



Leader in Targeted Protein Modulation

Discovery and development of targeted protein modulators for the treatment of hematologic malignancies and solid tumors

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American Society for Pharmacology and Experimental Therapeutics
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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)

Harness ligases
to decrease
specific protein levels

Inhibit ligases
to increase
specific protein levels

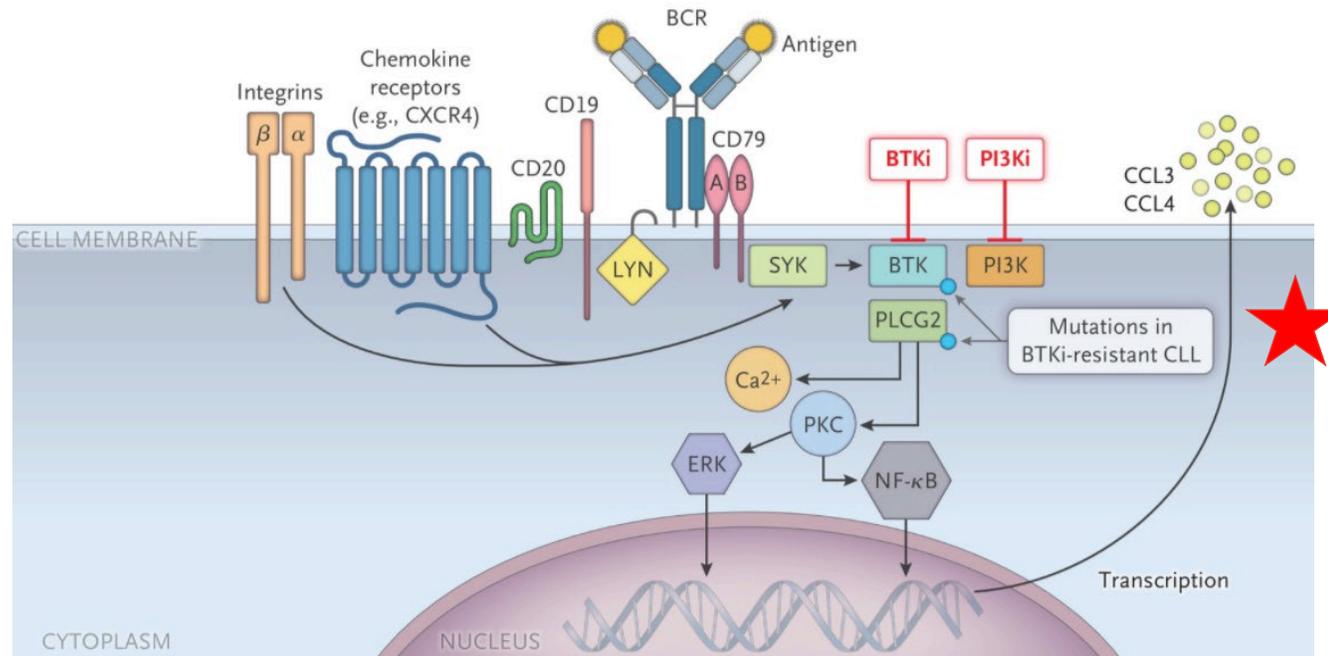
Targeted Protein
Degradation
(TPD)

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

Nurix is Advancing a Pipeline of Propriety and Partnered Programs in Oncology and Inflammatory Diseases

MOA	Drug program	Target/delivery	Therapeutic area	Discovery	IND enabling	Phase 1a	Phase 1b
TPD	NX-2127 Degradar	BTK-IKZF <i>Oral</i>	B-cell malignancies				
	NX-5948 Degradar	BTK <i>Oral</i>	B-cell malignancies				
	NX-0479 / GS-6791 Degradar	IRAK4 <i>Oral</i>	Rheumatoid arthritis and other inflammatory diseases	 			
TPE	NX-1607 Inhibitor	CBL-B <i>Oral</i>	Immuno-Oncology				
TPM	Wholly owned & partnered	14 targets	Multiple				

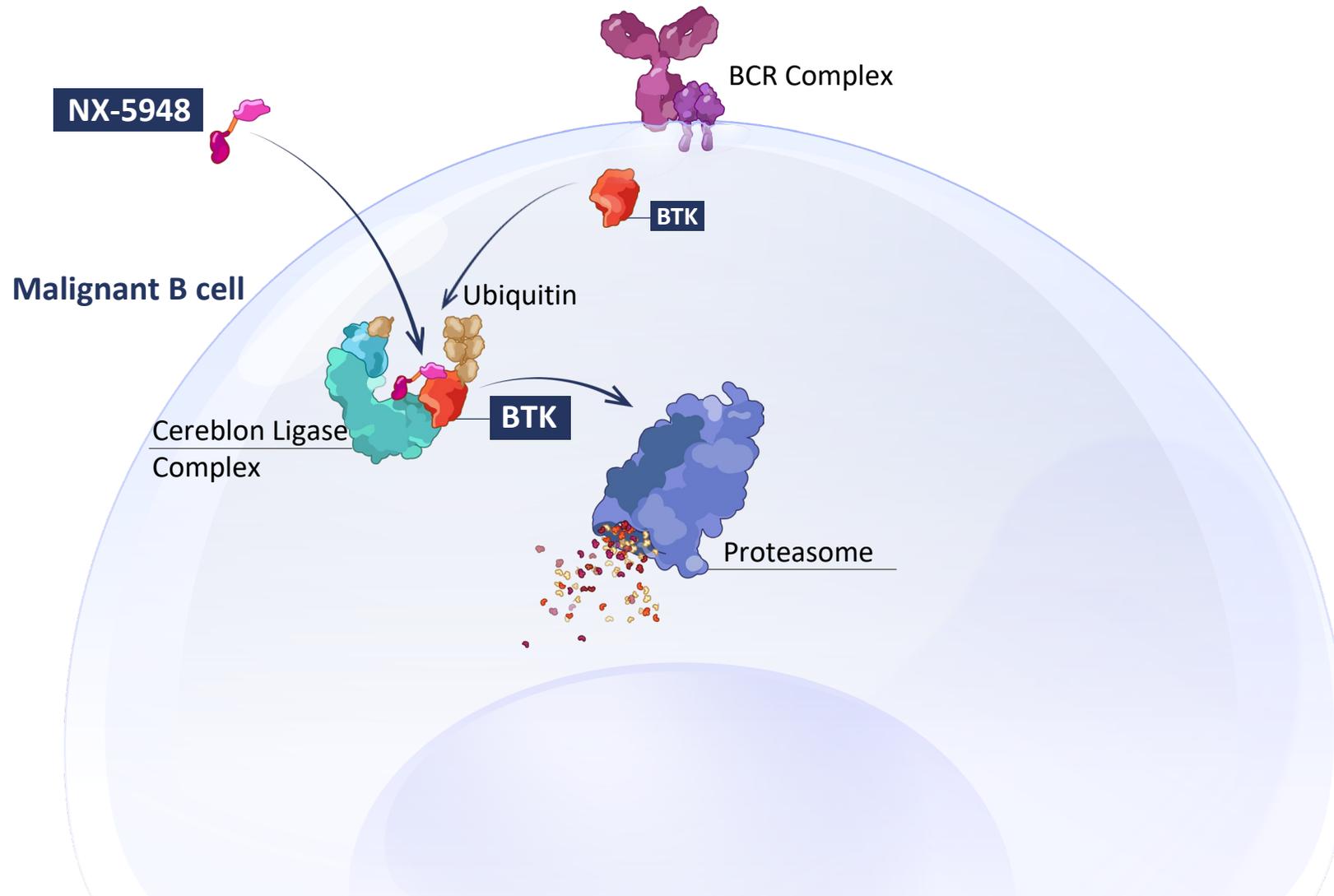
Treatment-Acquired Resistance to BTK Inhibitors are an Increasing Clinical Challenge



- Majority of patients have identified mutations in *BTKC481* at the time of disease progression on ibrutinib; ~53-87% of patients
- Mutations also identified in PLCG2, immediately downstream of BTK
- *BTKC481* mutations are also the main mechanism of resistance for acalabrutinib; 69% of patients

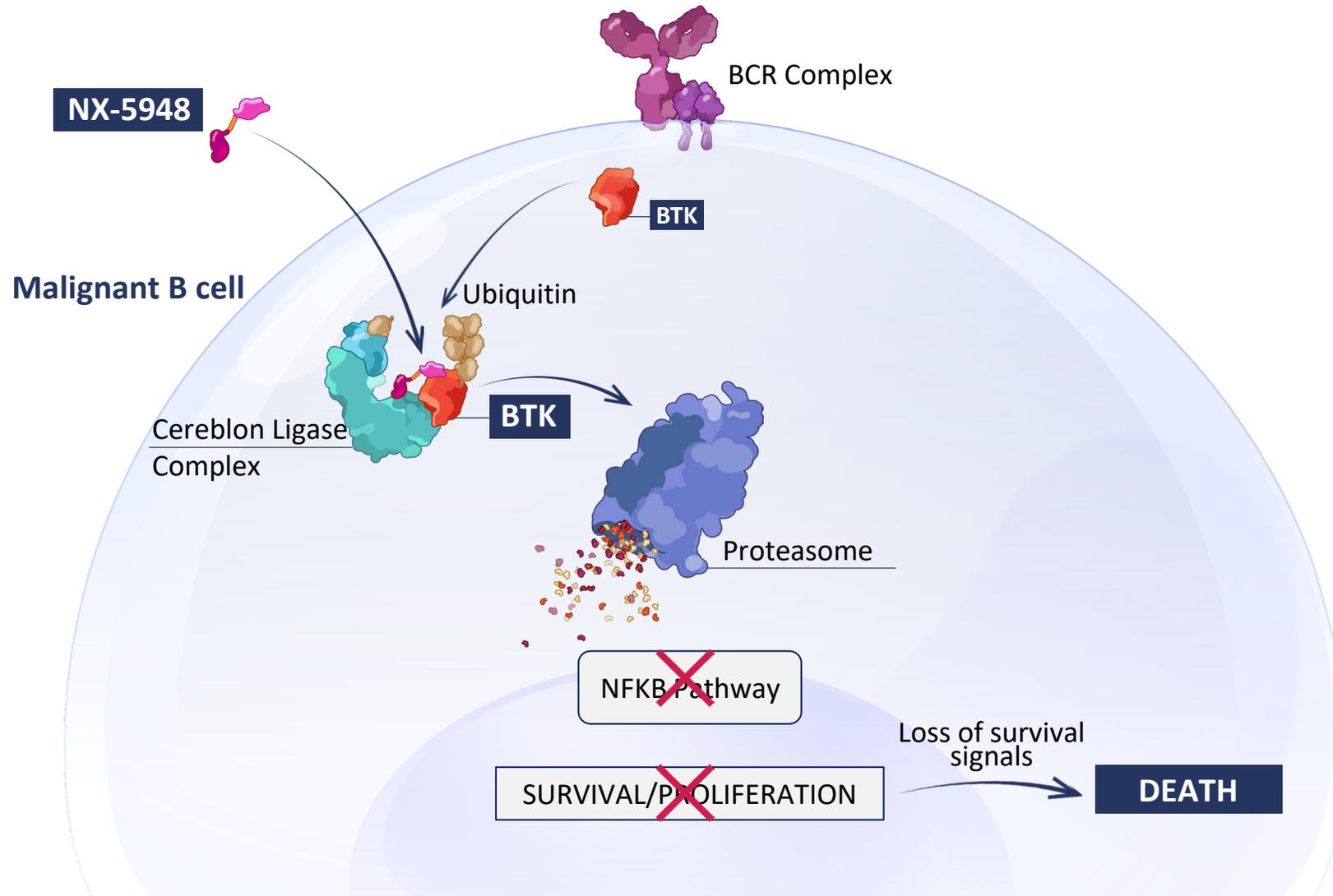
NX-5948 is a Potent and Selective Degradator of BTK

Targeted degradation of Bruton's Tyrosine Kinase Can Address BTKi Resistance



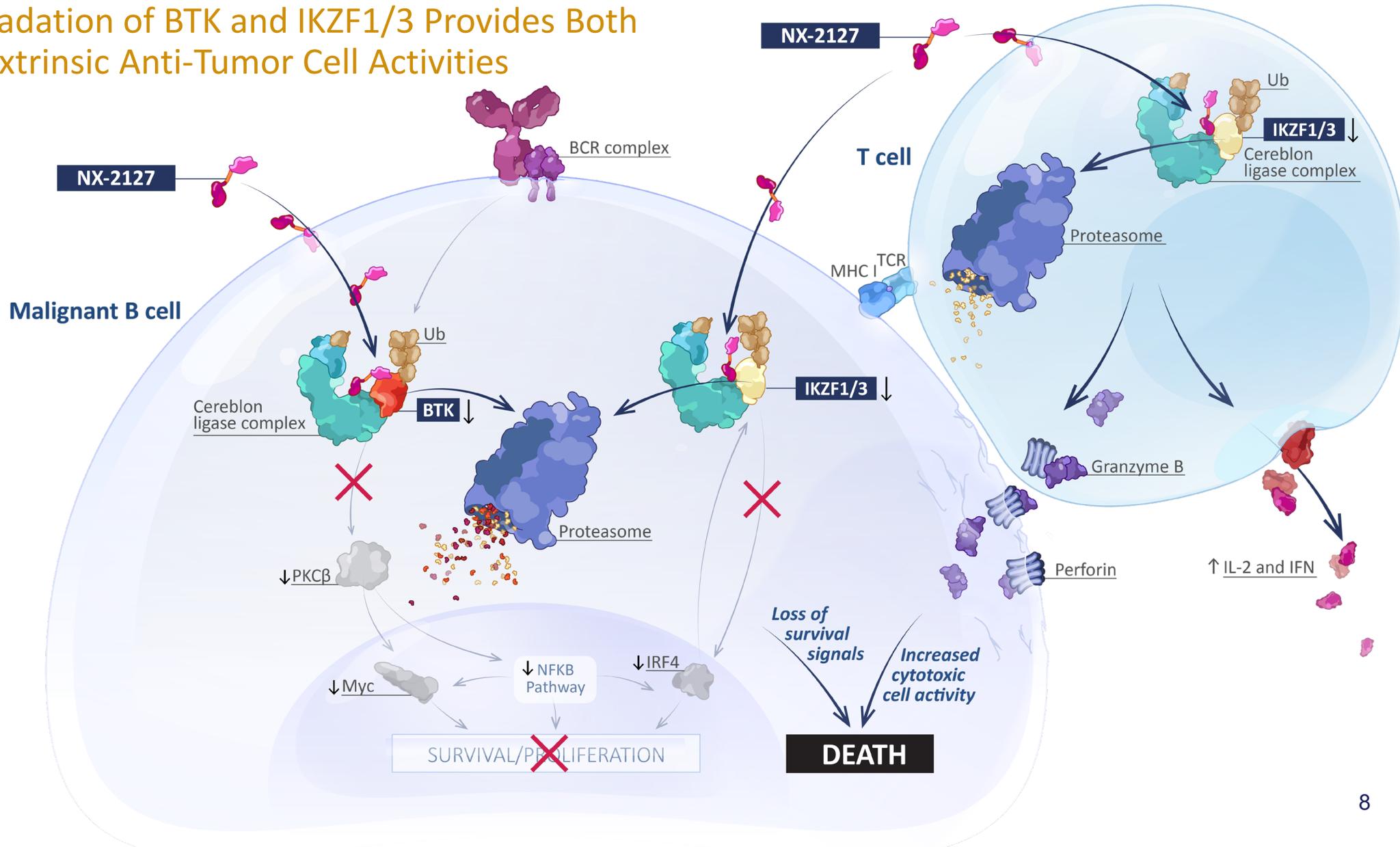
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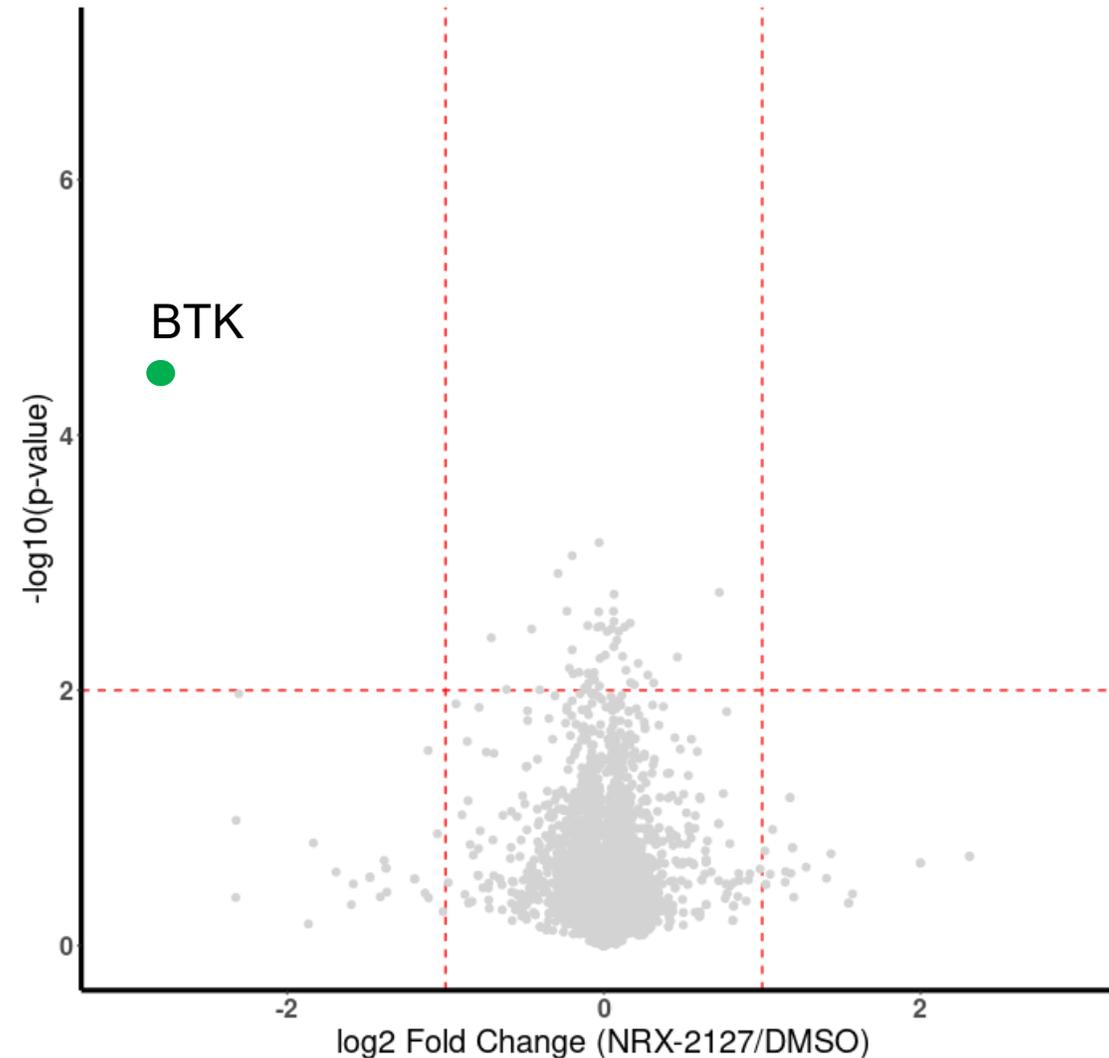
NX-2127 Dual Mechanism of Action

Targeted Degradation of BTK and IKZF1/3 Provides Both Intrinsic and Extrinsic Anti-Tumor Cell Activities



Targeted Protein Degraders Can Display Exquisite Selectivity

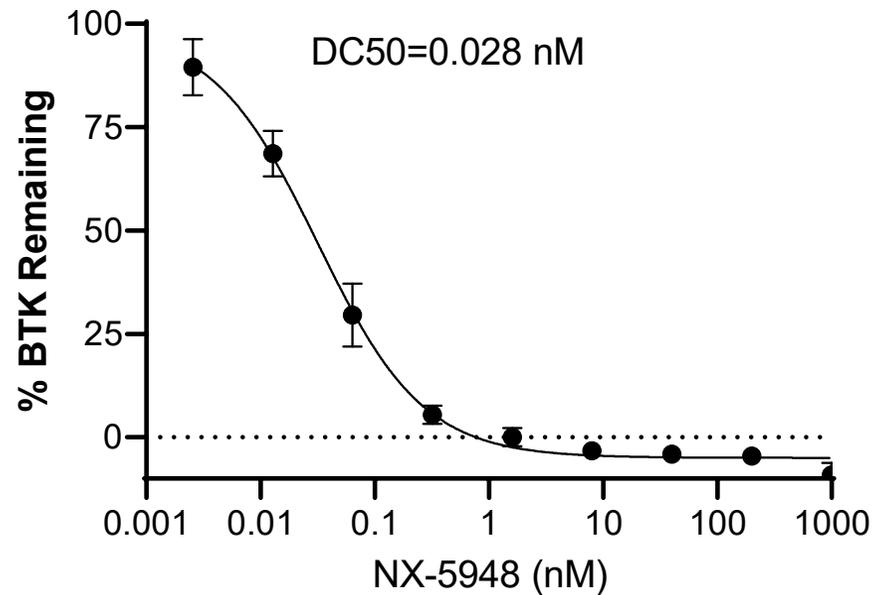
Global Proteomics Analysis in Human Donor PBMCs



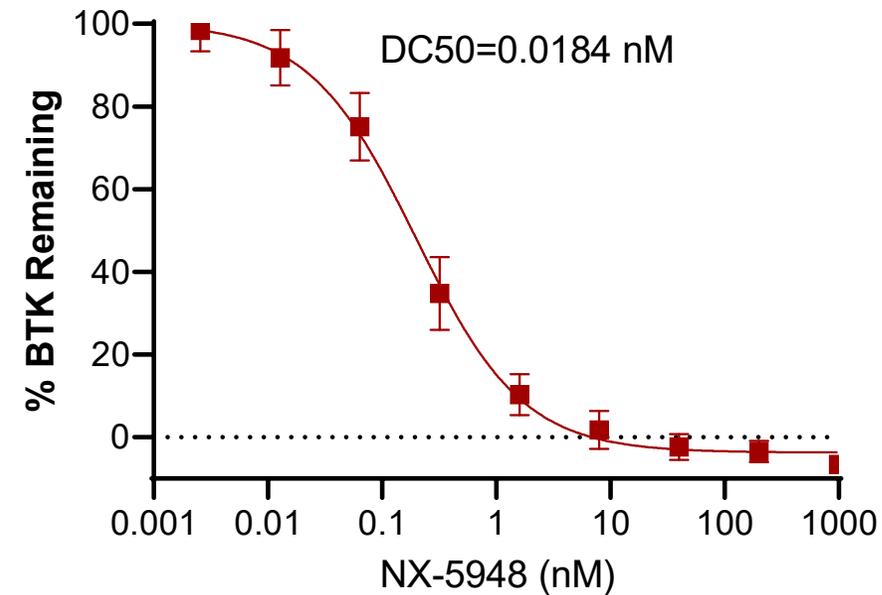
NX-2127, 50 nM, 4h

Nurix BTK Degraders Were Designed for Potent and Rapid Degradation of Wildtype and C481S-Mutated BTK

WT BTK TMD8 Cells

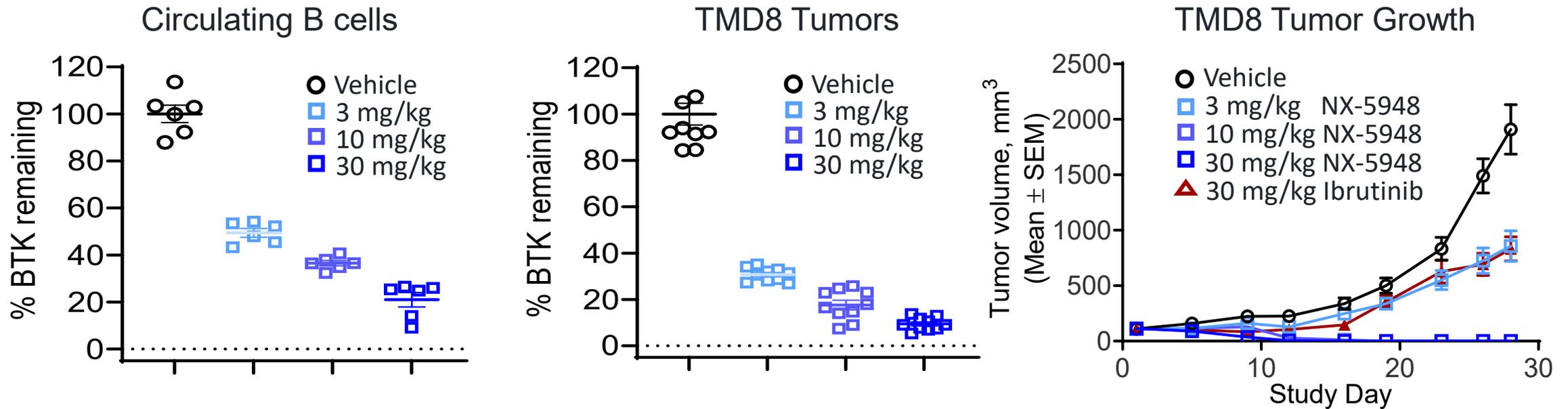


BTK-C481S TMD8 Cells



TMD8 cells harboring WT BTK or a knock-in BTK mutation (C481S) were incubated with NX-5948 for 24 hours, and BTK degradation was assessed by flow cytometry.

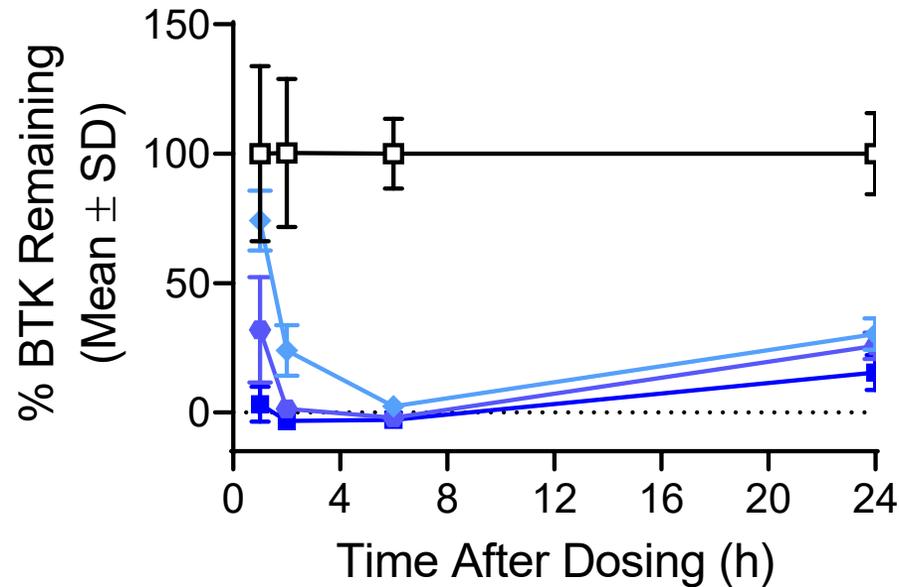
Degradation of BTK by NX-5948 Correlates with Significant Tumor Growth Inhibition



Treatment	Oral gavage dose (mg/kg)	% BTK degradation in circulating B cells	% BTK degradation in TMD8 tumor tissue	% TGI vs Vehicle (Day 26)	P value vs Vehicle
Vehicle	0	0.0±3.7	0.0±4.7	N/A	N/A
NX-5948	3	50.5±1.9	69.2±0.9	54%	0.0025
	10	63.5±1.1	82.4±2.1	100%	<0.0001
	30	79.0±3.1	90.5±0.5	100%	<0.0001
Ibrutinib	30	N/A	N/A	57%	0.0015

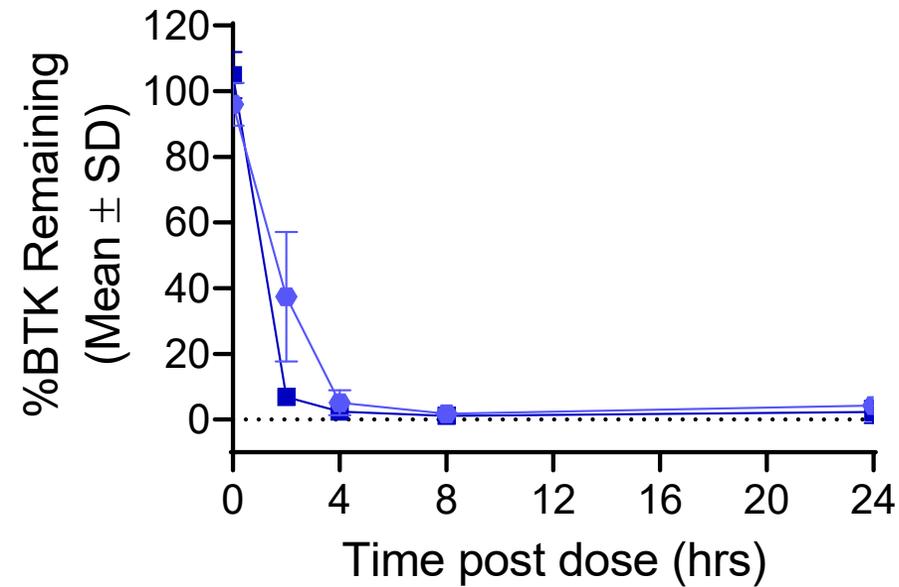
A Single Oral Dose of NX-5948 Promotes Rapid and Complete BTK Degradation in Mouse and Primate B cells

BTK Levels in Mouse Circulating B Cells



□ Vehicle ● NX-5948 10 mg/kg
◆ NX-5948 3 mg/kg ■ NX-5948 30 mg/kg

BTK Levels in Cyno Circulating B Cells

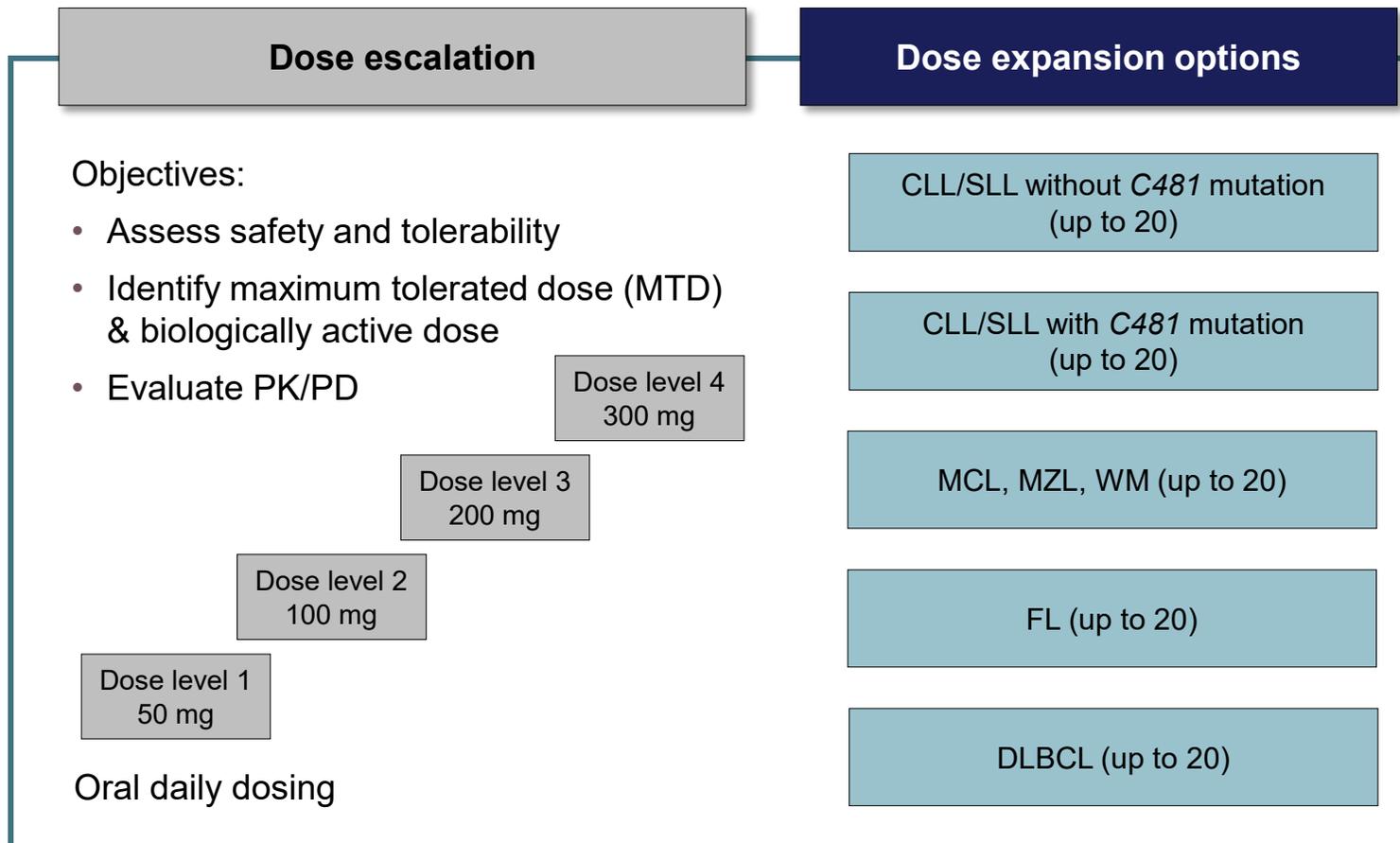


● NX-5948 10 mg/kg
■ NX-5948 100 mg/kg

- In mice, BTK levels increased 24 hours after dosing from BTK resynthesis
- In cynomolgus monkeys, BTK levels remained suppressed at 24 hours

NX-5948-301: Trial design

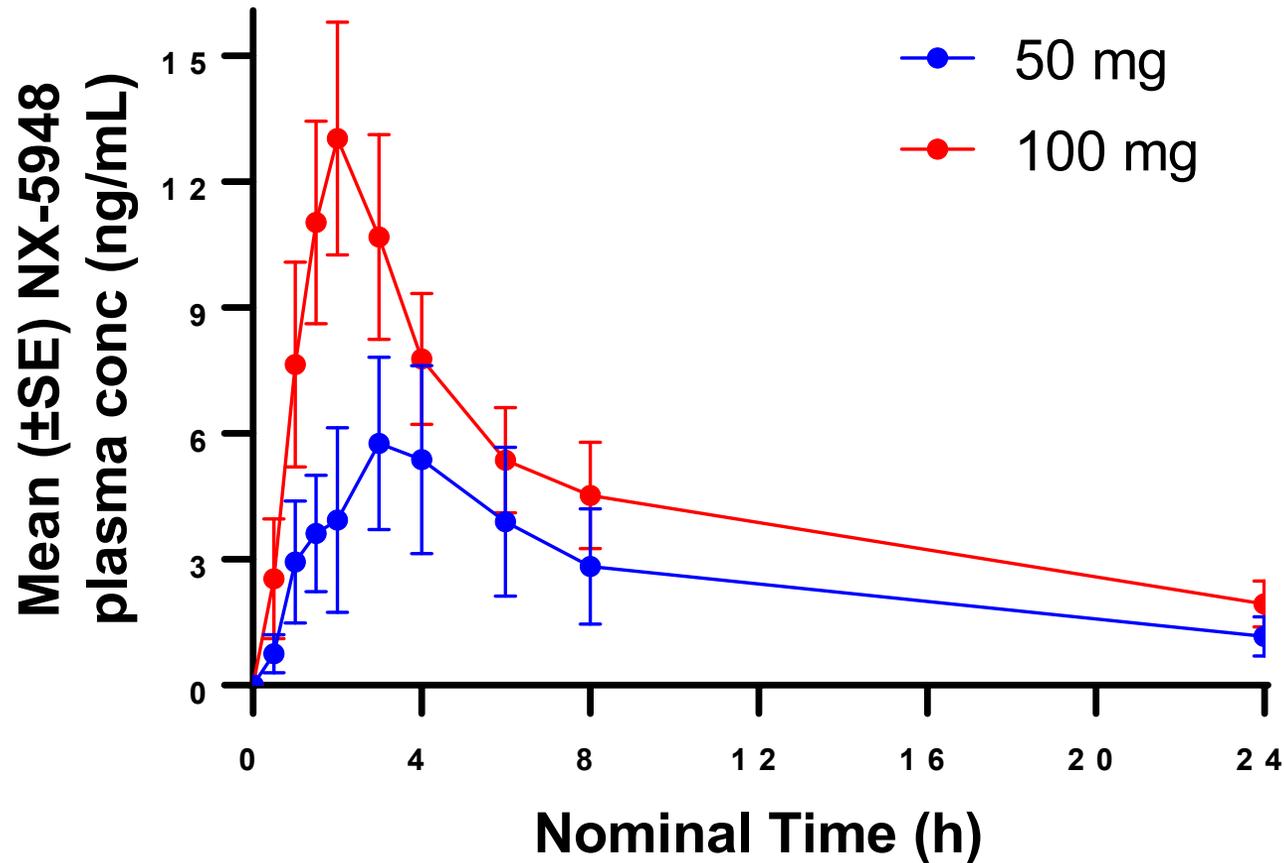
Phase 1 trial in adults with relapsed/refractory B-cell malignancies



- Phase 1a dose escalation is ongoing at clinical sites in the U.K.
- Plans to initiate U.S. sites in early 2023

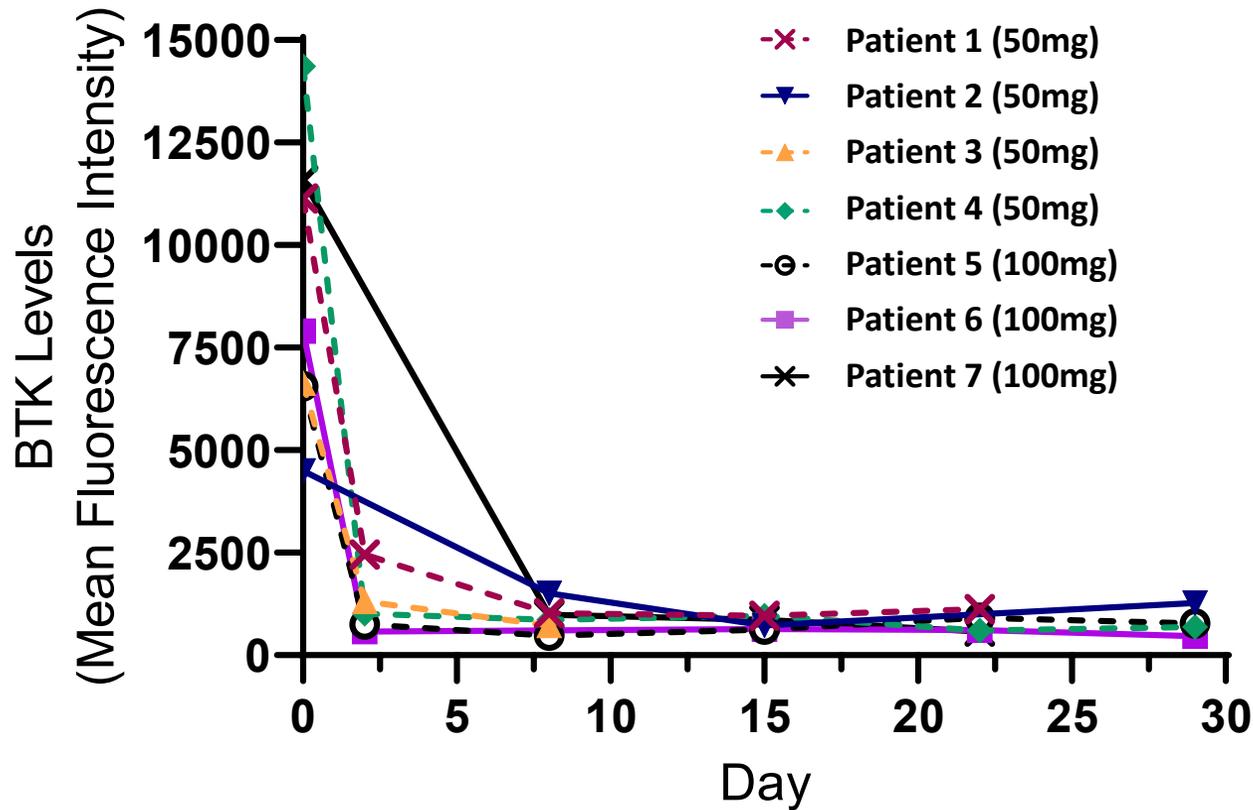
CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; WM, Waldenstrom's macroglobulinemia

Preliminary Data Suggests NX-5948 Exhibits Linear PK and Supports Daily Dosing



- Half-life ~12 hours
- T_{max} of 2-3 hours
- Exposures (both AUC and C_{max}) increase linearly with dose

NX-5948: Rapid, Robust and Sustained BTK Degradation

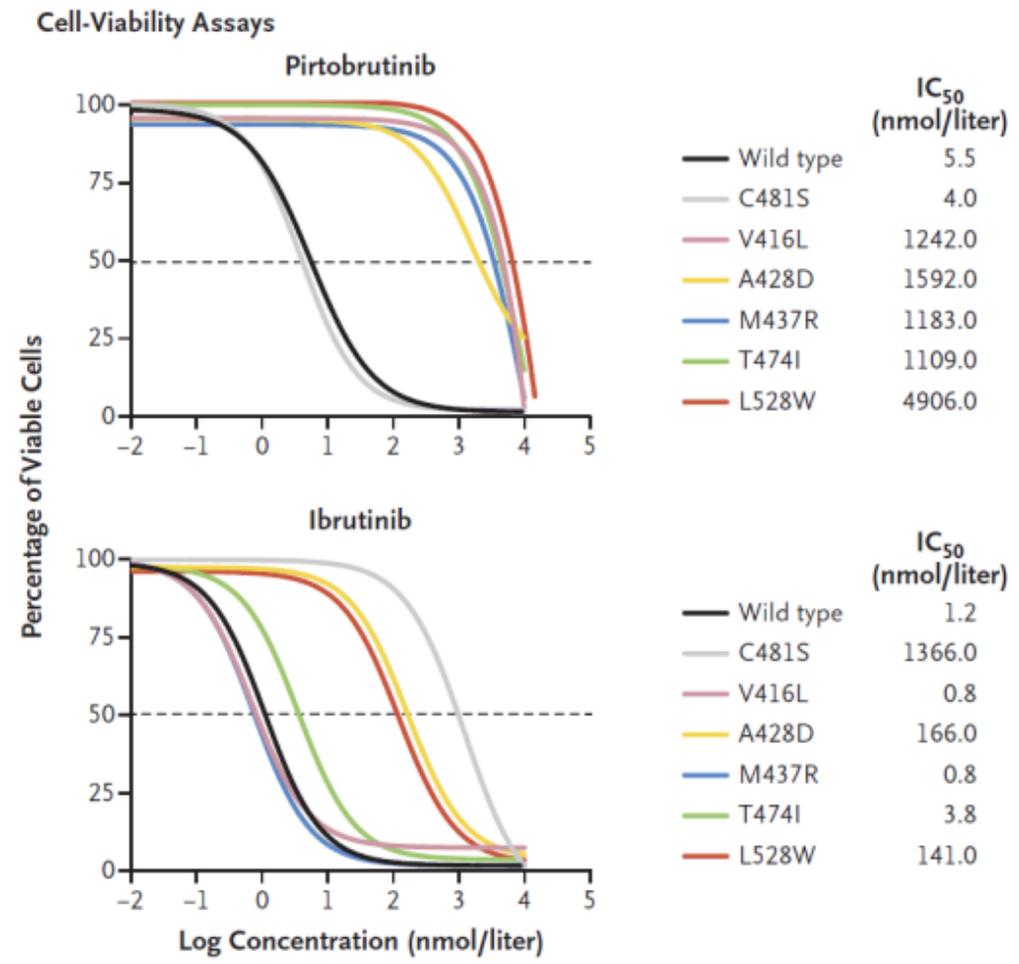
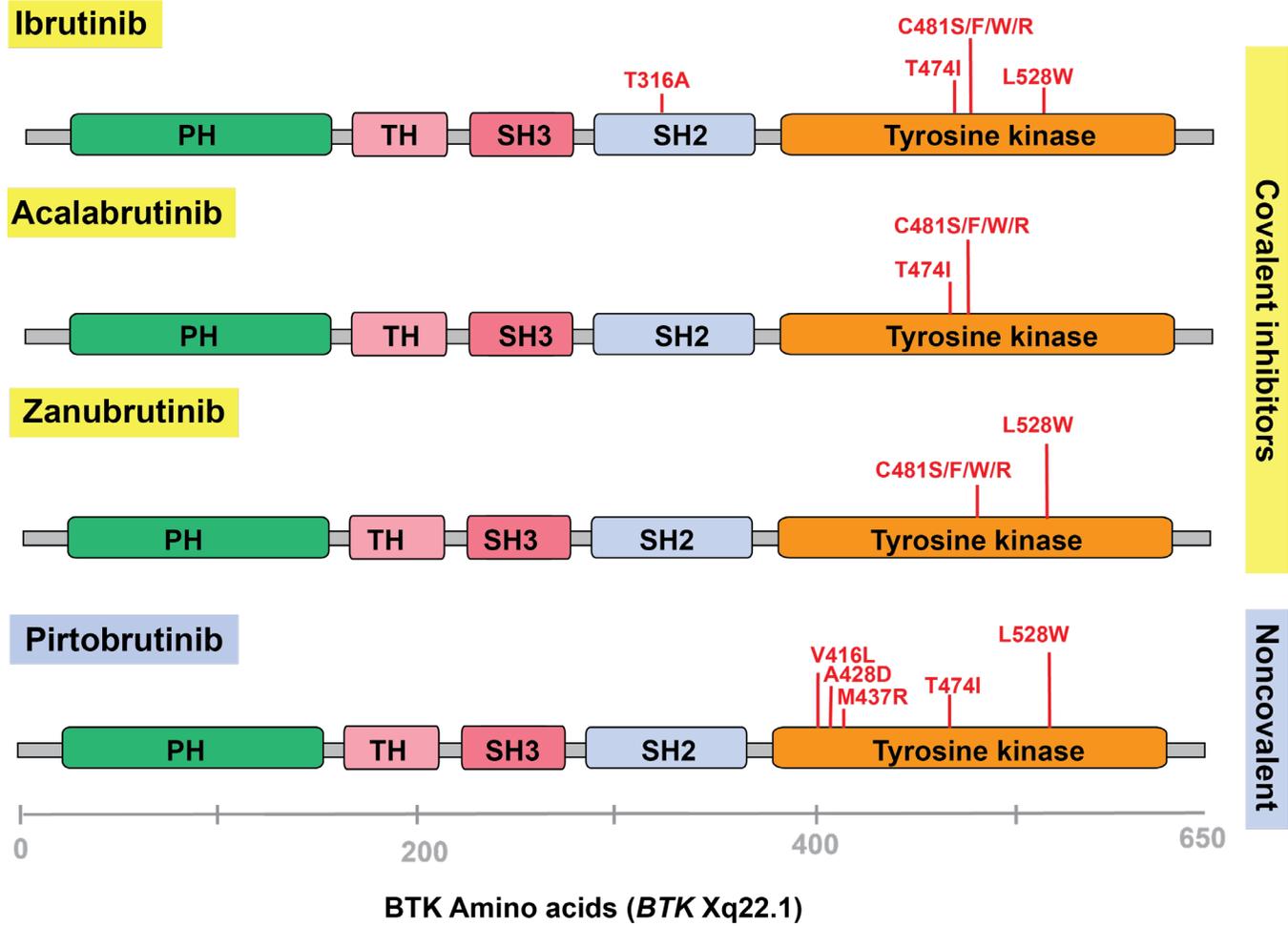


BTK levels are evaluated in real time in a FACS-based assay on whole blood from patients treated with NX-2127

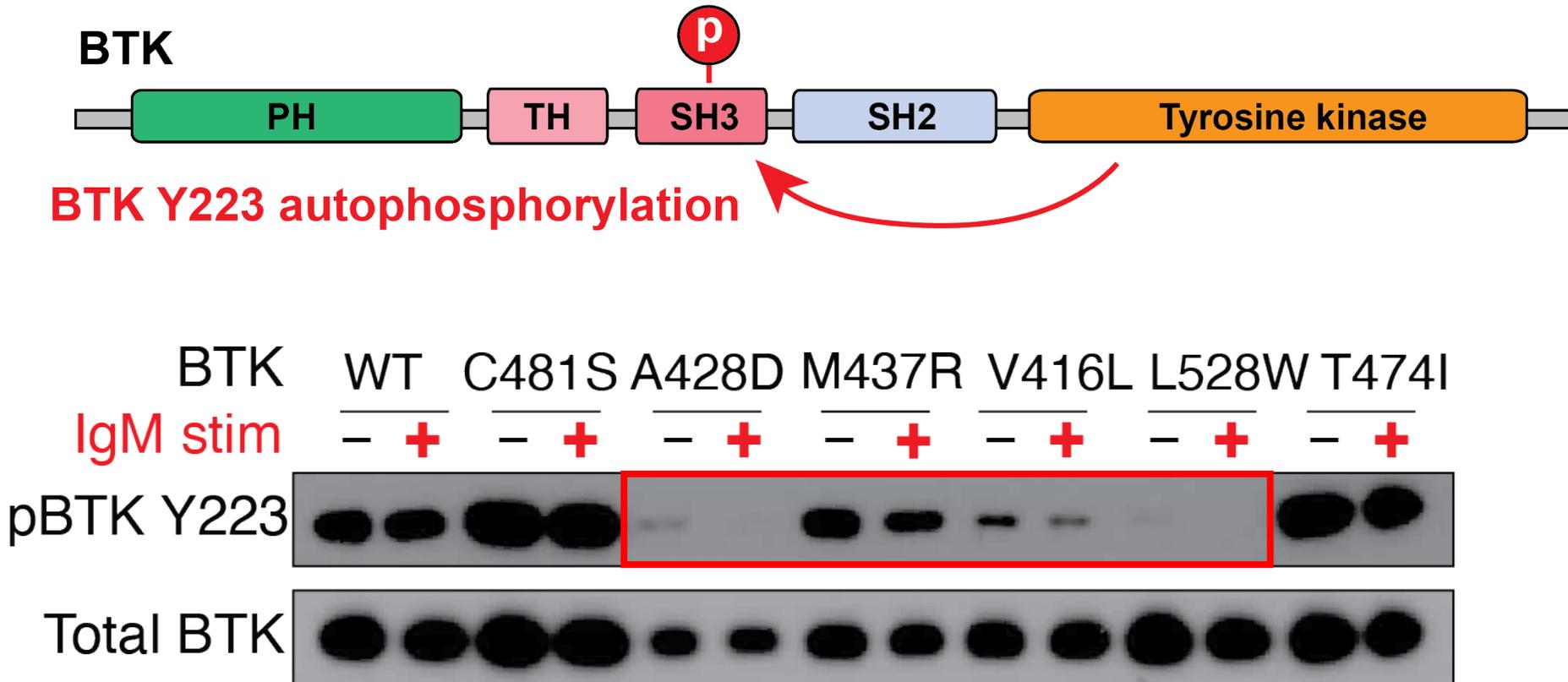
Initial proof of mechanism

- Rapid and sustained degradation of BTK
- Robust BTK degradation observed in all patients tested to date
- Dose escalation ongoing in patients with relapsed/refractory B cell malignancies

Clinical Landscape of Treatment-Emergent Resistance to Inhibitors Is Evolving



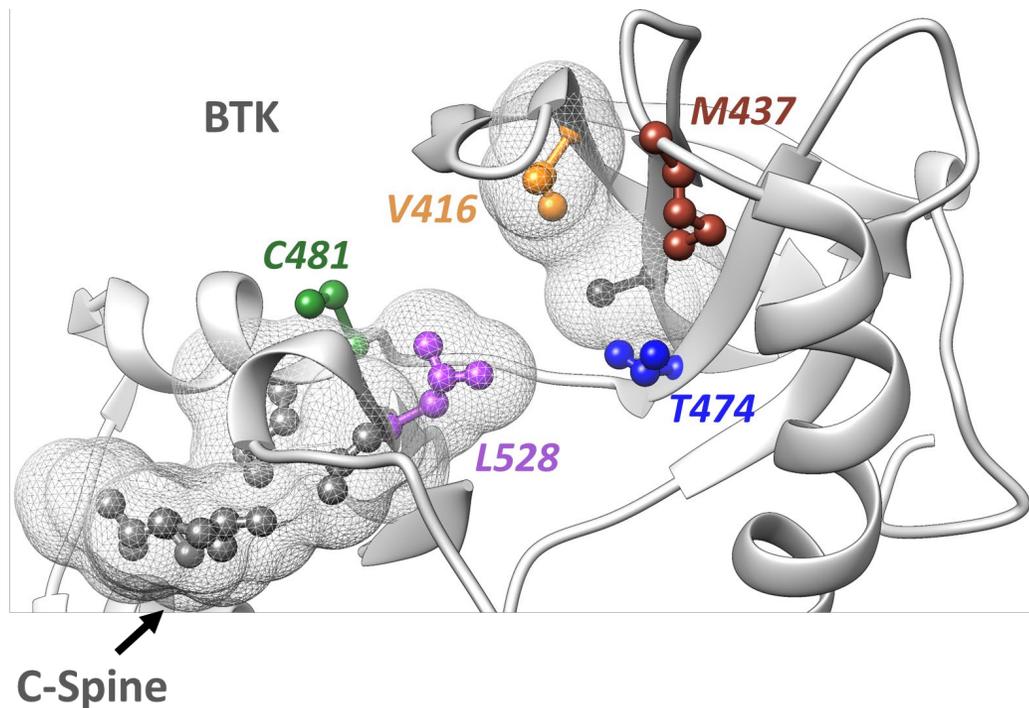
Drug Induced Mutations in BTK Render this Protein Target "Undruggable"



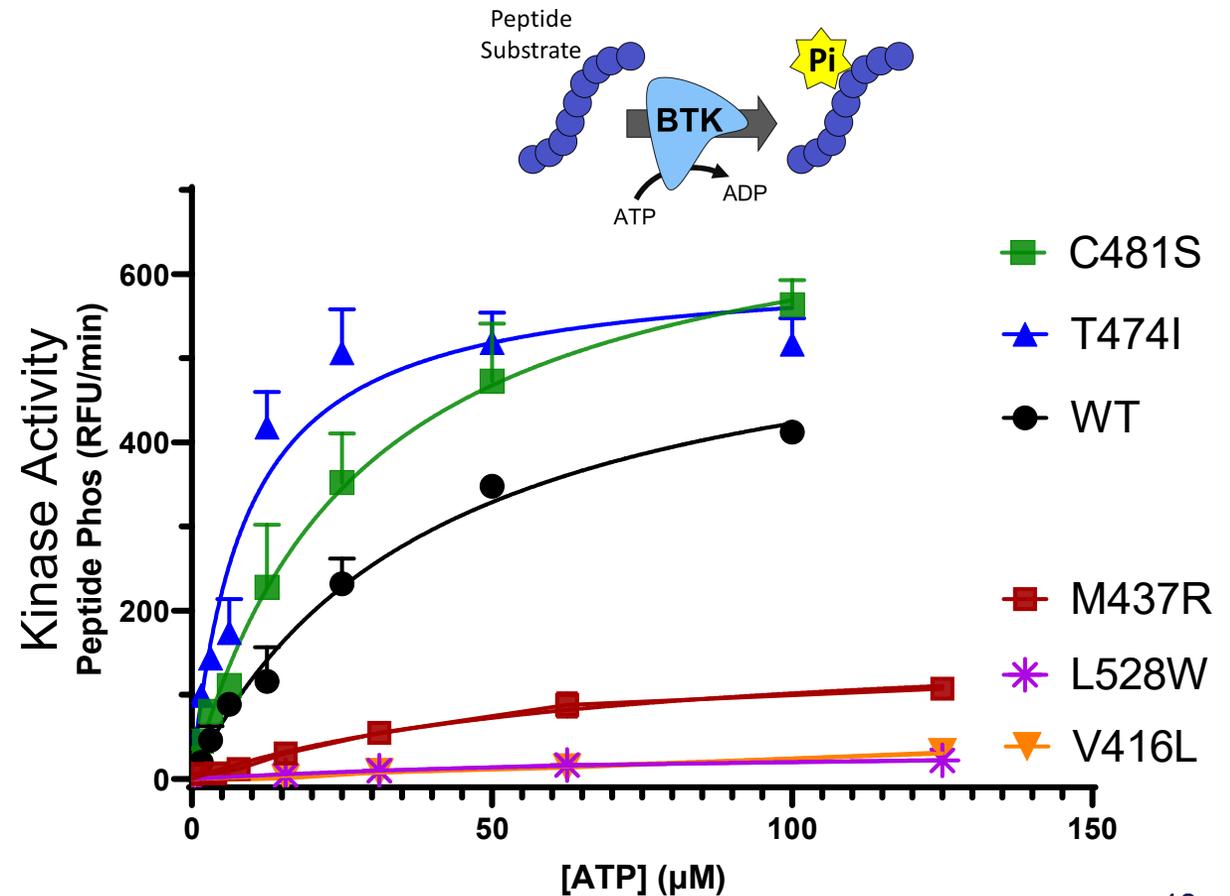
Wang, Mi, Thompson, et al. NEJM 2022

Structural and Enzymatic Studies of New BTKi-Resistant Mutations Confirm BTK Scaffolding Function

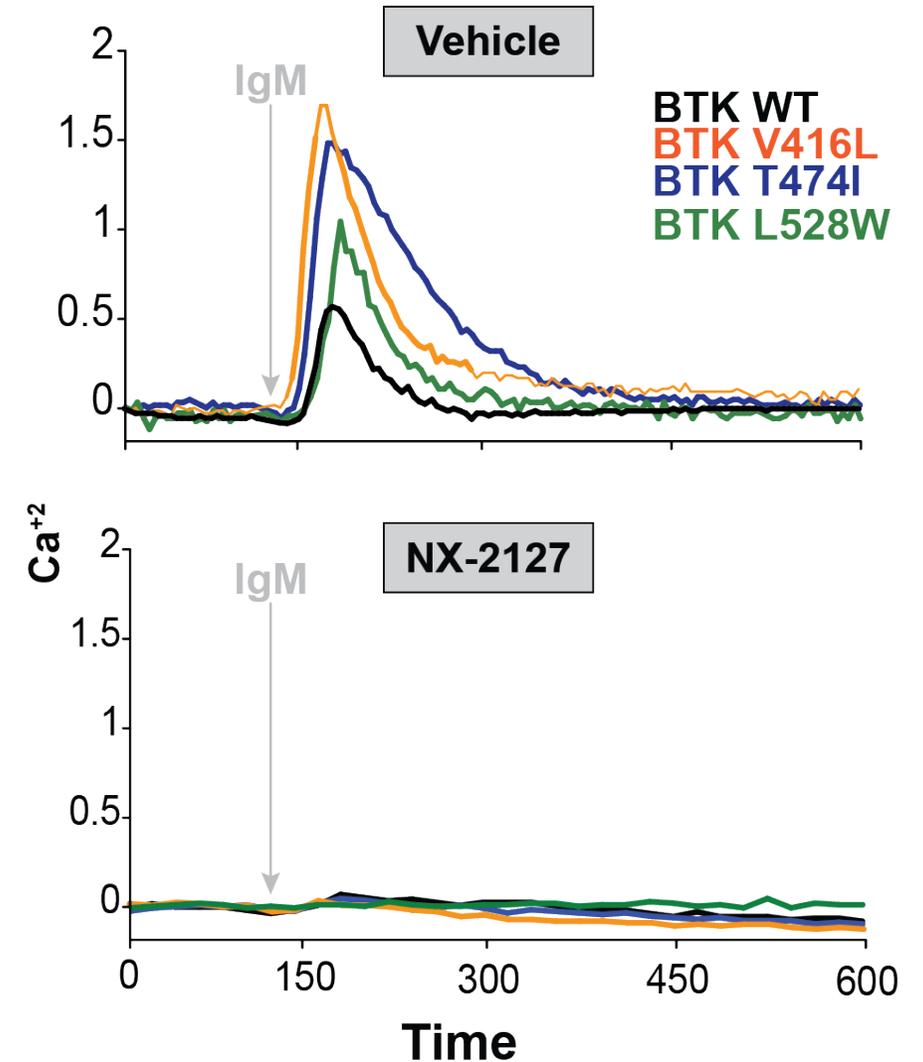
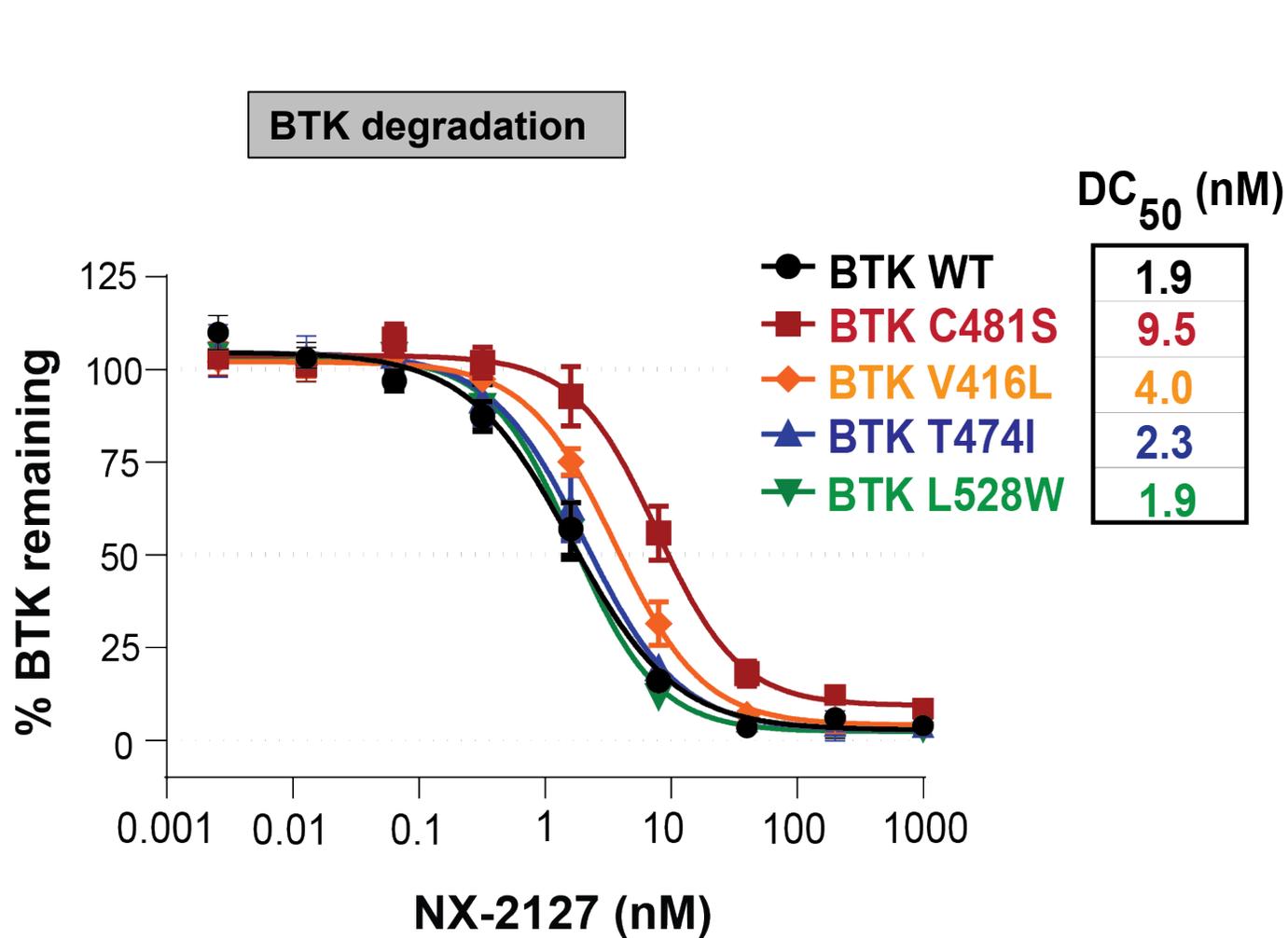
Mutations revealed by non-covalent inhibitors interrupt the catalytic C-spine of kinase domain



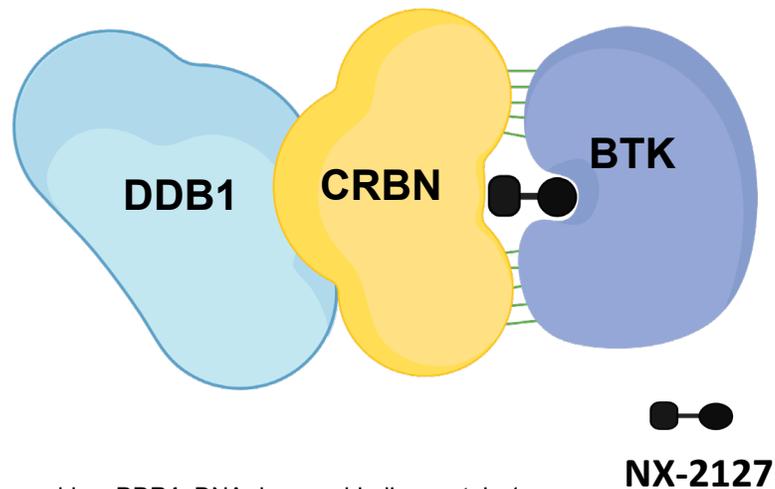
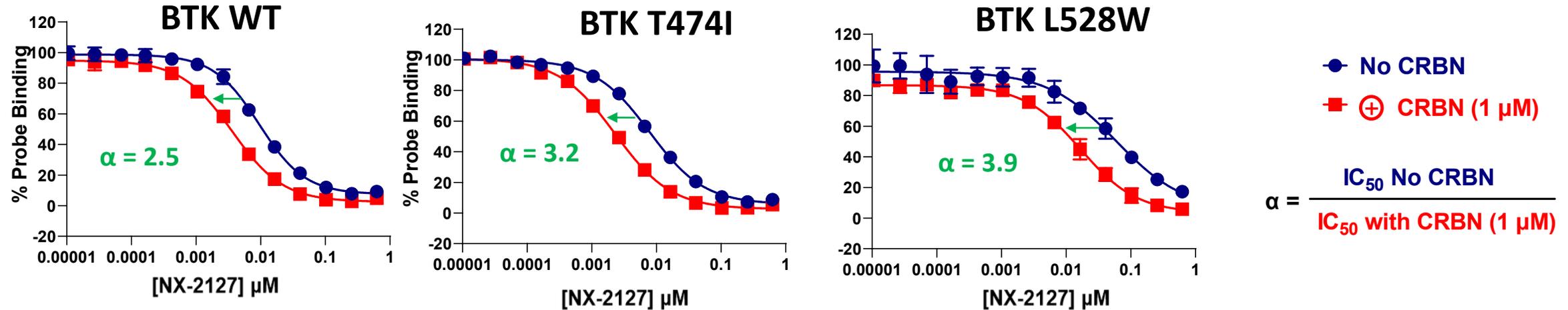
Some mutations that confer resistance to BTKis lack kinase activity yet still potentiate BCR signaling



NX-2127 Degrades Both Wild-Type and Kinase Dead BTK and Suppresses Ca²⁺ Signaling



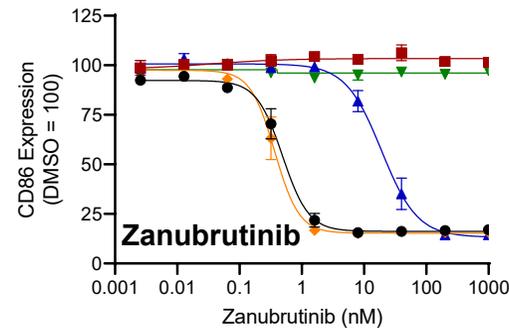
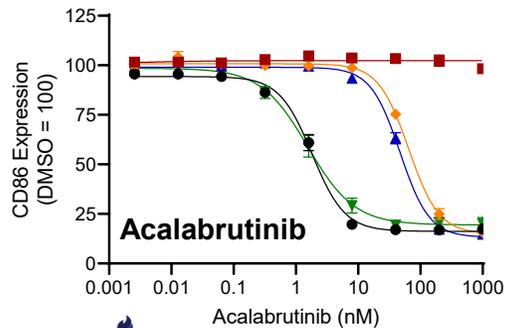
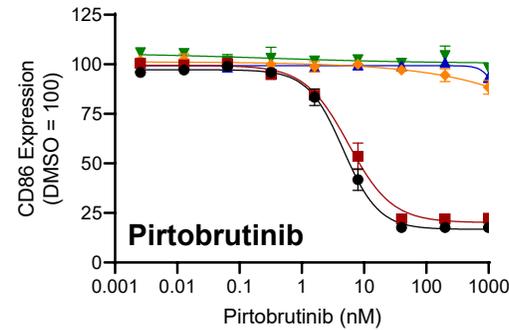
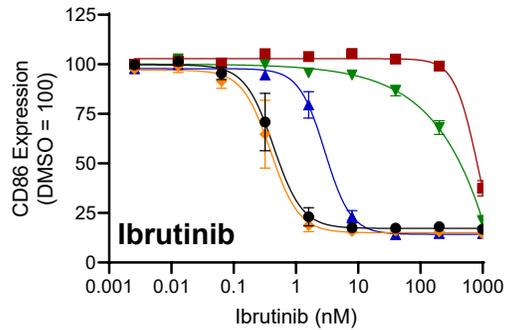
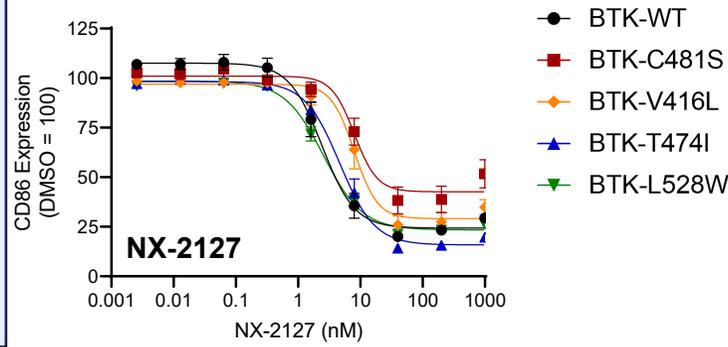
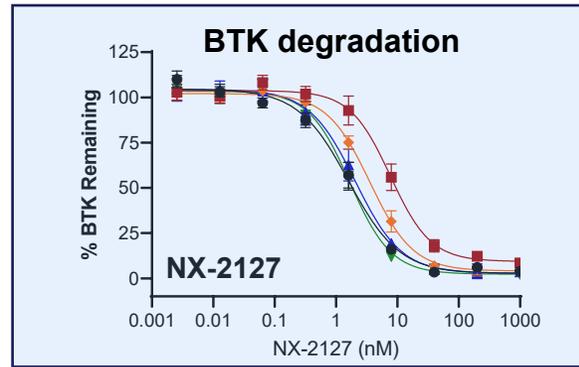
Nurix BTK Degraders Form Stable Ternary Complexes Between BTK and CRBN Irrespective of Mutation Status



- Positive Cooperativity ($\alpha > 1$)
- Stable ternary complex
- Induced protein-protein interactions
- Greater tolerance for reduced binary affinity

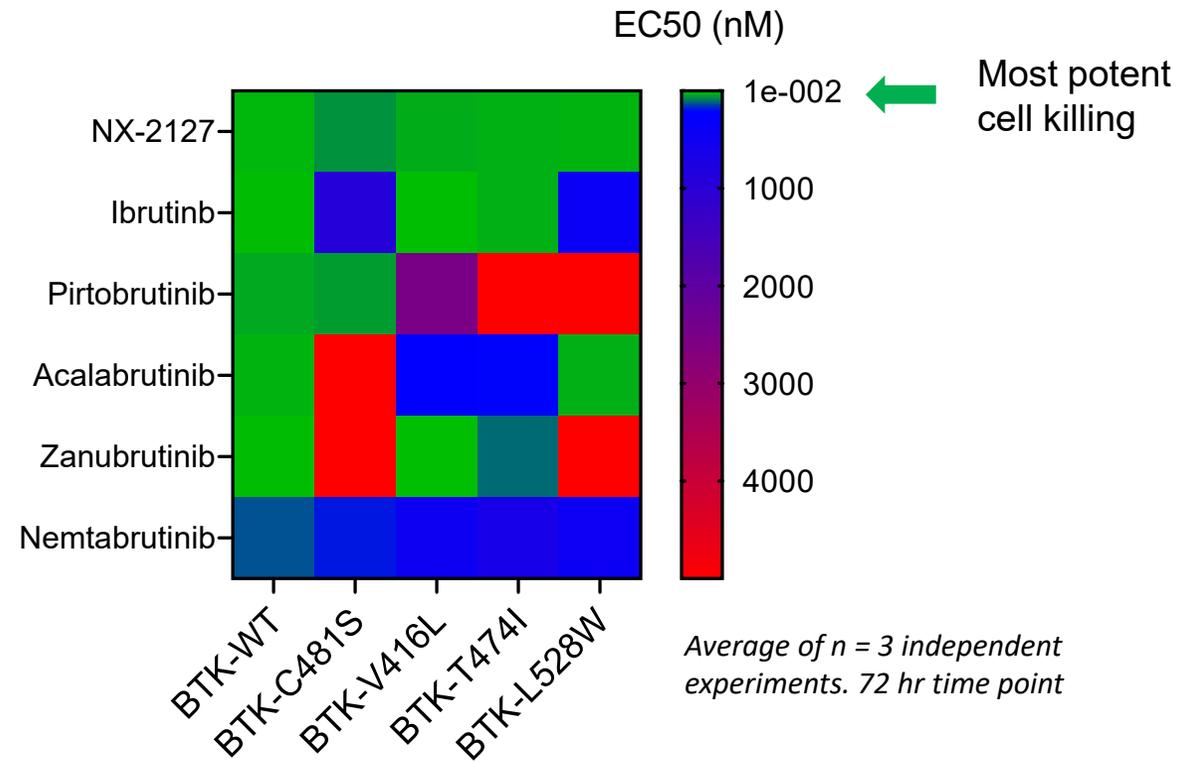
NX-2127 Is Potent and More Broadly Active Than All BTK Inhibitors Tested

BTK degradation and activation marker suppression in TMD8 tumor cells



Average of n = 3 independent experiments +/- SEM

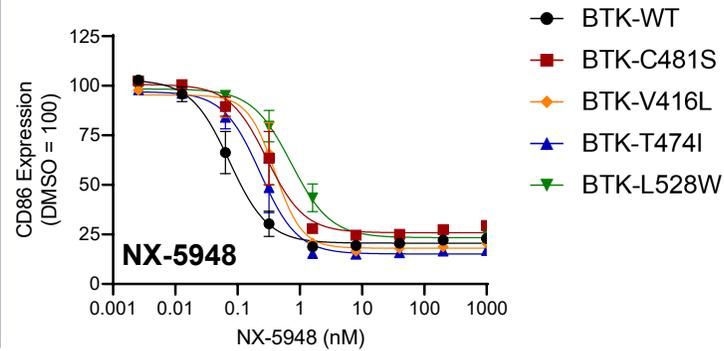
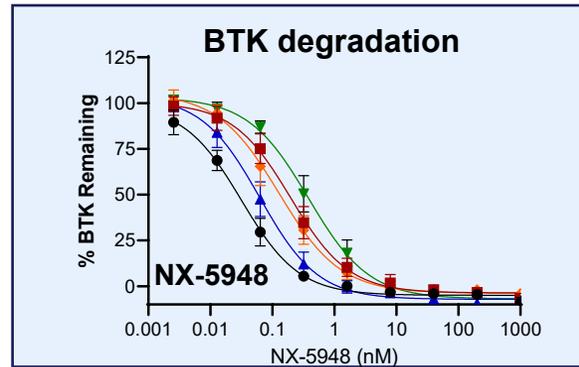
TMD8 tumor cell killing



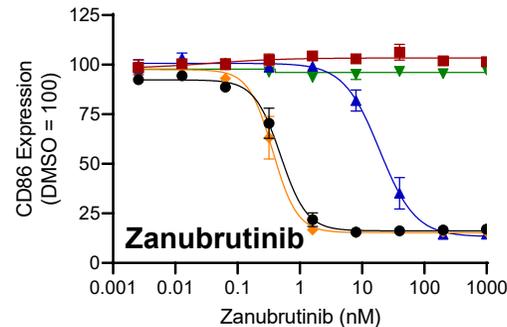
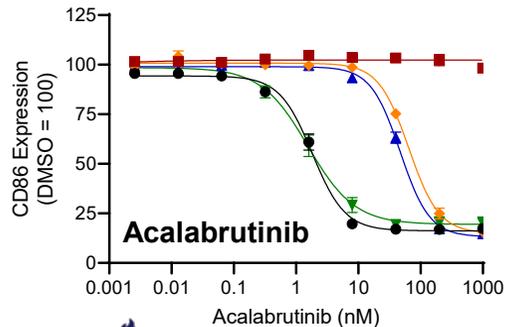
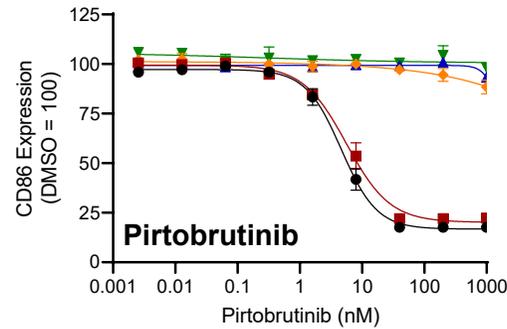
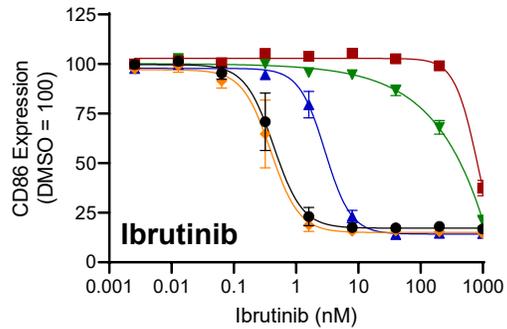
- All inhibitors have resistance mutation liabilities
- NX-2127 displays potent cell killing and maintains suppression of CD86 in the context of key resistance mutations

NX-5948 Is More Potent and Broadly Active Than All BTK Inhibitors Tested

BTK degradation and activation marker suppression in TMD8 tumor cells

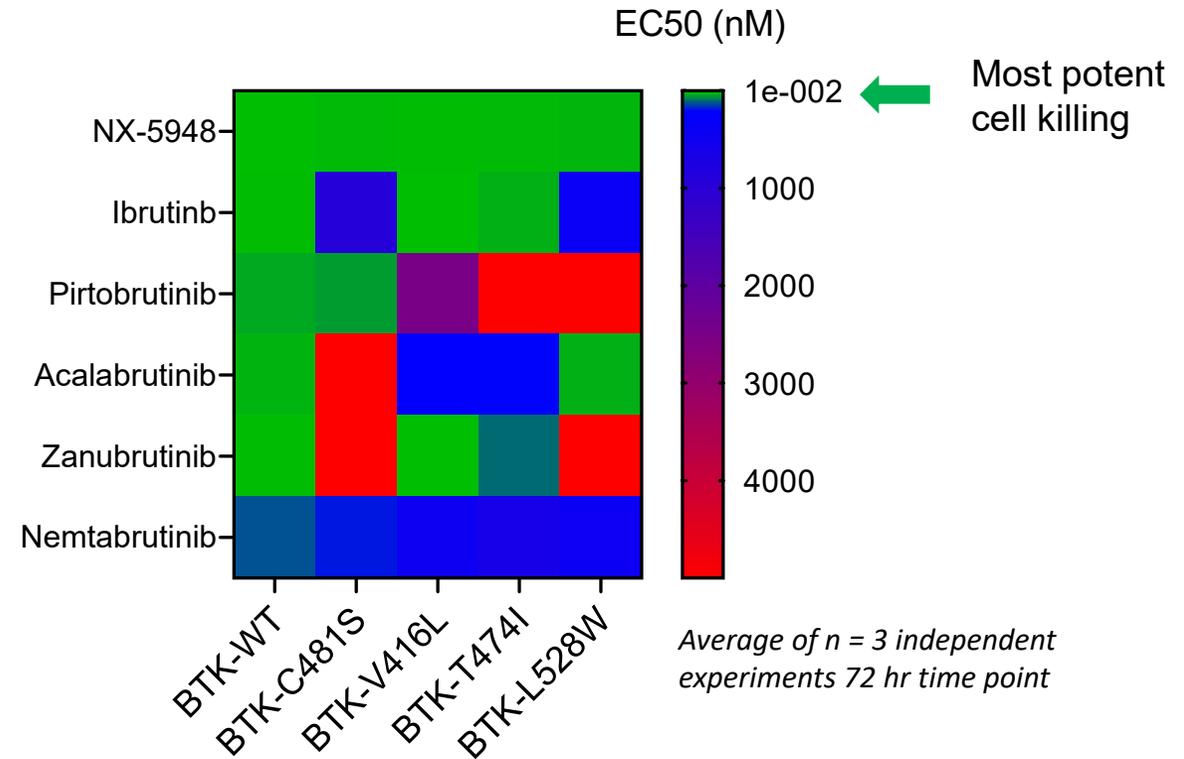


- BTK-WT
- BTK-C481S
- ◆ BTK-V416L
- ▲ BTK-T474I
- ▼ BTK-L528W



Average of n = 3 independent experiments +/- SEM

TMD8 tumor cell killing

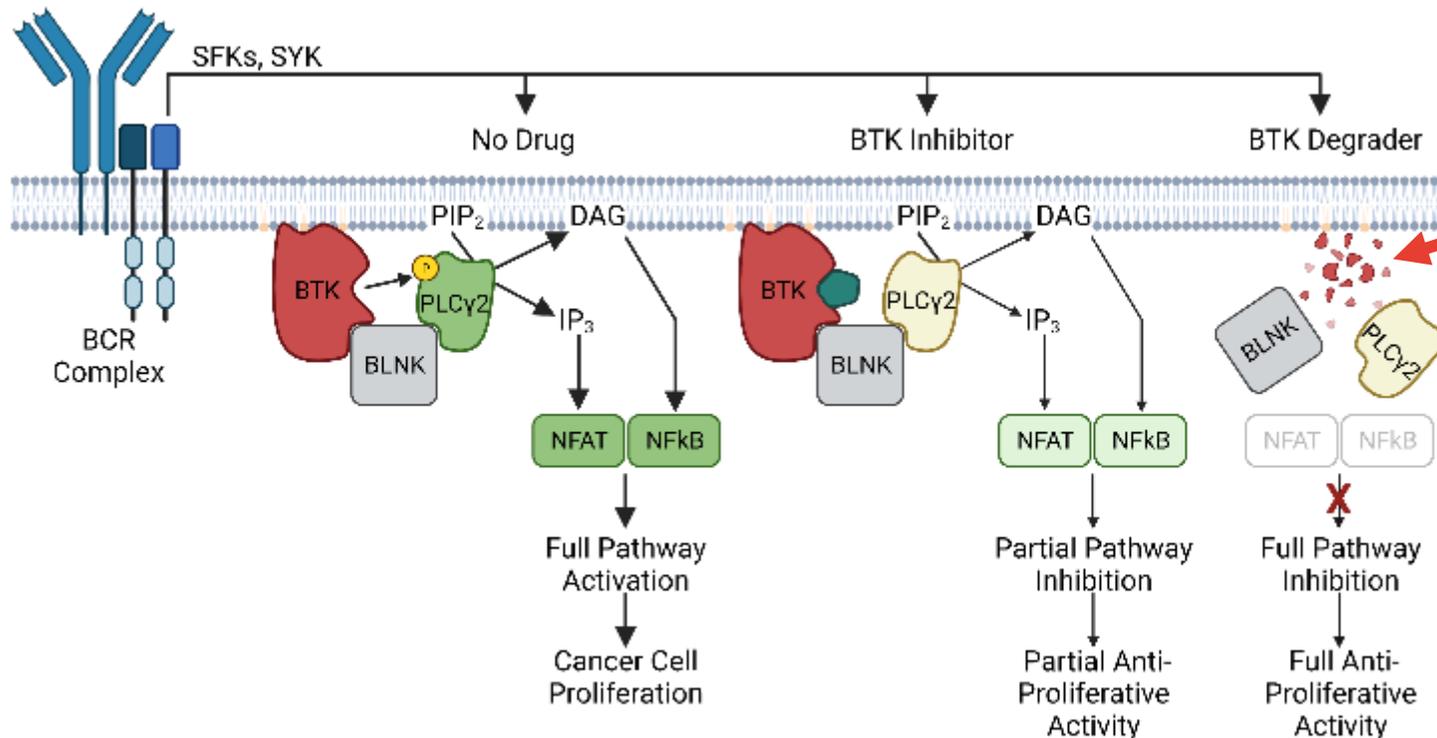


- All inhibitors have resistance mutation liabilities
- NX-5948 displays potent cell killing and maintains suppression of CD86 in the context of key resistance mutations

Degraders More Completely Disrupt BCR Signaling

Nurix Degraders:

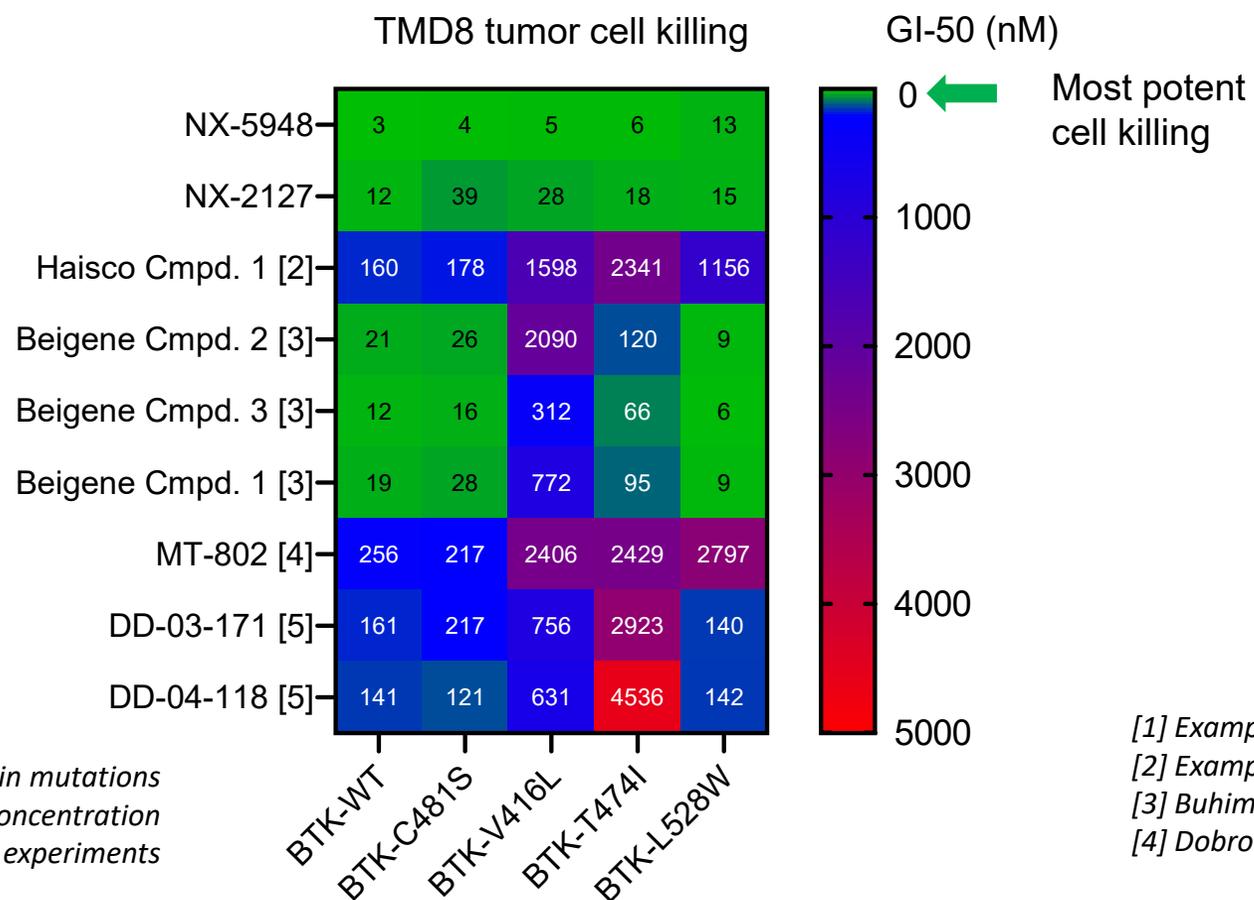
- 1) Are effective against resistance mutations through binding cooperativity between BTK and the ligase complex
- 2) Eliminate the scaffolding function of BTK oncogenic signals



Removal of BTK disrupts the signaling complex effectively destroying the scaffolding function of the protein

Not All BTK Degraders Are Created Equal

Nurix degraders have superior coverage of novel BTKi resistance mutations compared to other BTK degraders



The ability of NX-5948 and NX-2127 to induce TMD8 tumor-cell killing was compared to other reported degraders in a 72 hour viability assay

TMD8 cells with knock-in mutations
72 hr time point, 5000 nM top concentration
Average of $n \geq 4$ independent experiments

[1] Example 1. WO2022111449 (Haisco)

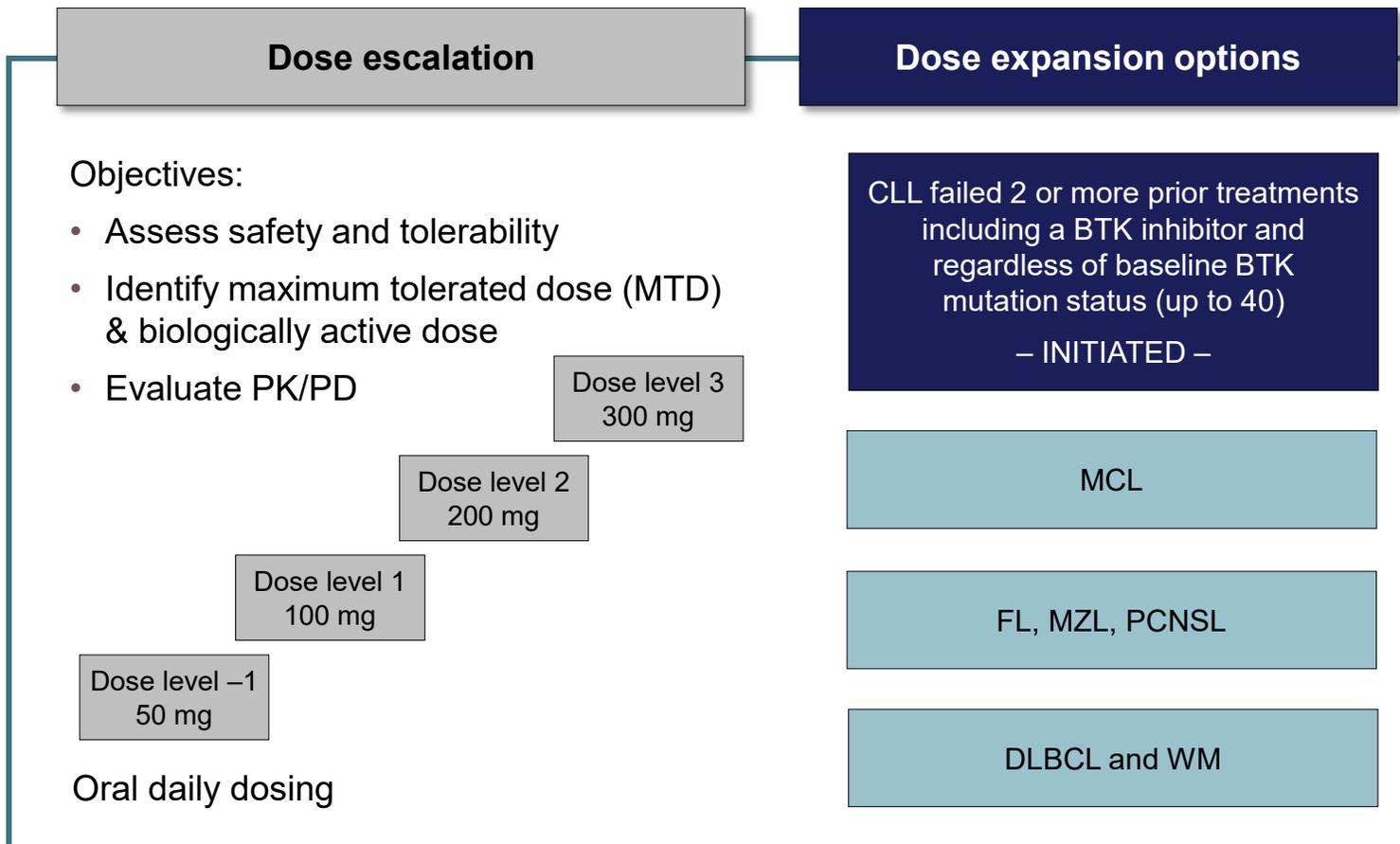
[2] Example 10, Example 9, Example 11. WO2021/219070 (BeiGene)

[3] Buhimschi et al. 2018. *Biochemistry* 57(26): 3564-3575.

[4] Dobrovolsky et al. 2019. *Blood* 133(9): 952-961.

NX-2127-001: Trial Design

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

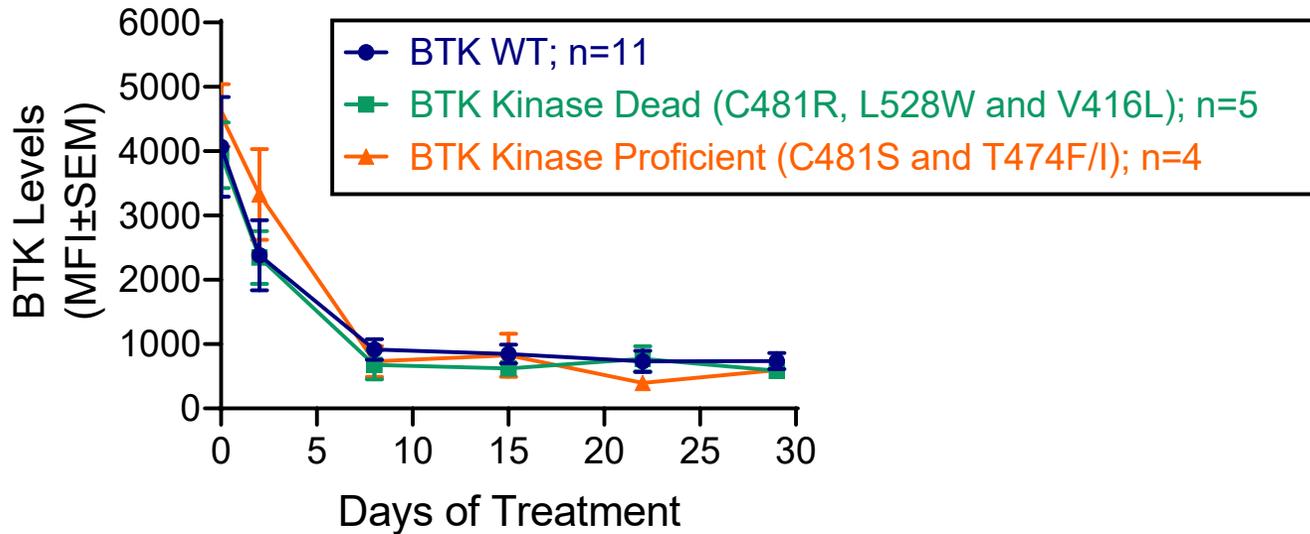


- CLL Phase 1b expansion cohort ongoing at 100 mg dose
 - MTD not established
 - 100 mg dose chosen as expansion dose based on PD, clinical activity and safety profile
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL (e.g., DLBCL, MCL, MZL, WM, FL)

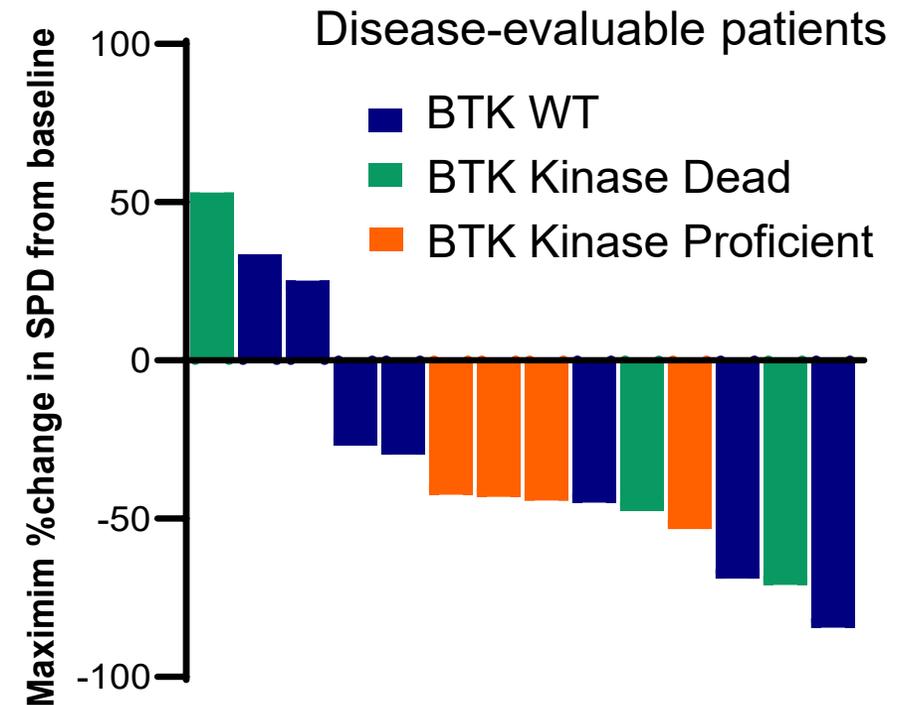
First Demonstration of Clinical Activity of a Degradator Against a Range of BTK Mutations

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



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

Montoya, Dec. 2022 ASH

Mechanistic Rationale for Dual Degradator in DLBCL

CLINICAL TRIALS AND OBSERVATIONS

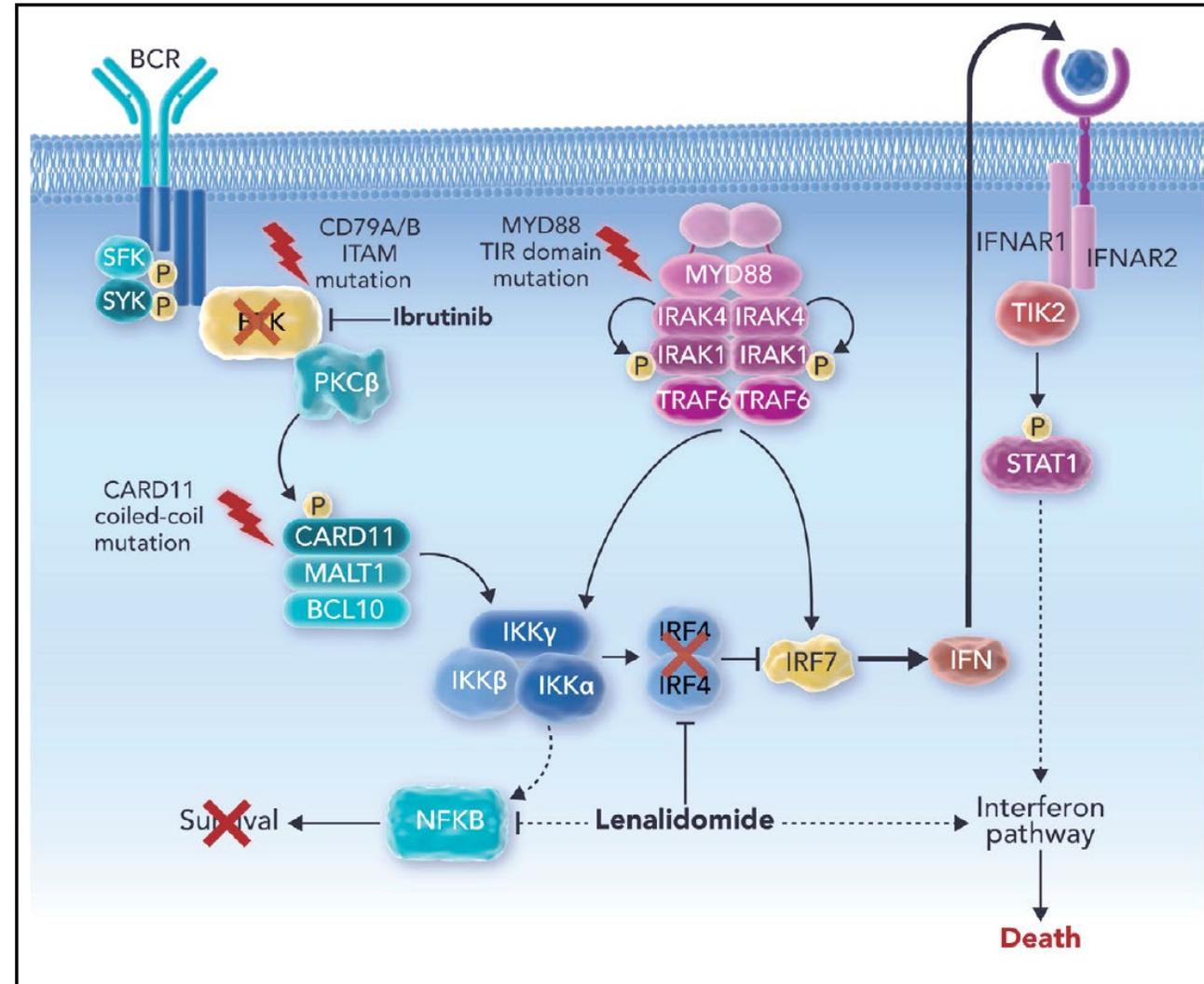
Comment on Goy et al, page 1024

Ibrutinib and lenalidomide: when $1+1 = >2$

Jason Westin | MD Anderson Cancer Center

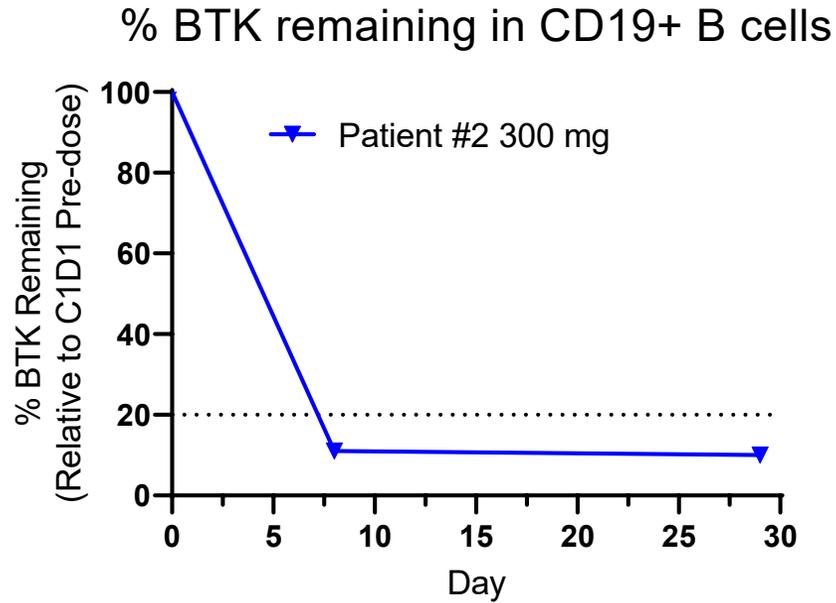
Hyper-activated BCR (CD79b-mut) and TLR (MyD88-mut) signaling are hallmarks of non-GCB DLBCL:

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



Rapid BTK Degradation and Confirmed Complete Response Following NX-2127 Therapy

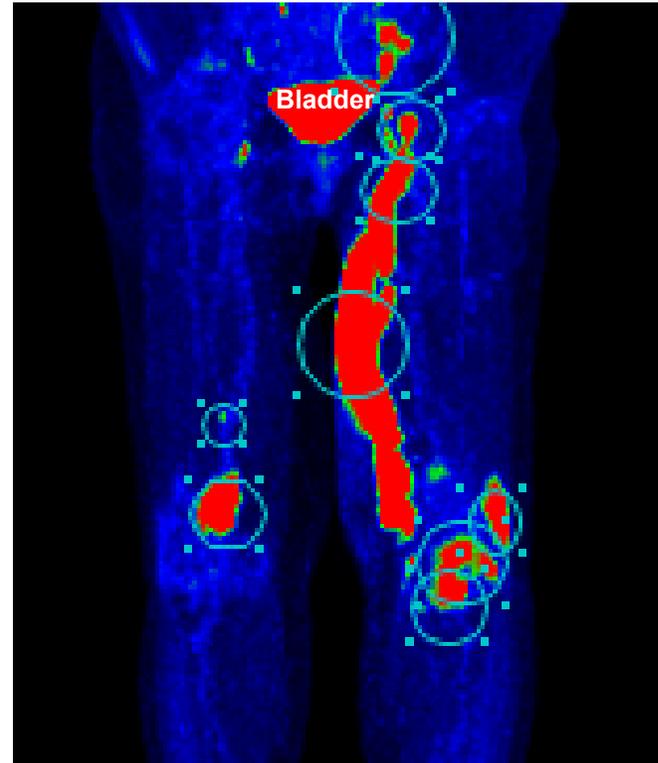
FDG-PET CT Scan Disease Assessment



% BTK calculated in PBMC

Significant Ikaros and Aiolos degradation also confirmed by day 8

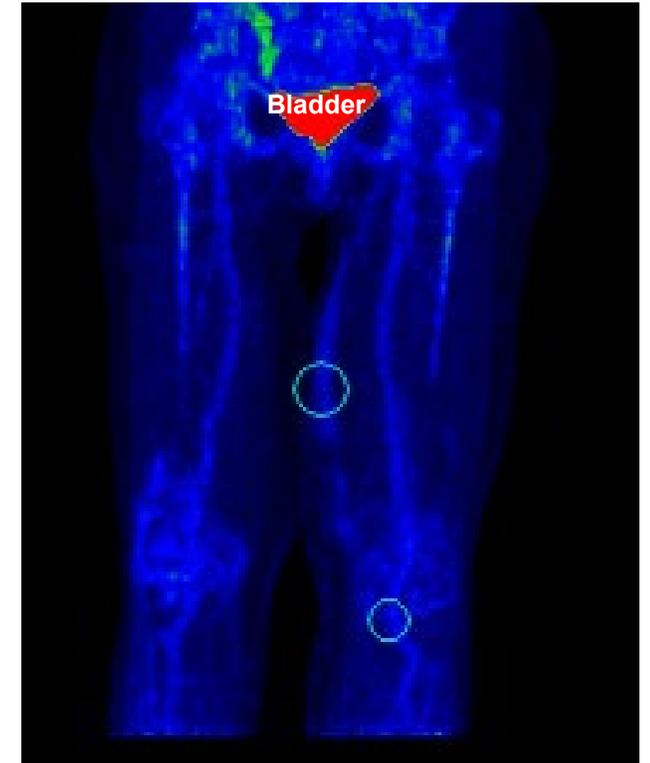
Baseline



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.

Targeted Protein Degradation Holds Promise For Treating Cancer

Ligase Complex

Target



Increased target coverage

- Catalytic, event-driven pharmacology
- One degrader can degrade many target protein molecules

Durable target depletion

- Protein resynthesis (rather than drug clearance) is required to restore target function
- Degraders can demonstrate extended pharmacodynamic effects

Resilient to acquired mutations

- Nurix's BTK degraders have demonstrated potency against clinically relevant BTK inhibitor resistance mutations, both known and novel
- Degradation benefits from cooperativity associated with ligase-target binding

Addresses Scaffolding Function

- Unlike an inhibitor, a degrader can address both the enzymatic and non-enzymatic scaffolding functions of a protein

Thank you!

