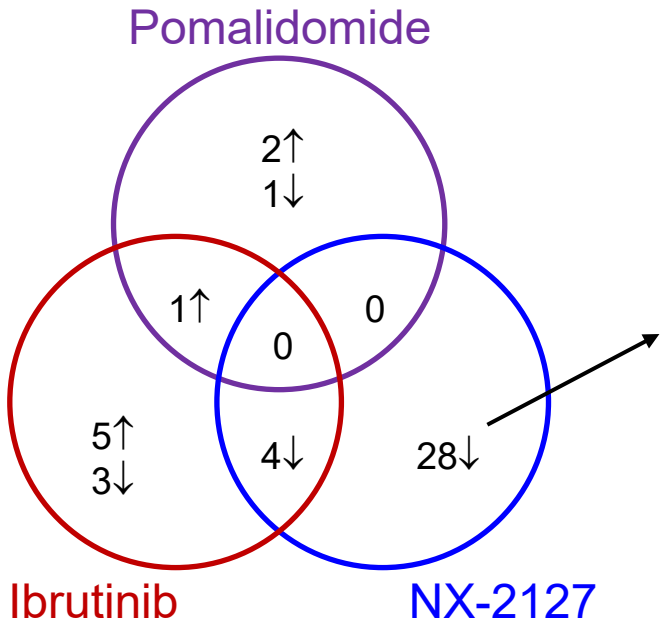


- BTK inhibitors only partially kill REC-1 cell line
- NX-2127 promotes complete killing of REC-1 cells and does so more potently than pomalidomide
- Anti-proliferative activity in REC-1 cells correlates with degradation or downregulation of IKZF1, and partial suppression of IKZF1 is sufficient to achieve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

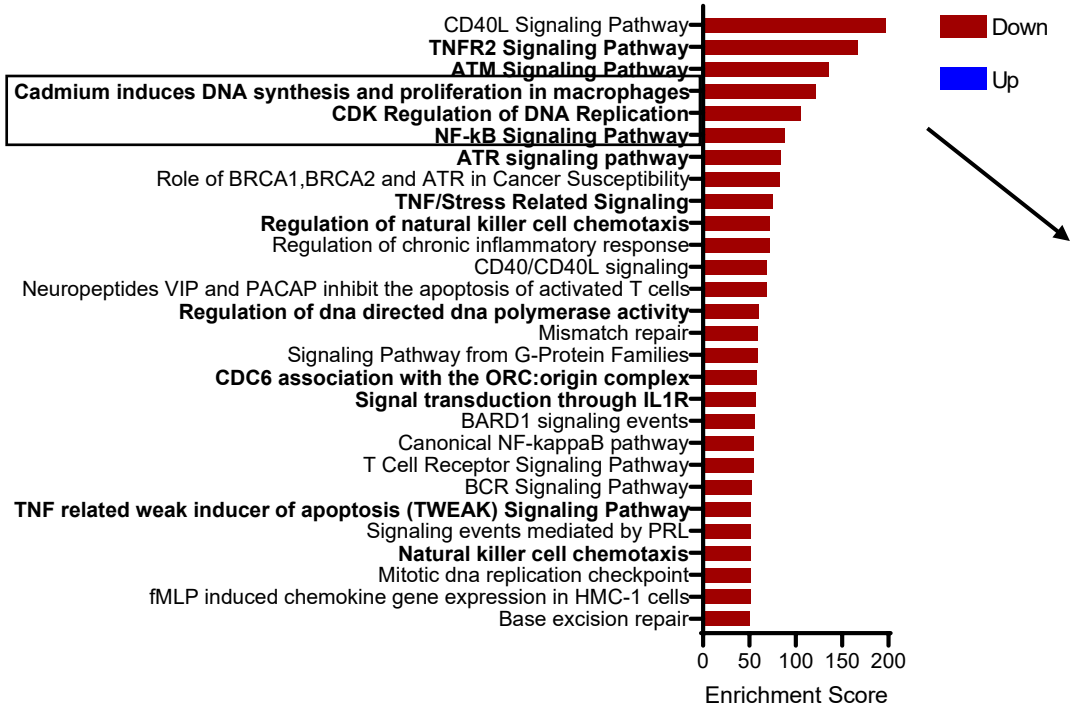
Noviski et al. AACR 2022. New Orleans, LA. Poster presentation.

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

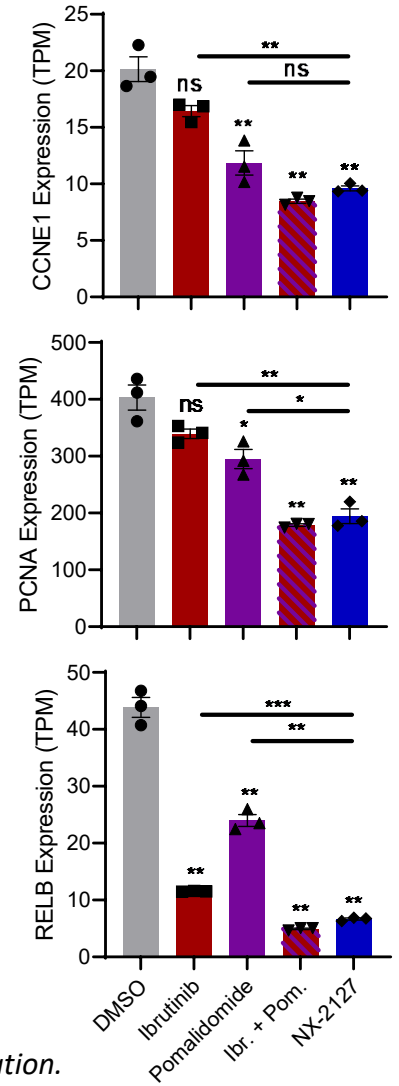
RNAseq in REC-1: Gene Set Modulation



Unique NX-2127 Gene Sets



Representative Genes



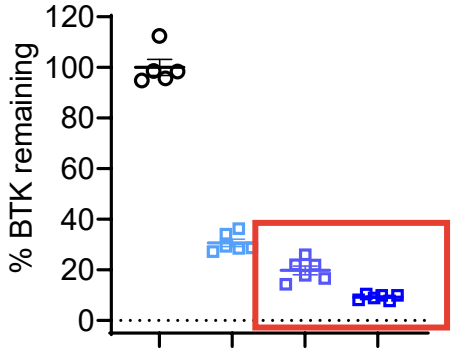
- Treatment with NX-2127 or ibrutinib + pomalidomide leads to downregulation of Cyclin E1, PCNA, and RELB in REC-1 mantle cell lymphoma line
- Combined effect is stronger than what BTK inhibition or immunomodulation achieves in isolation

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

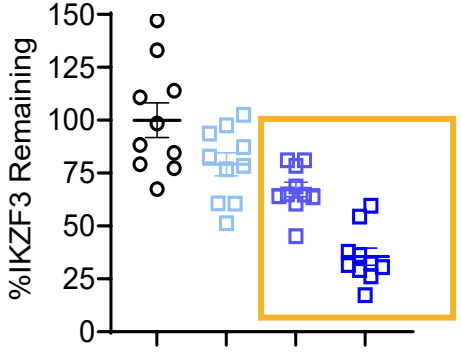
BTK Degradation of 80%+ Drives Potent Anti-tumor Activity in Preclinical Models

IKZF1 and IKZF3 degradation also achieve target range at therapeutic doses

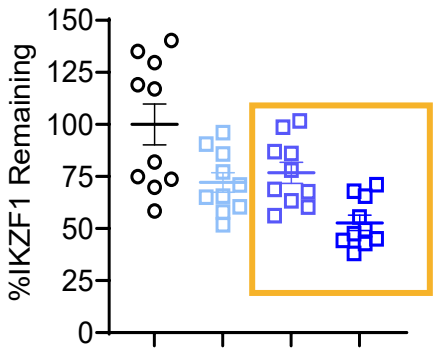
BTK Degradation in Peripheral B cells



IKZF3 Degradation in TMD8 Tumor Tissue

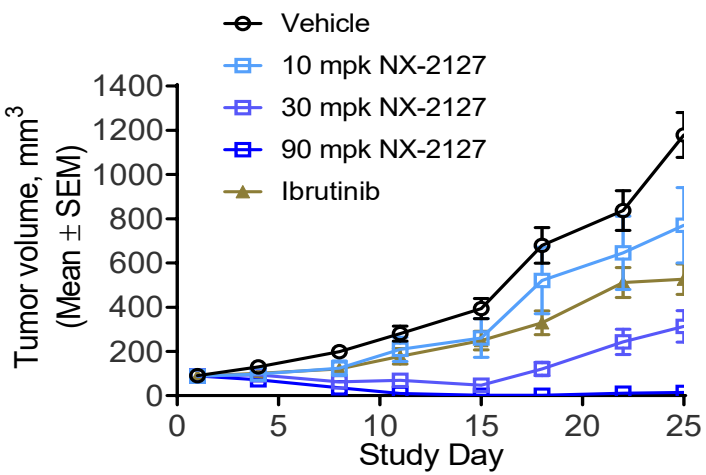


IKZF1 Degradation in TMD8 Tumor Tissue



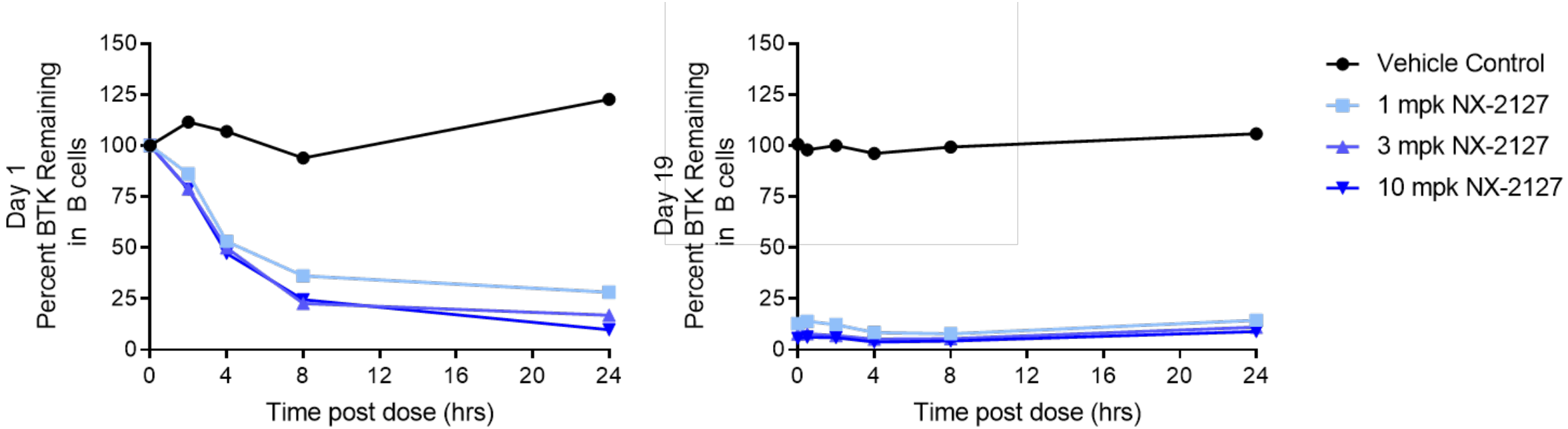
Vehicle 30 mpk
10 mpk 90 mpk

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%

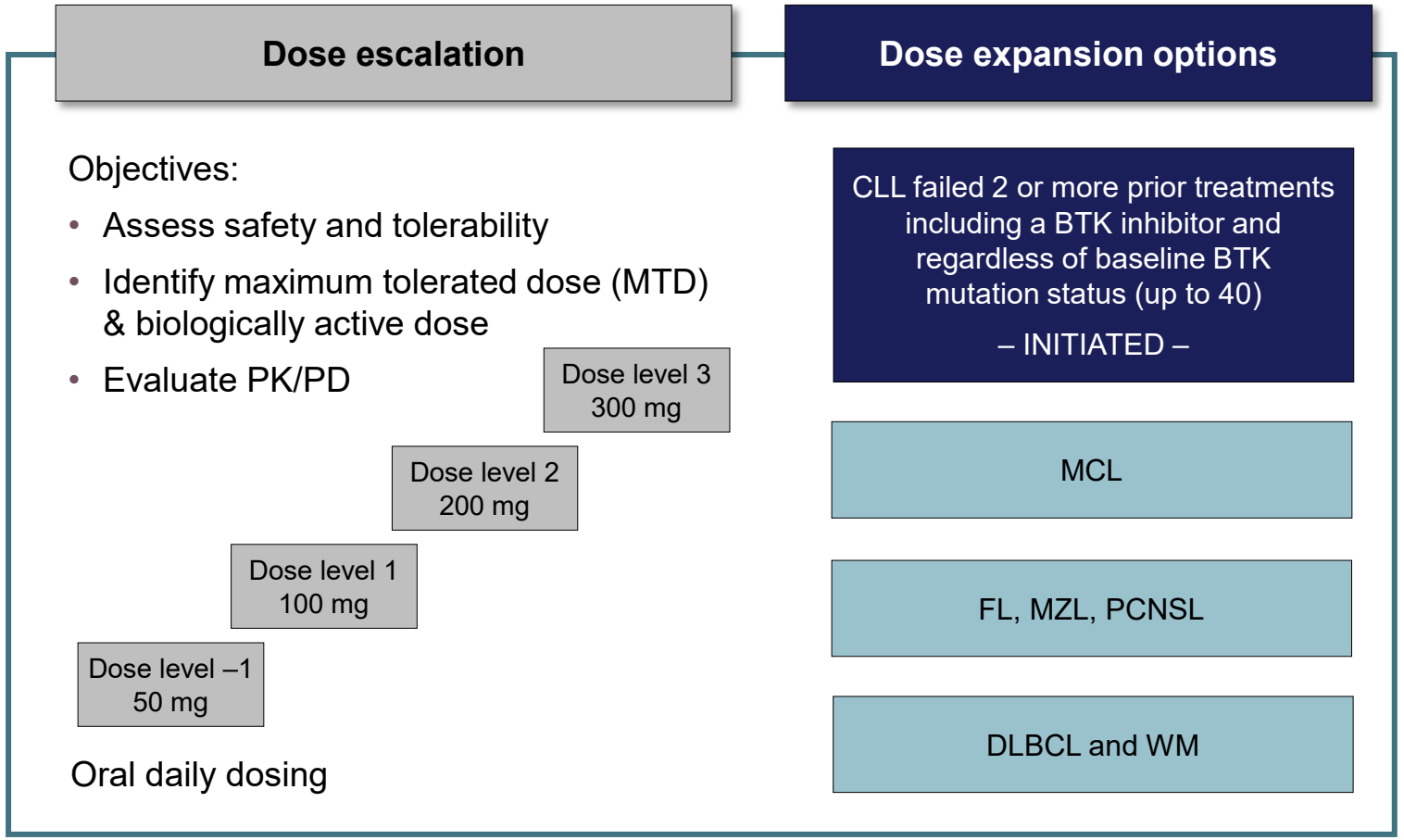
Oral Dosing of NX-2127 Degrades BTK in Non-Human Primates



- 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



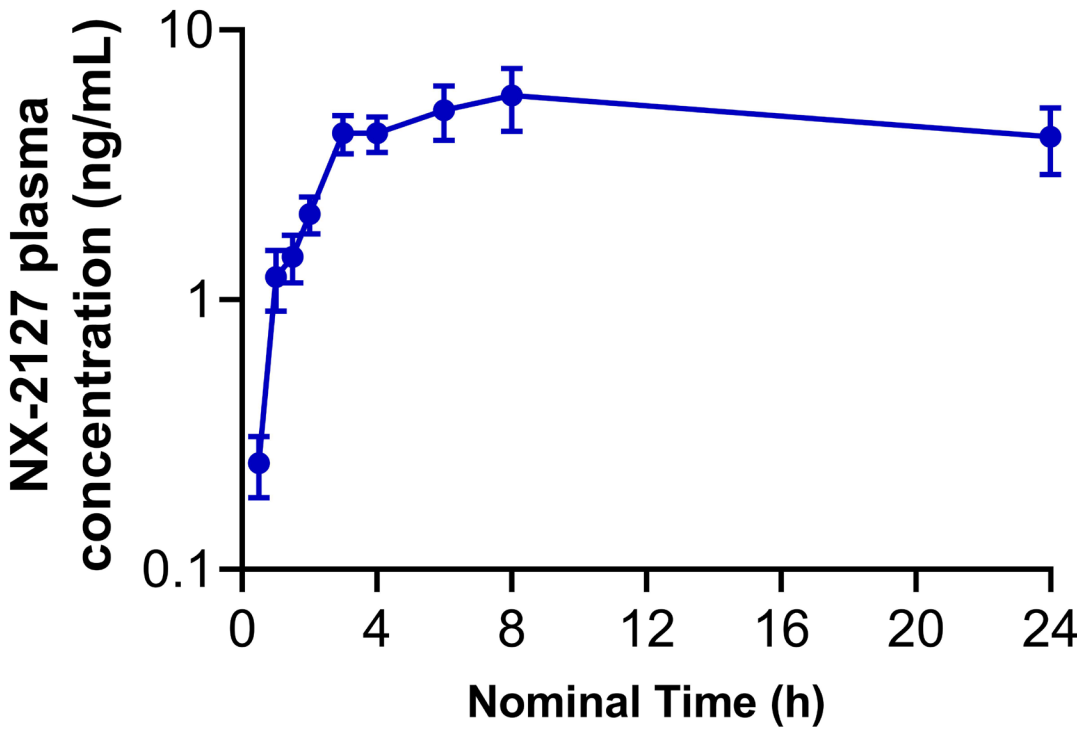
- CLL Phase 1b expansion cohort ongoing at 100 mg dose
  - MTD not established
  - 100 mg dose chosen as expansion dose based on PD, clinical activity and safety profile
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL (e.g., DLBCL, MCL, MZL, WM, FL)

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; **PCNSL**, primary CNS lymphoma; **PD,** pharmacodynamics; **PK,** pharmacokinetics; **WM**, Waldenstrom's macroglobulinemia

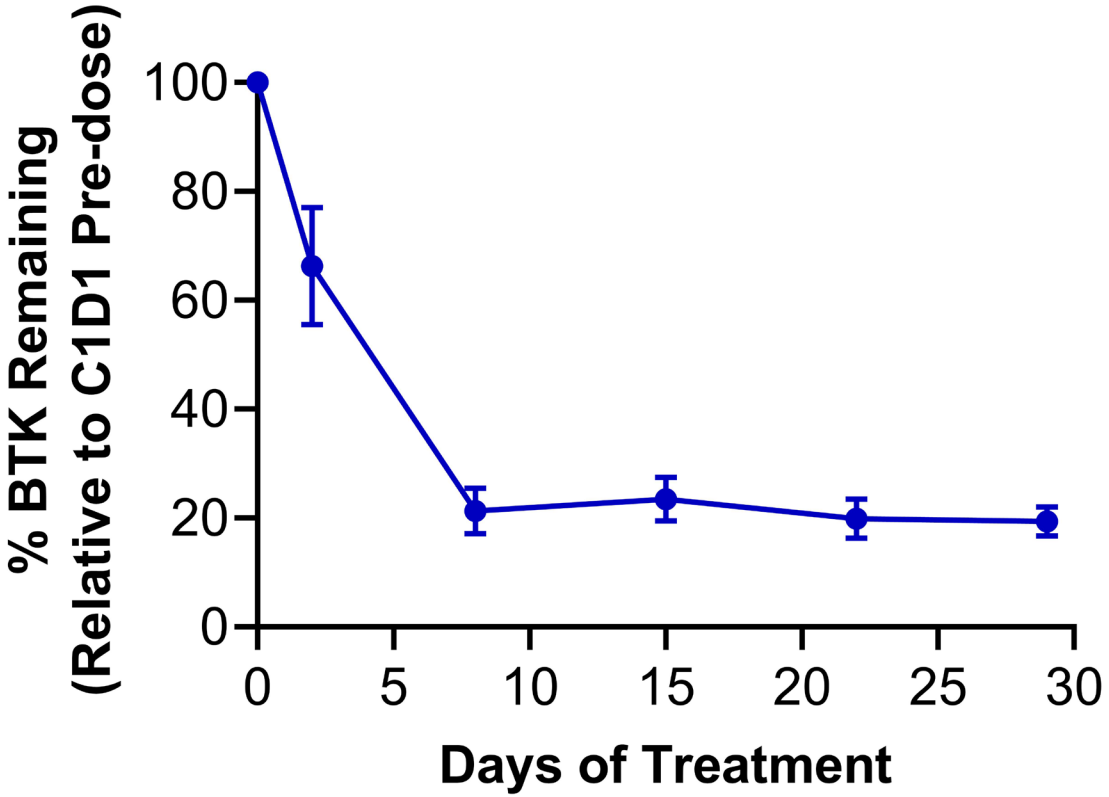
Degradation of BTK observed in Phase 1 patients

Cohort 1 - 100 mg N = 14

Cycle 1, Day 1



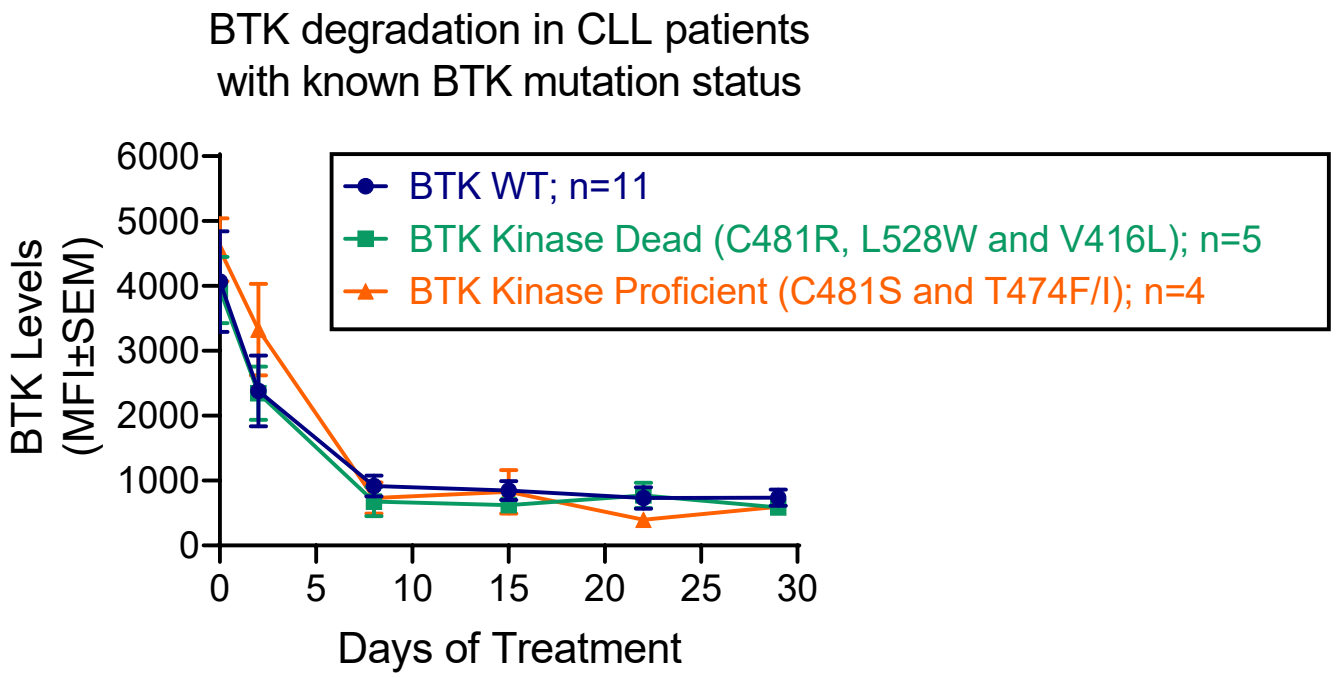
% BTK remaining in CD19+ B cells



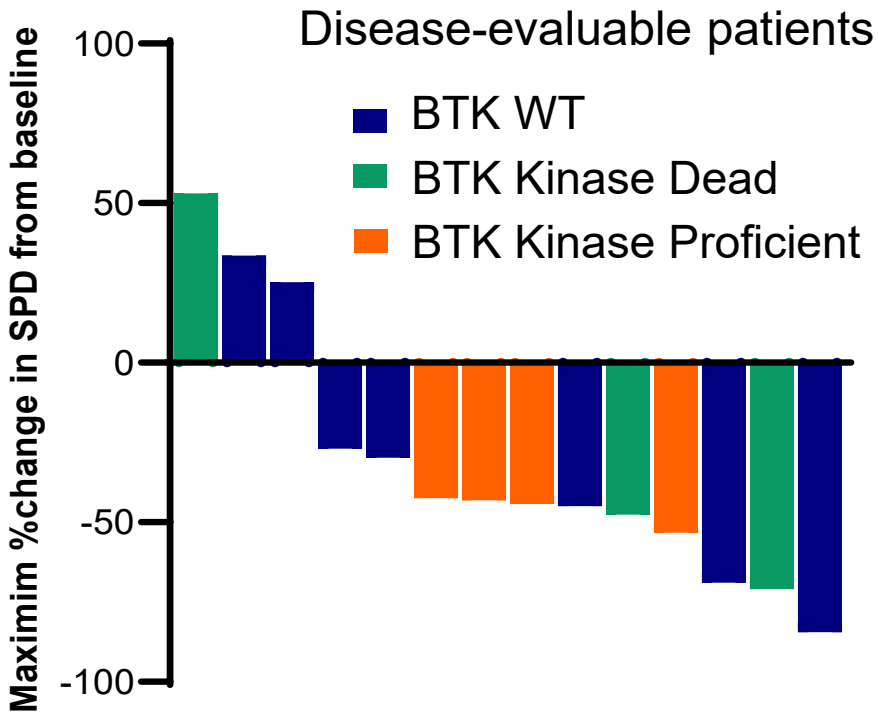
Clinical trial NCT04830137

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



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

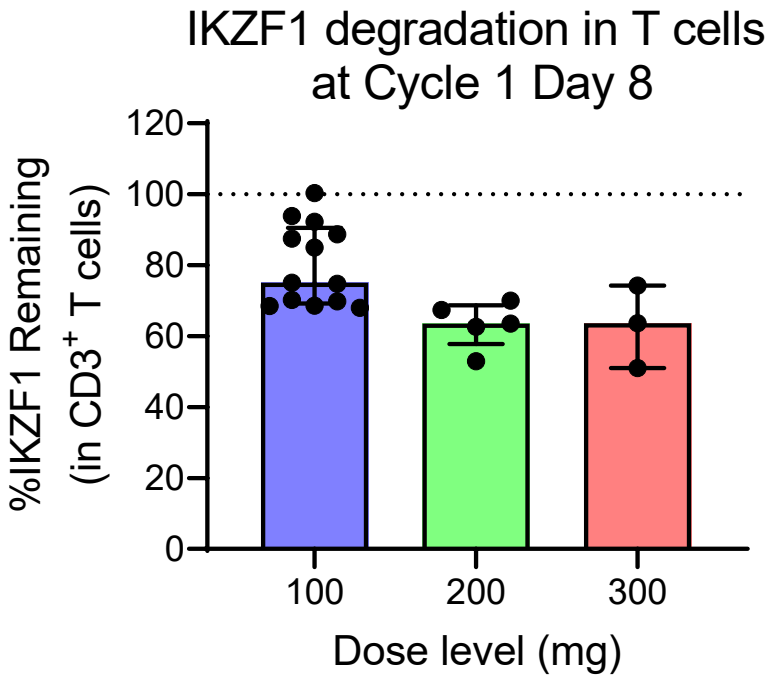


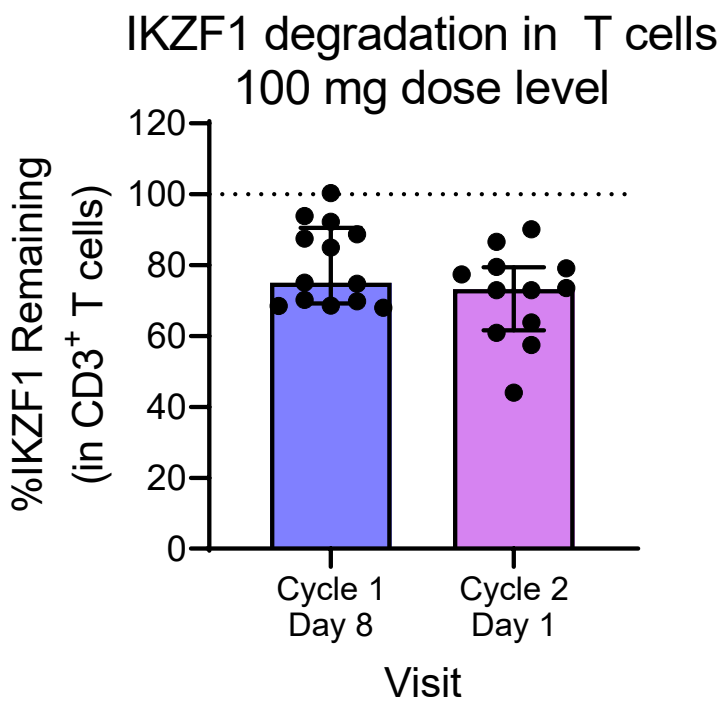
- BTK degradation of 80% achieved in CLL patients including those harboring BTK C481, T474, L528, and V416 resistance mutations

nurix Data Cut-off Date: September 21, 2022

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

NX-2127 Promotes Degradation of the Cereblon Neo-Substrate IKZF1 in Patients





IKZF1 measured by flow cytometry in circulating T cells in all patients
Data normalized to each patient's baseline IKZF1 levels (dashed line)
Error bars represent median +/- IQR

Note: Lenalidomide treatment cycles achieve transient 46-63% Ikaros degradation in Immune Cells

Source: Franssen et al; Oncotarget,Vol. 9 (No. 74), 2018

- IKZF1 degradation is observed at all dose levels in all patients at all dose levels receiving daily treatment of NX-2127
- NX-2127 promoted sustained IKZF1 degradation through one cycle (28 days) of NX-2127 treatment as shown in the graph above

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

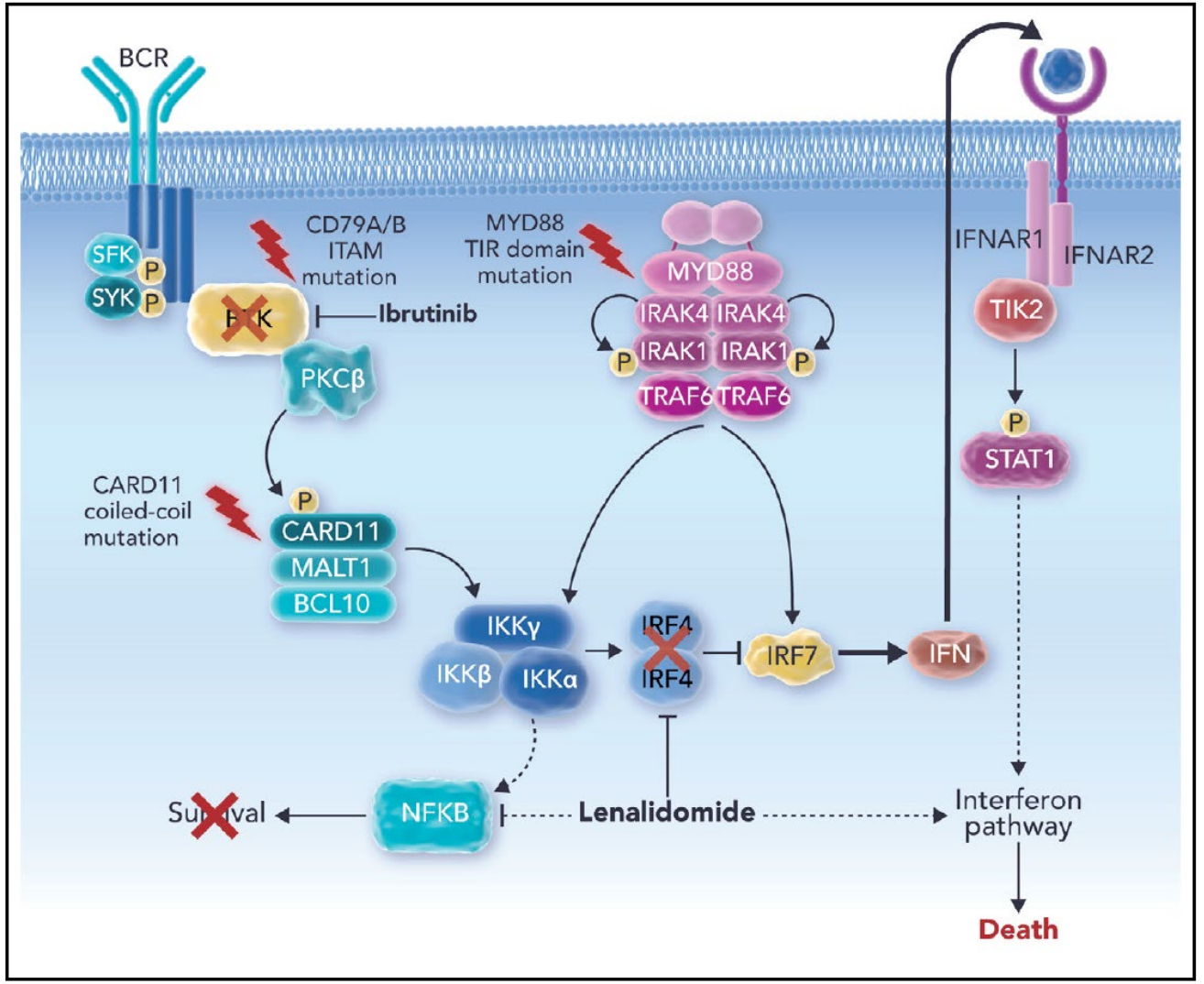


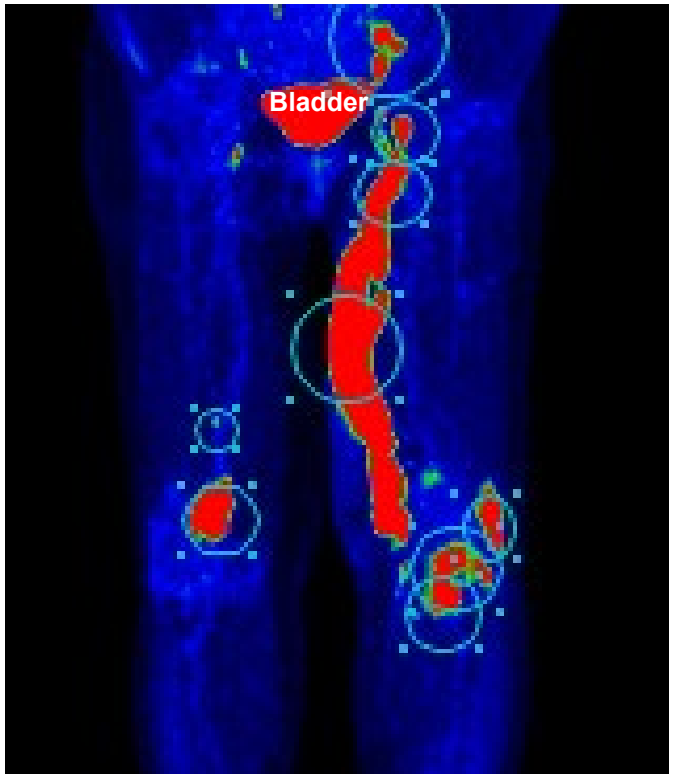
Figure from Westin J. Blood 2019;134:996–8

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

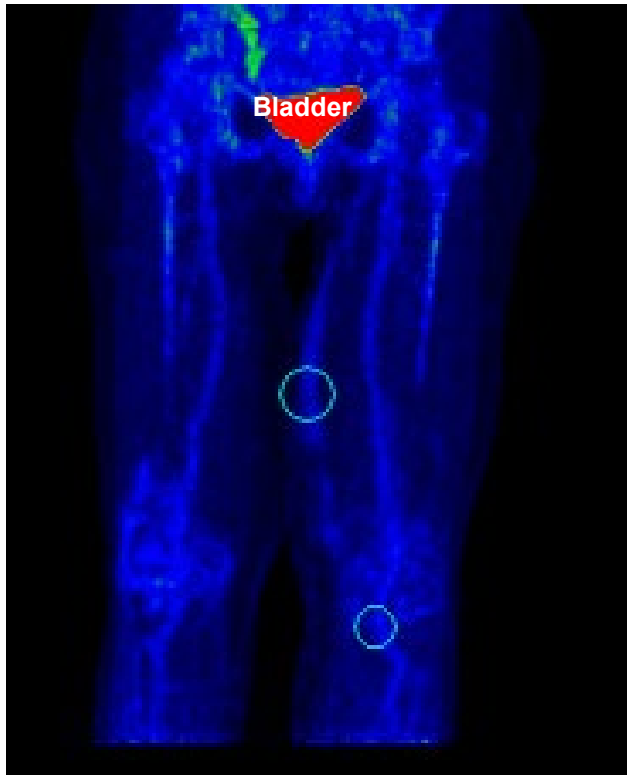
Baseline



Max SUV: 17.6
Deauville 5PS: 5

SUV: Standard Uptake Value

Week 16



Max SUV: 2.5
Deauville 5PS: 2

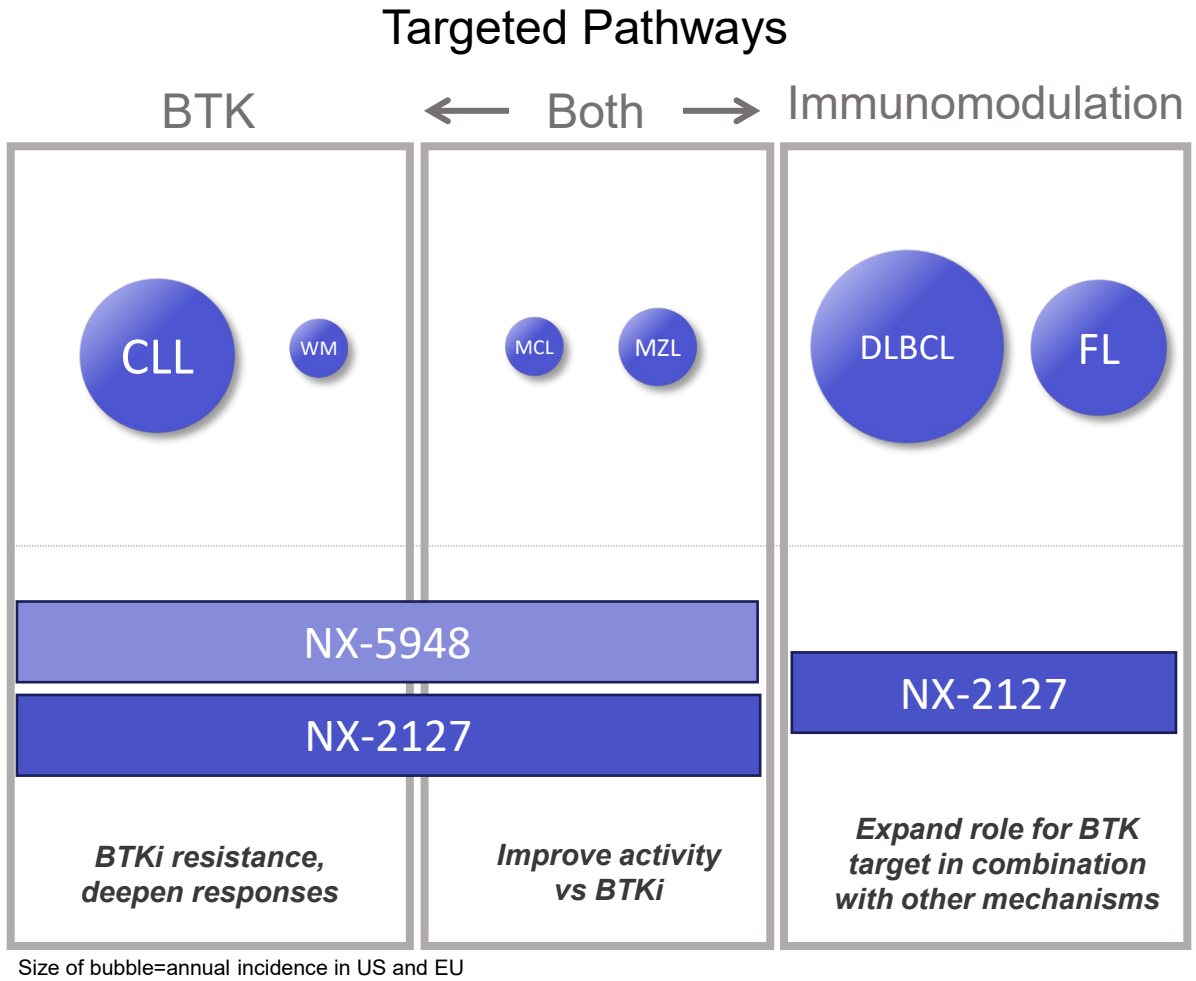
Normal SUV

- 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 BTK Degrader Franchise: Two BTK Degraders to Cover the Landscape of B Cell Malignancies

NX-2127 for BTK inhibitor resistance in CLL and for aggressive NHL

NX-5948 may be the degrader of choice for single-target therapy with potential in autoimmunity



Size of bubble=annual incidence in US and EU

B-CELL MALIGNANCIES ANNUAL INCIDENCE (US & EU)	
Chronic Lymphocytic Leukemia (CLL)	39,700
Diffuse Large B-Cell Lymphoma (DLBCL)	55,100
Follicular Lymphoma (FL)	26,200
Mantle cell lymphoma (MCL)	6,200
Marginal Zone Lymphoma (MZL)	10,700
Waldenstrom's macroglobulinemia (WM)	6,300

Estimates based on 2020 incidence from DRG, GlobalData and secondary research; EU comprised of France, Germany, Italy, Spain and UK

BTK, Bruton tyrosine kinase; 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

Thank you

nurix