nurix

Leader in Targeted Protein Modulation

Overcoming Acquired Inhibitor Resistance & Addressing Novel Scaffolding Functions of BTK in the Clinic

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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)

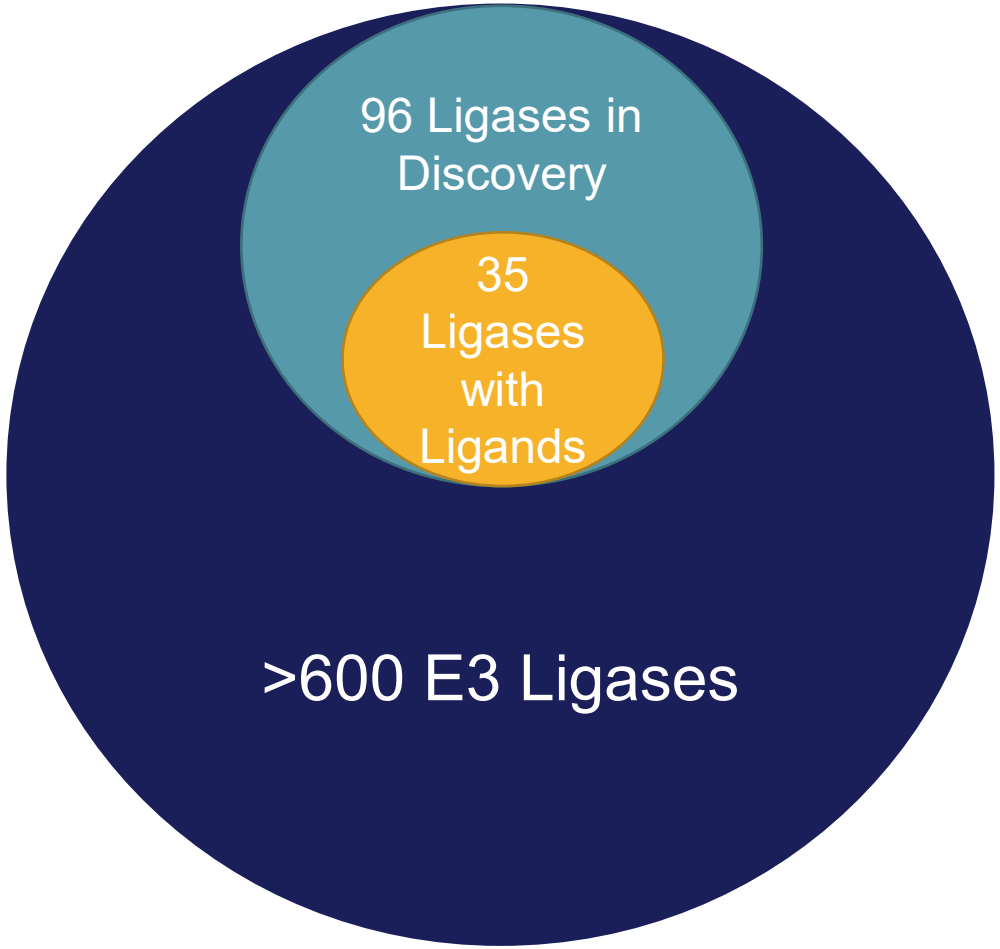
Inhibit ligases to increase specific protein levels

Harness ligases to decrease specific protein levels

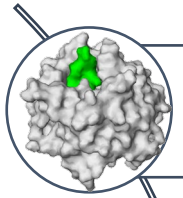
Targeted Protein Degradation (TPD)

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

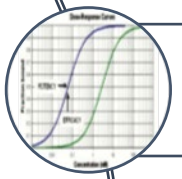
Ligase Discovery May Unlock Unique TPM Opportunities



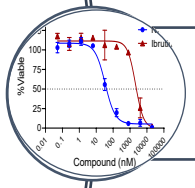
Nurix's Ligand-First Approach Using DEL



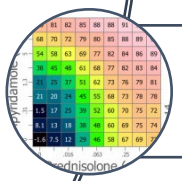
Unlock novel targets and pathways



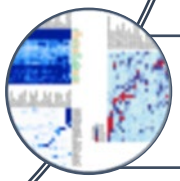
Improve target coverage and selectivity



Overcome inhibitor resistance



Neosubstrate synergy with target biology

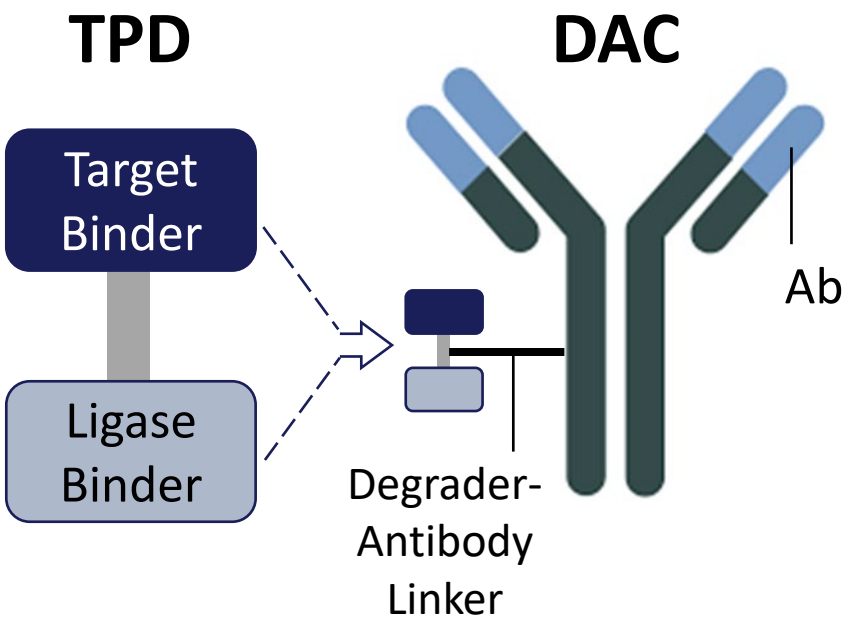


Enhance selectivity through ligase specificity

A New Therapeutic Class:
Degrader-Antibody Conjugates (DACs)

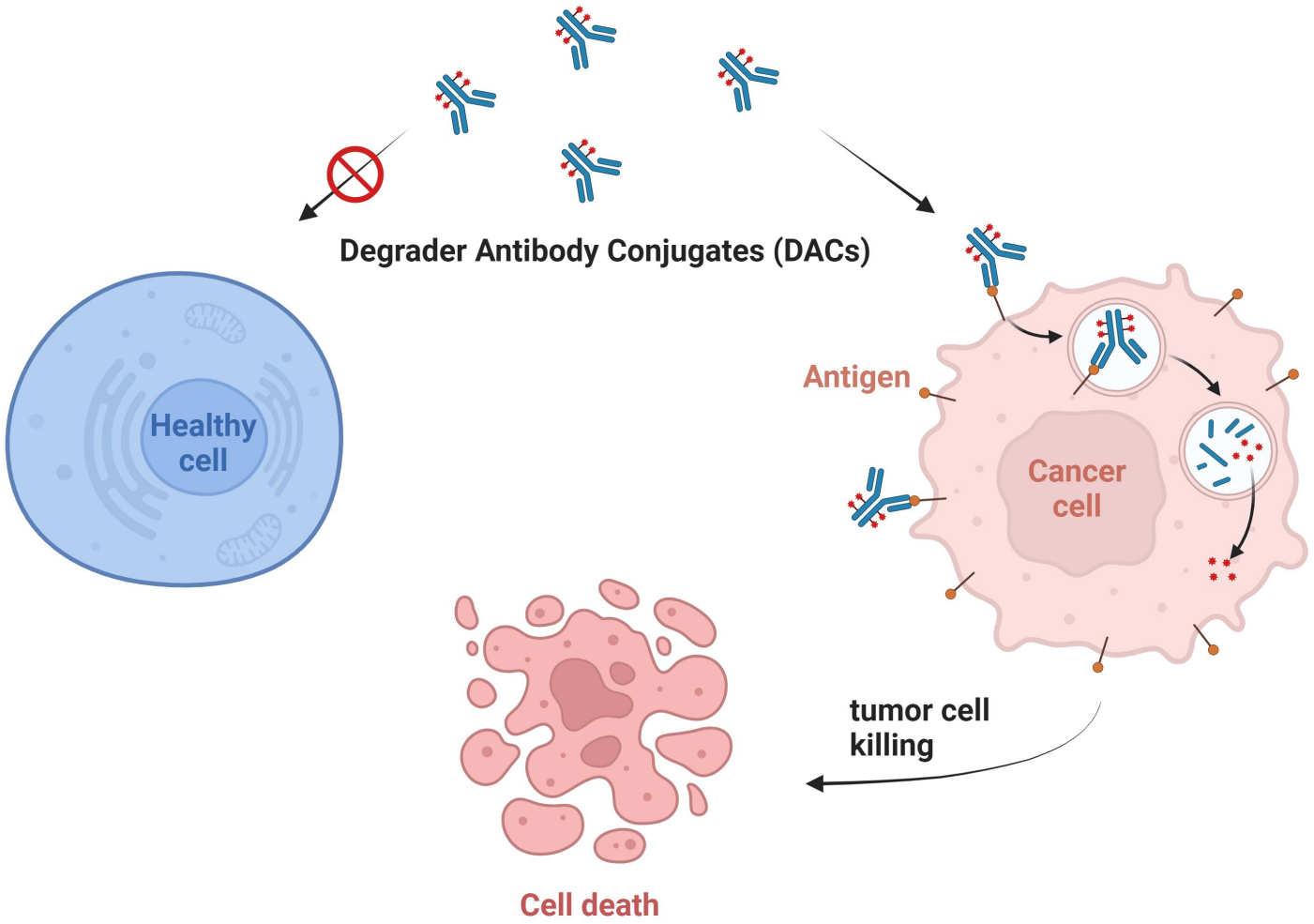
Achieving Tissue-Selective Degradation Using Antibodies

- DACs combine the catalytic activity of a Targeted Protein Degrader (TPD) with the specificity of an antibody
- DACs represent a next generation of antibody-drug conjugates (ADCs) technology with the potential for enhanced efficacy and improved safety
- DACs allow a broader exploration of degrader chemical space



DACs: Cell and Tissue-Specific Delivery of Potent Protein Degraders

The next generation of ADCs



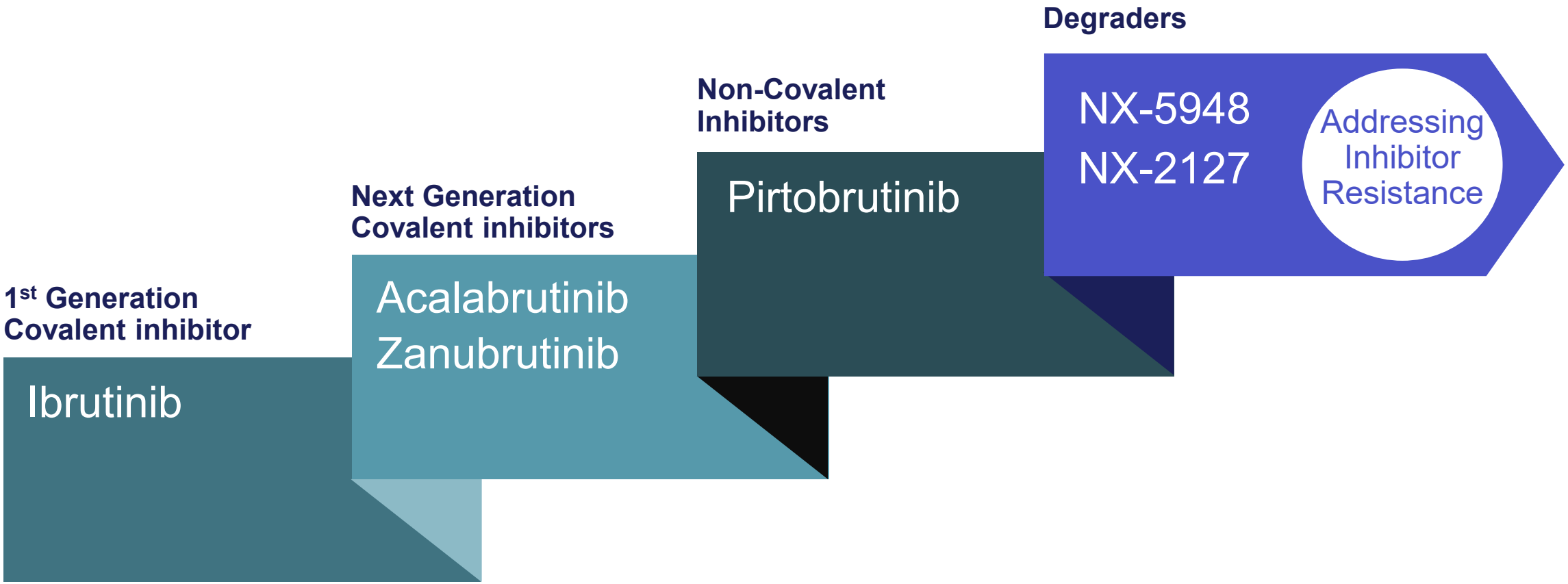
- Degraders replace highly toxic ADC payloads
- DACs allow for selective delivery of degraders to target cells and tissues; example: cancer cells
- Degraders eliminate driver proteins essential for cancer cell growth and survival

Note: Four degraders shown per antibody is illustrative; actual number may vary.

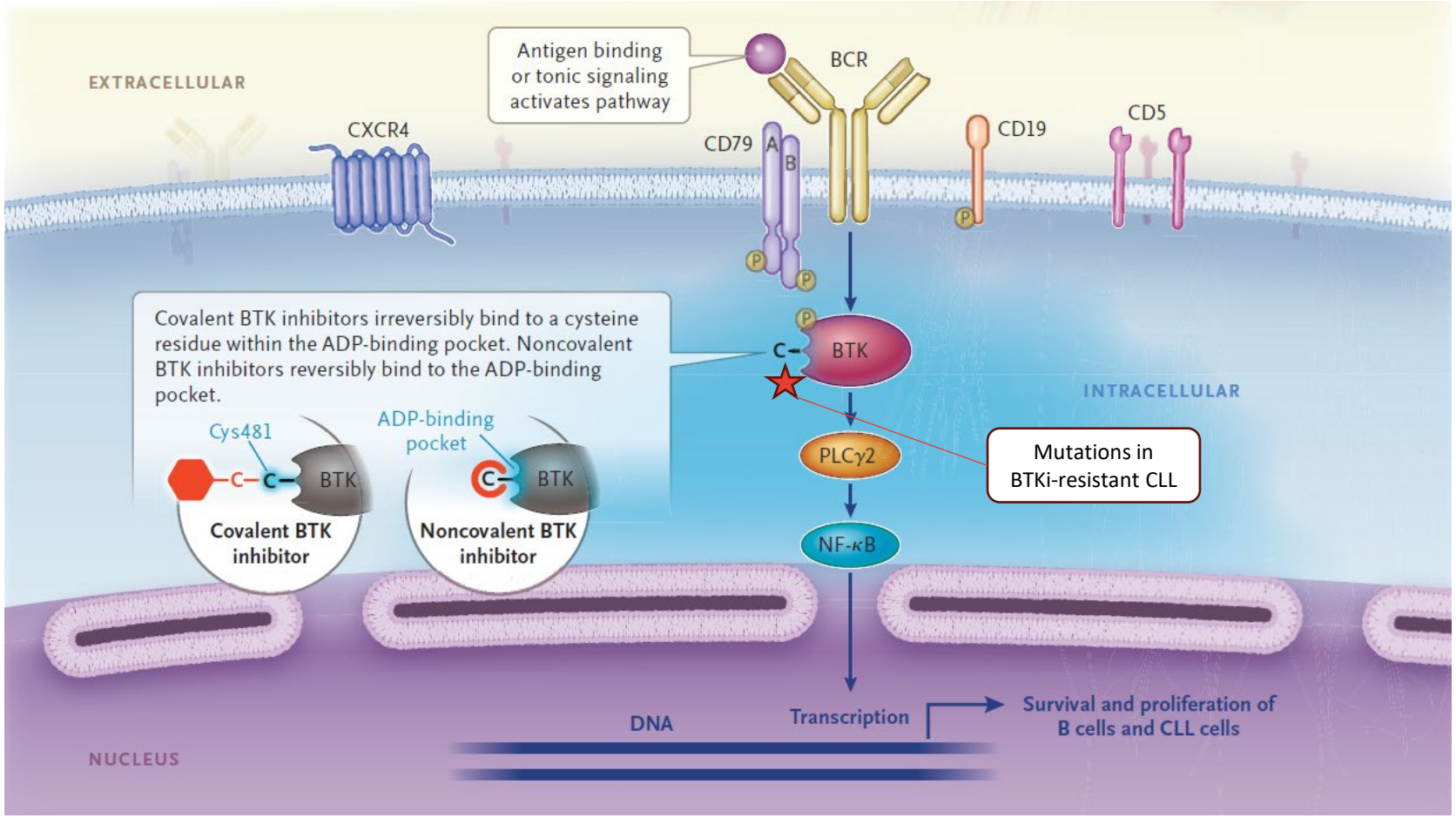
Nurix Is Advancing a Pipeline of Propriety and Partnered Programs in Oncology and Autoimmune/Inflammatory Diseases

MOA	Drug program	Target	Therapeutic area	Discovery	IND enabling	Phase 1a	Phase 1b
TPD	NX-2127	BTK-IKZF	B-cell malignancies				
	NX-5948	BTK	B-cell malignancies				
	NX-0479 / GS-6791	IRAK4	Rheumatoid arthritis and other inflammatory diseases				GILEAD
	Multiple	Undisclosed	Oncology / autoimmune disease				
	Multiple	Undisclosed	Undisclosed				GILEAD
	Multiple	Undisclosed	Undisclosed				sanofi
TPE	NX-1607	CBL-B	Immuno-Oncology				
DAC	Multiple	Undisclosed	Oncology				Seagen

Evolution of BTK Targeted Therapies



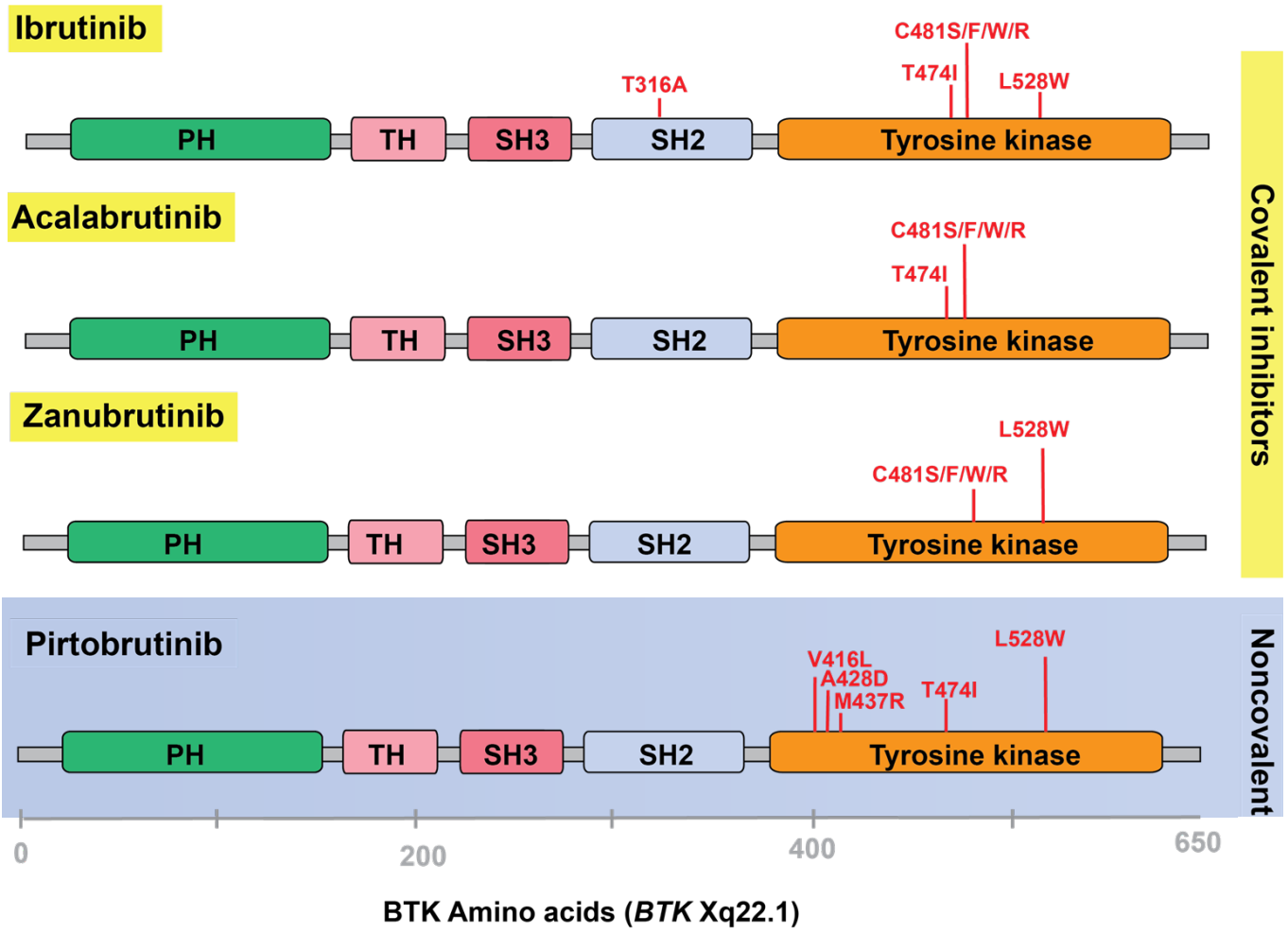
B-cell Malignancies Respond to BTK inhibitors, But Patients Eventually Progress as a Consequence of Inhibitor Resistance



Modified from Kater et al., NEJM 2023 and Nakhoda et al., Br. J. Haematol. 2023

- BTK is a nonreceptor tyrosine kinase and plays a crucial role in the B-cell receptor (BCR) signaling pathway
- Inhibition of BTK enzymatic activity has been established as an effective therapeutic strategy
- All patients eventually progress, and majority carry mutations in *BTK*C481 when treated with ibrutinib; ~53-87% of patients. Rates are similar for acalabrutinib; 69% of patients

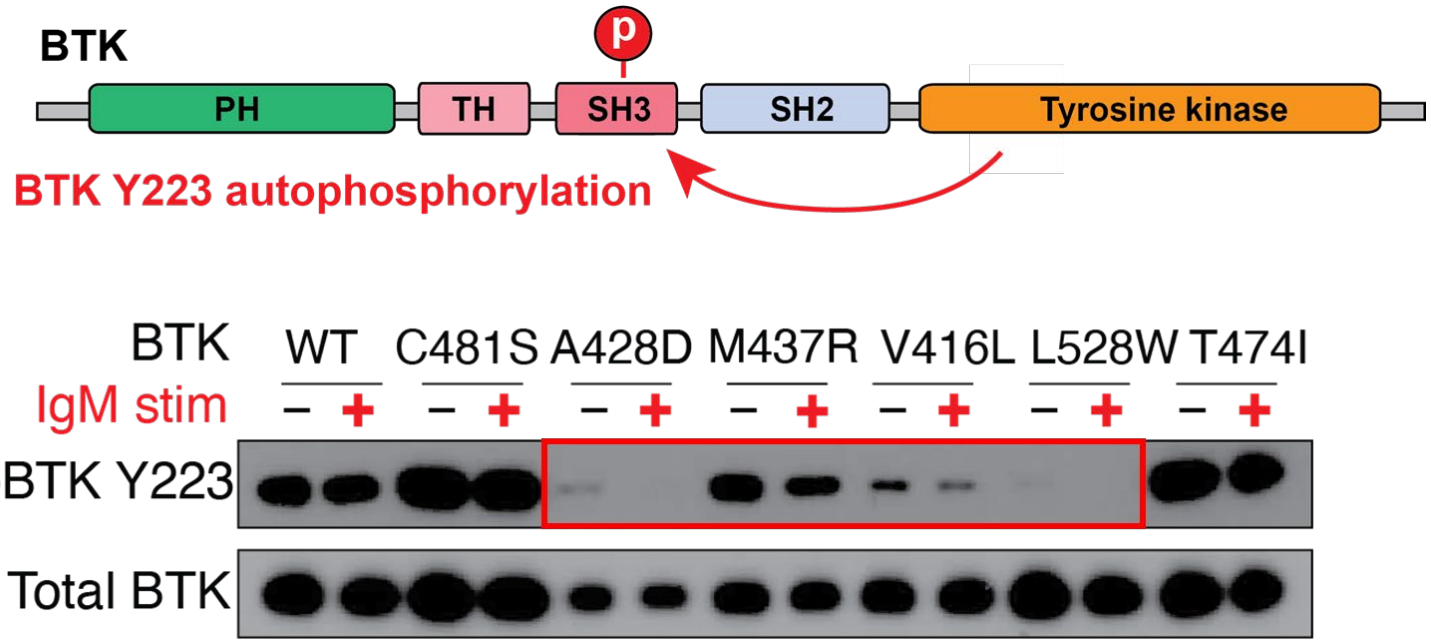
Treatment-Emergent Resistance to BTK Inhibitors Is Evolving:
Noncovalent BTK Inhibitor Resistance Shows Broader Mutation Profile



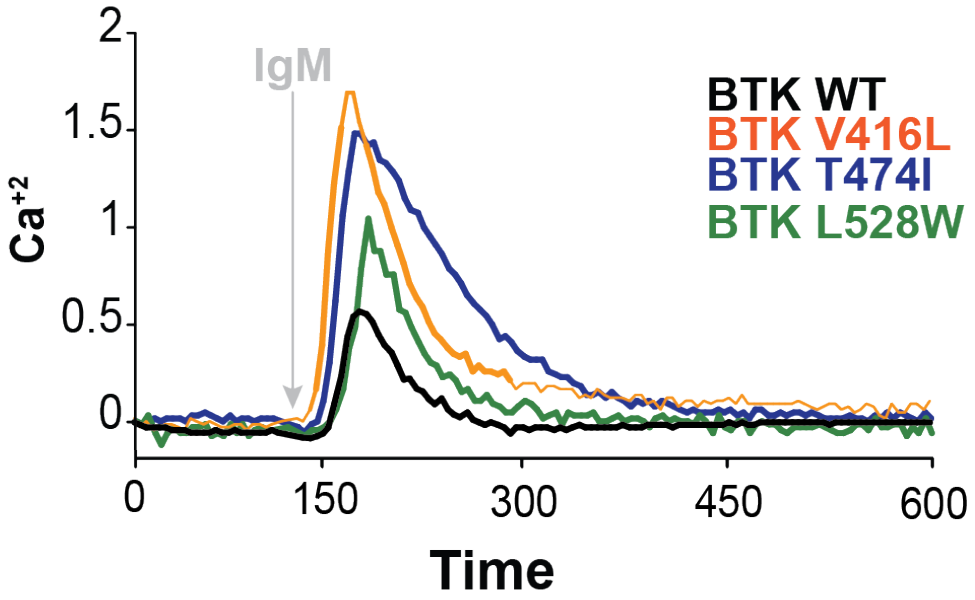
Wang, Mi, Thompson, et al. NEJM 2022

Inhibitor-Induced BTK Mutations Abrogate Phosphorylation Yet Propagate Downstream BCR Signaling: *Mutant BTK is 'Undruggable'*

BTK Y223 Phosphorylation in TMD8 Cells



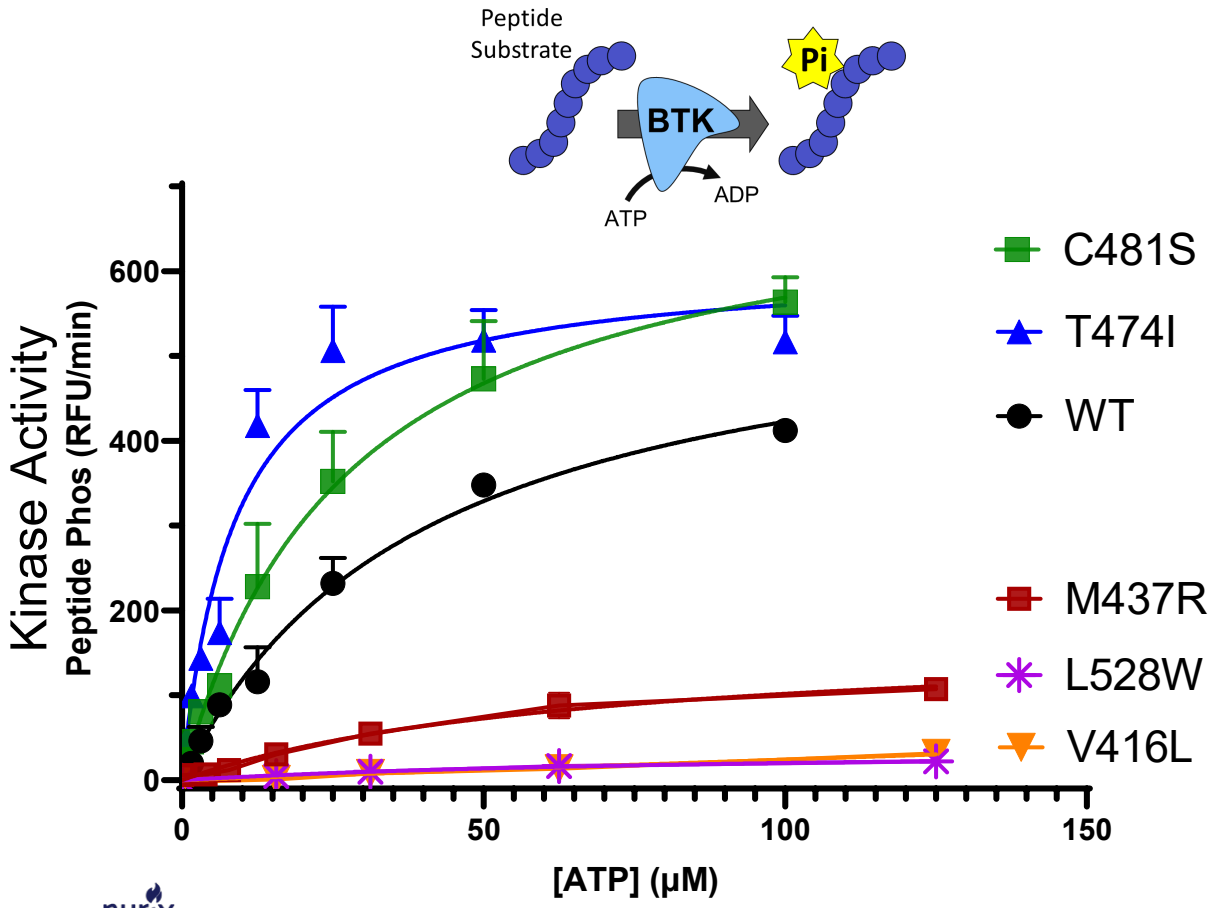
Calcium Ion Flux in TMD8 Cells



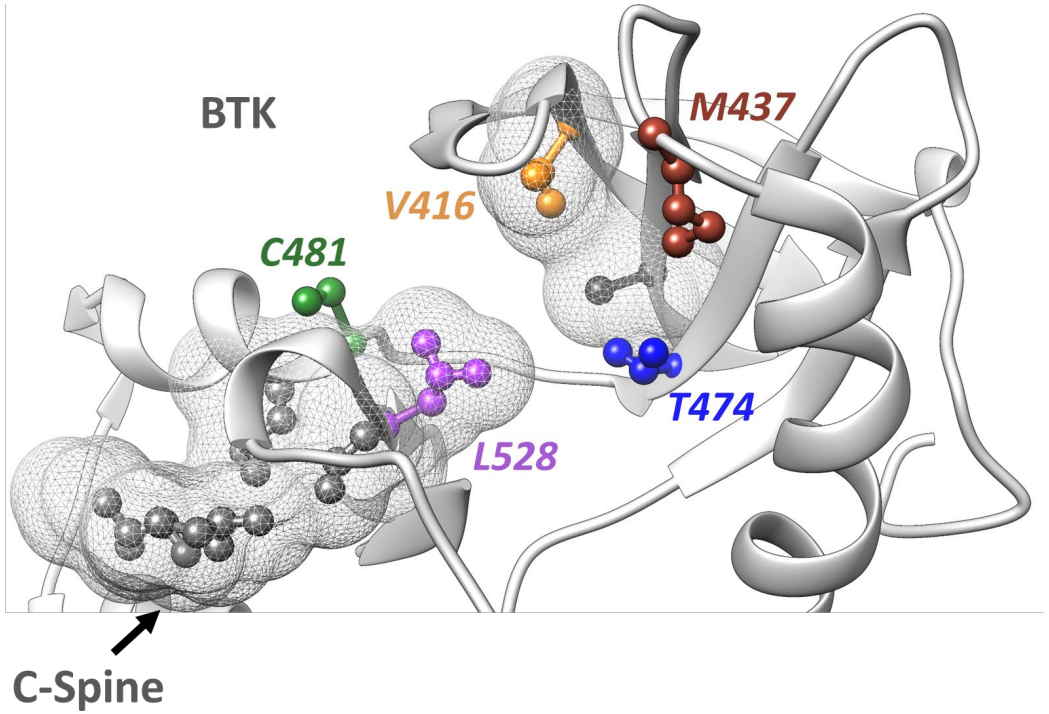
Montoya et al., ASH 2022

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

BTKi-resistant mutations V416L and L528W lack kinase activity

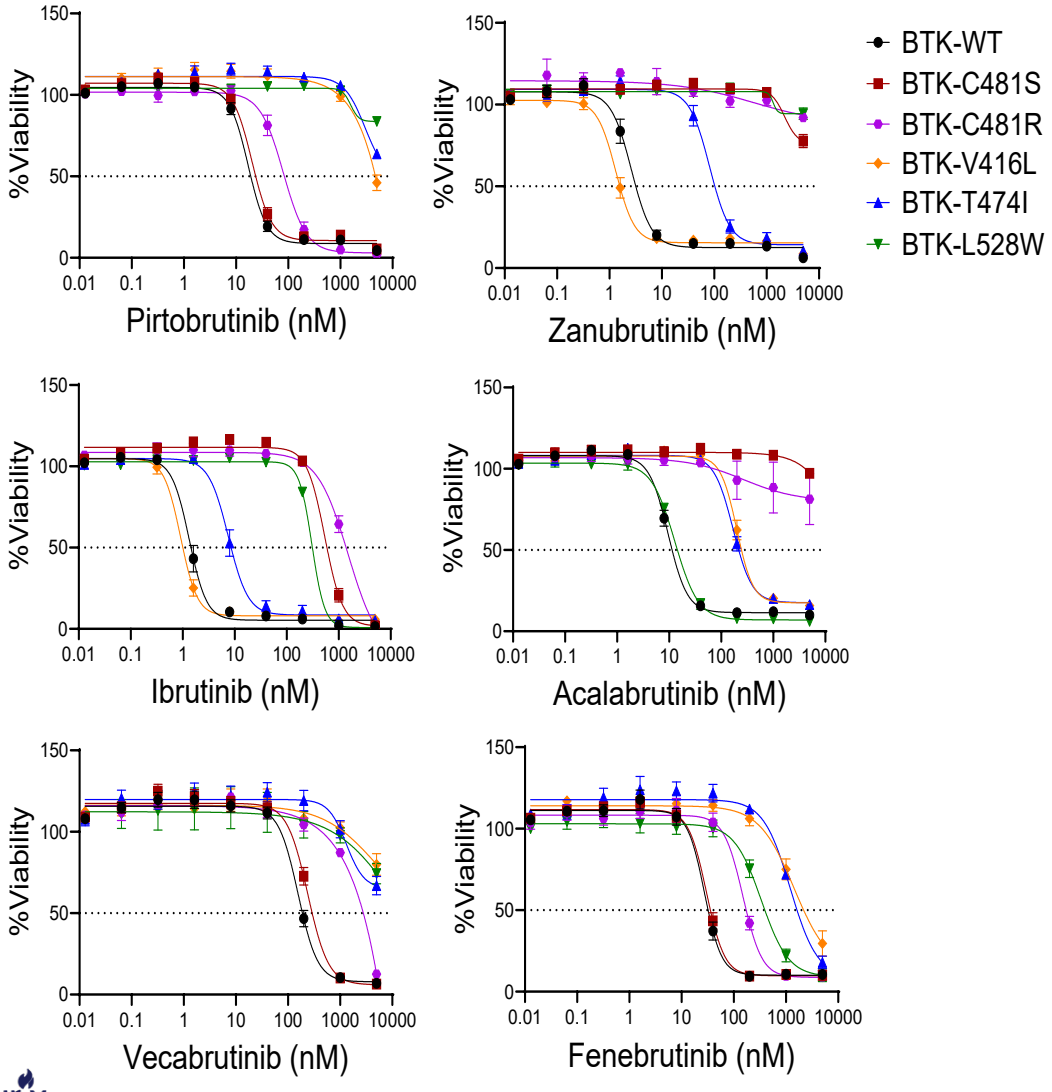


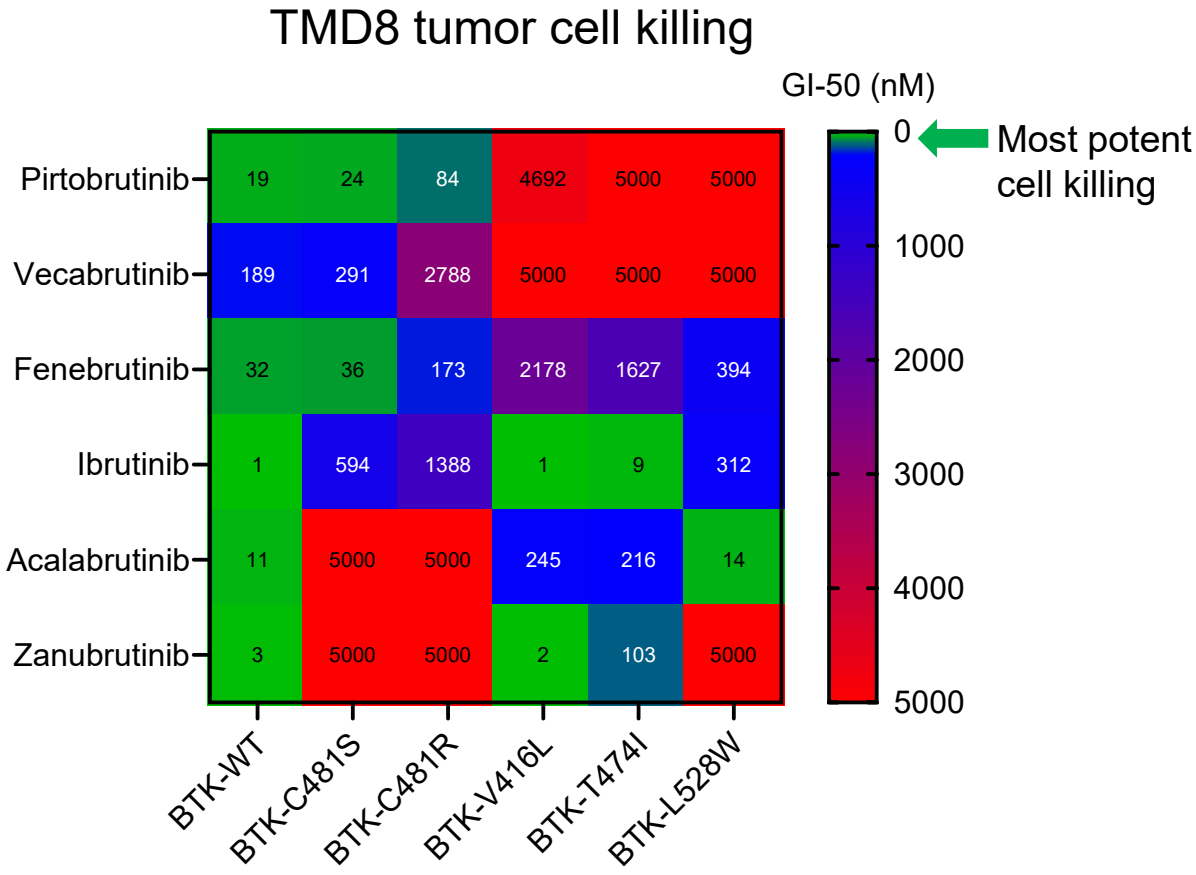
Mutations revealed by non-covalent inhibitors interrupt the catalytic C-spine of the kinase domain



Montoya et al., ASH 2022 and unpublished data

BTK inhibitors Rendered Ineffective by Spectrum of Resistance Mutations





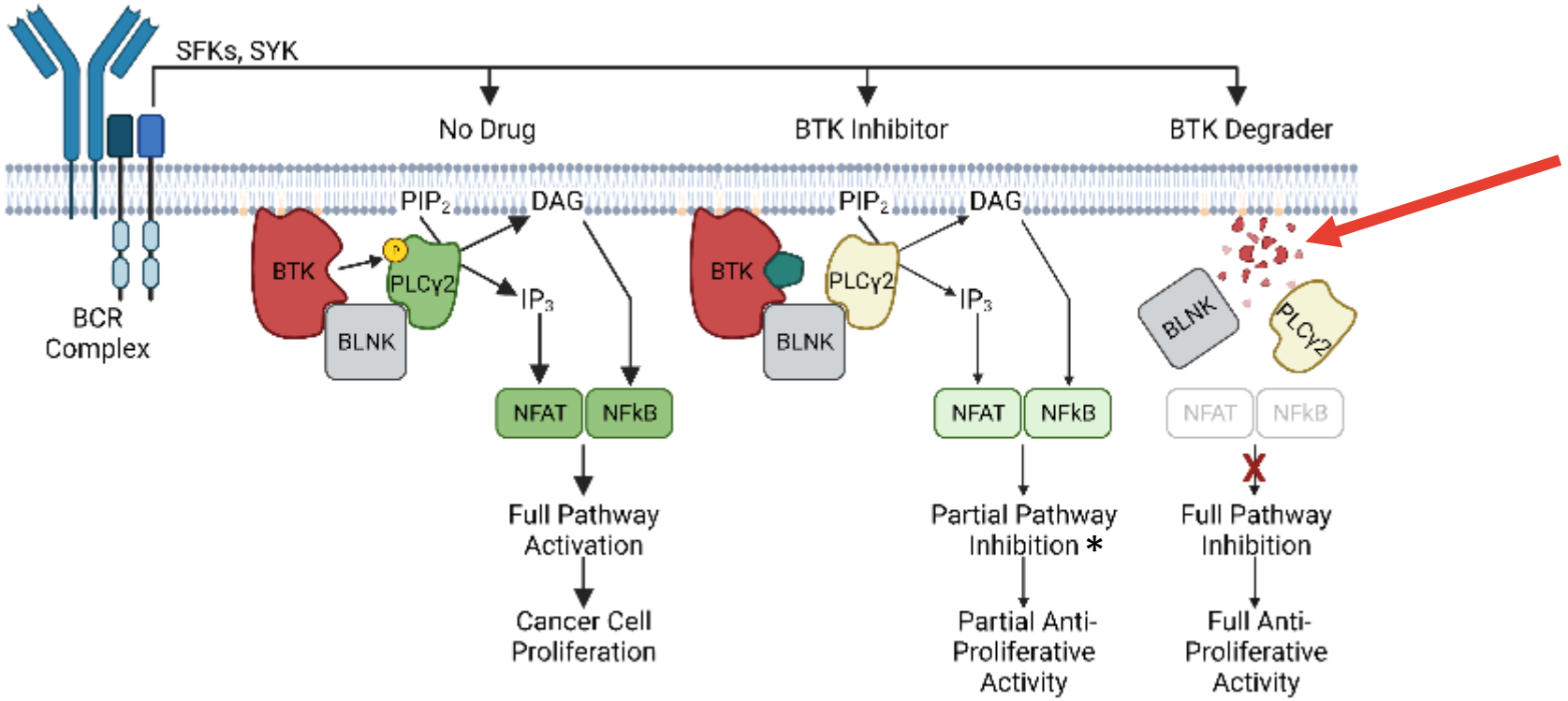
Assays were performed using TMD8 cells harboring WT BTK or knock-in BTK mutations (C481S, C481R, V416L, T474I, or L528W)
Cell viability was assessed at 72 hrs using CellTiter-Glo 2.0 (Promega).
Curves and GI_{50} values are averaged from n $\geq$ 3 independent experiments.

BTK Degraders Offer an Approach to Better Control BCR Signaling

Scaffolding Function of BTK was Previously Unrecognized as a Signaling Driver

Degraders Have the Potential to Eliminate Both the Enzymatic and Scaffolding Function of BTK

Degraders May be More Effective for Treating BCR-signaling Driven Disease



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

*Li et al., 2023 Mol Cancer Ther. (RAC2 bypass)

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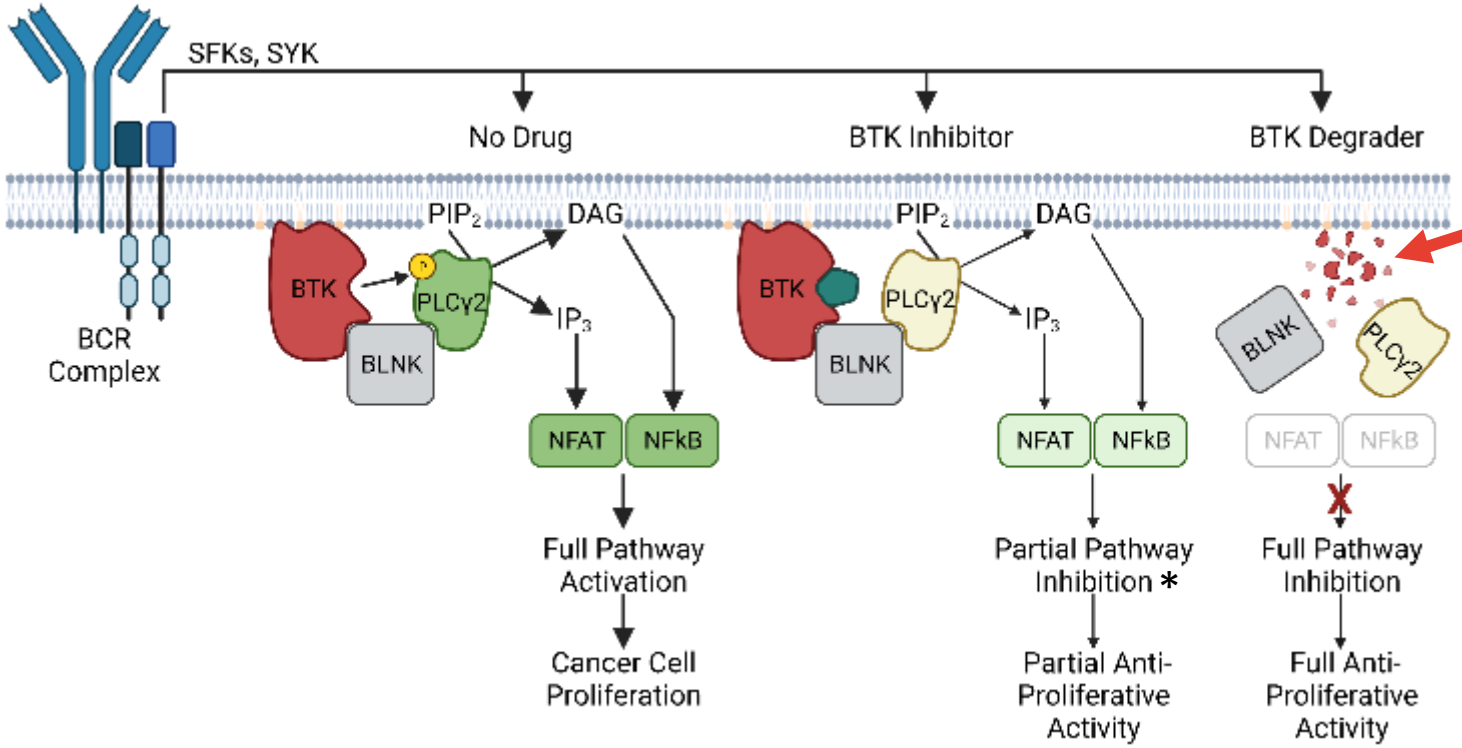
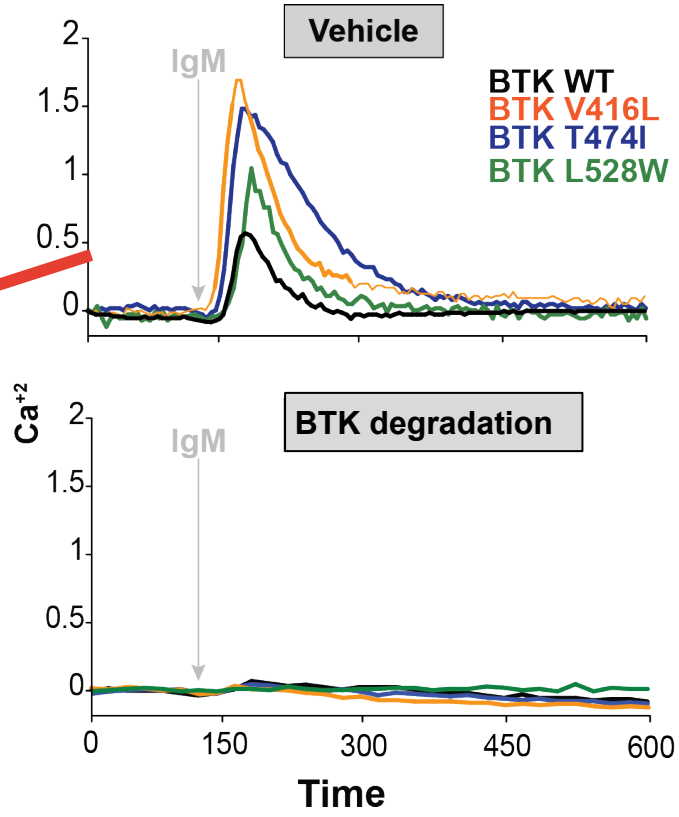
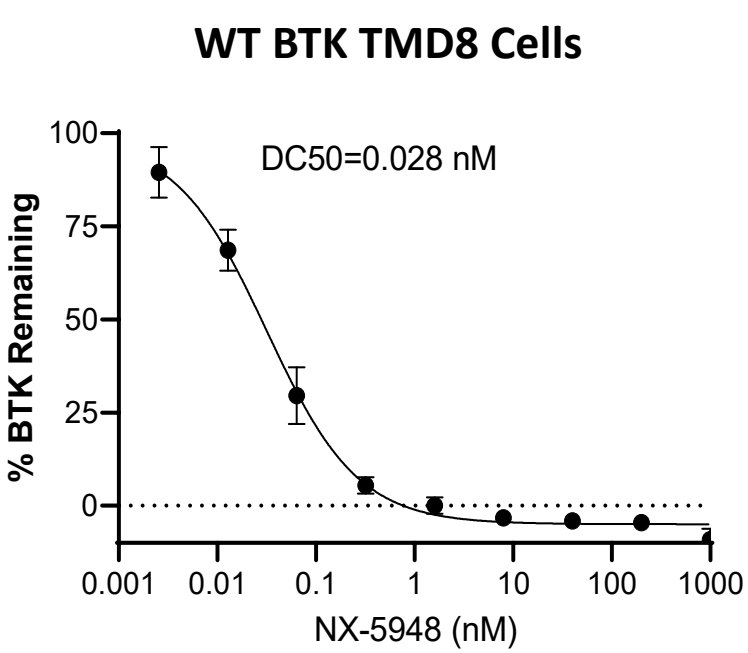


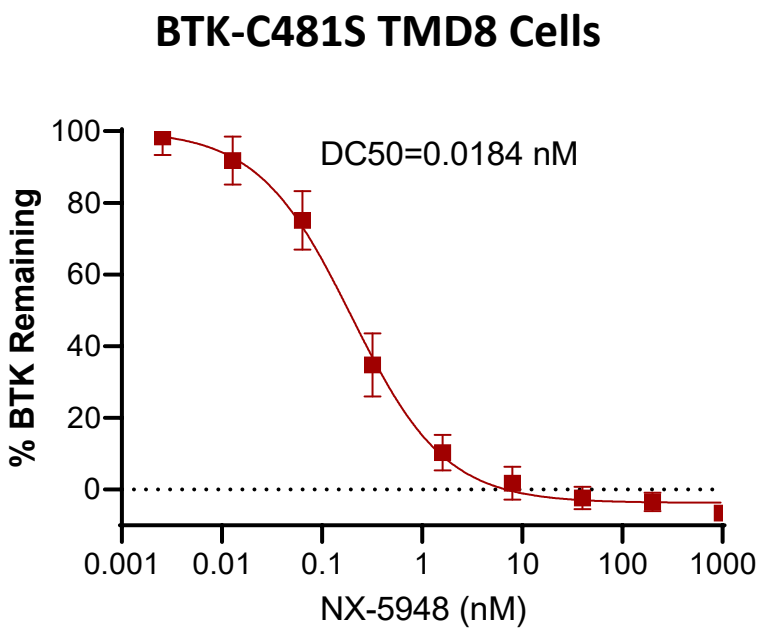


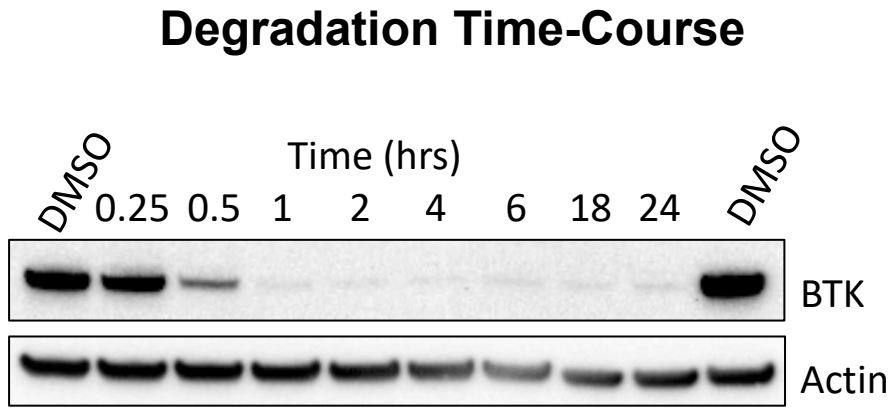
*Li et al., 2023 Mol Cancer Ther. (RAC2 bypass)

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

- NX-5948 degrades WT and mutant forms of BTK with sub-nanomolar potency in ABC DLBCL TMD8 cells
- BTK degradation is observed within 1 hour and is complete within 2 hours in Ramos cells



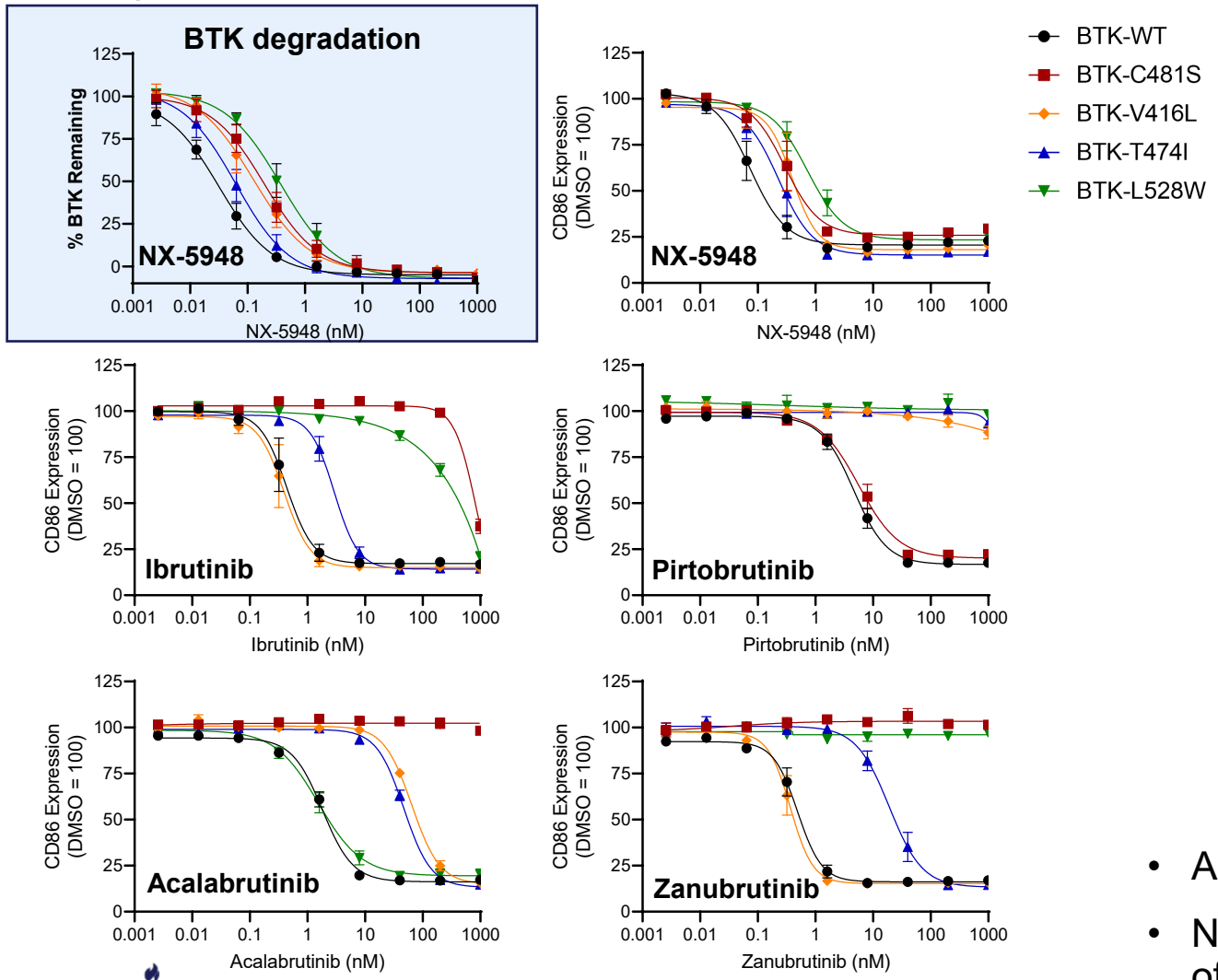




TMD8 cells harboring WT BTK or a knock-in BTK mutation (C481S) were incubated with NX-5948 for 24 hours, and BTK degradation was assessed by flow cytometry. Ramos human Burkitt's lymphoma B cells incubated with 10 nM NX-5948 and assessed by western blot

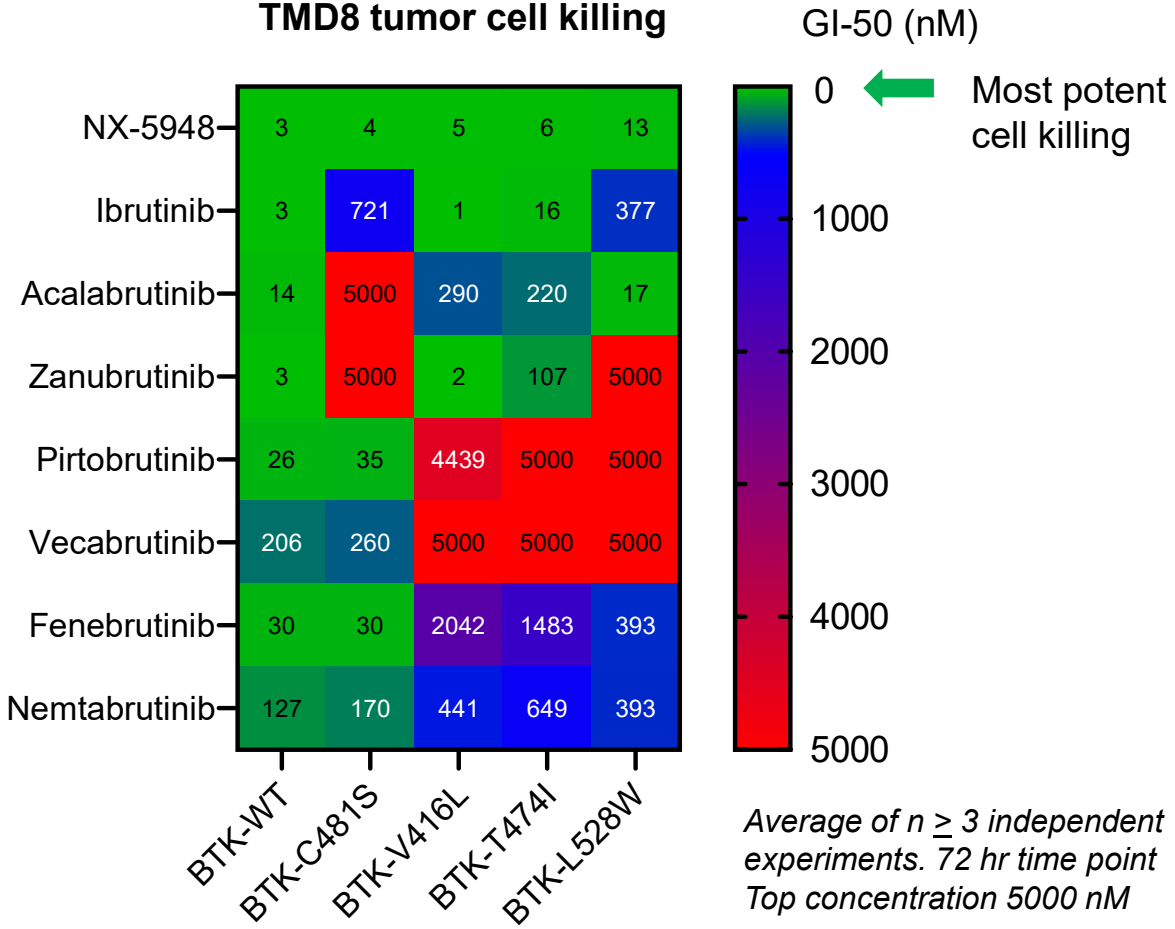
NX-5948 Is More Potent and Broadly Active Than All BTK Inhibitors Tested

BTK degradation and activation marker suppression in TMD8 tumor cells



Average of n = 3 independent experiments +/- SEM

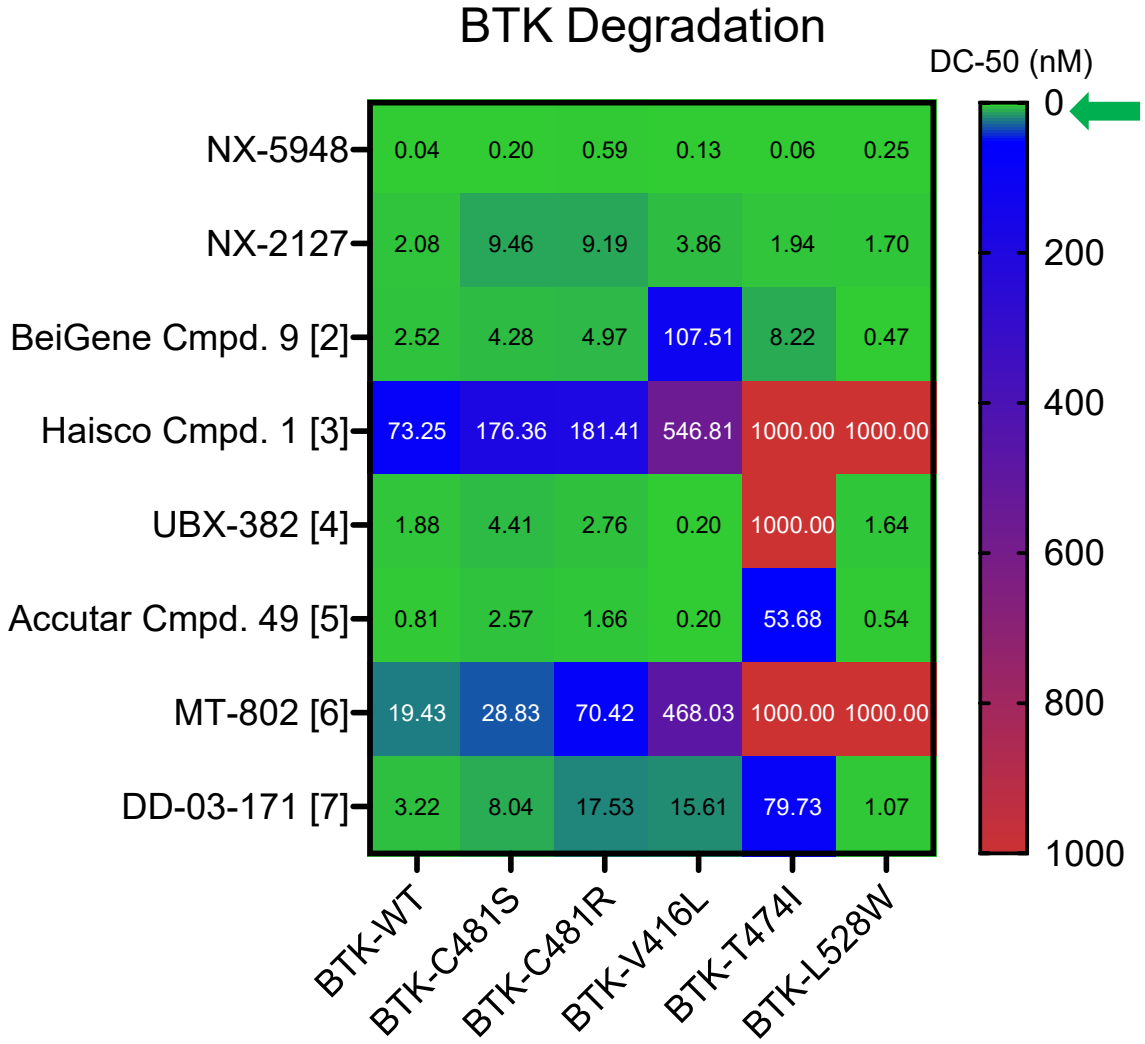
TMD8 tumor cell killing

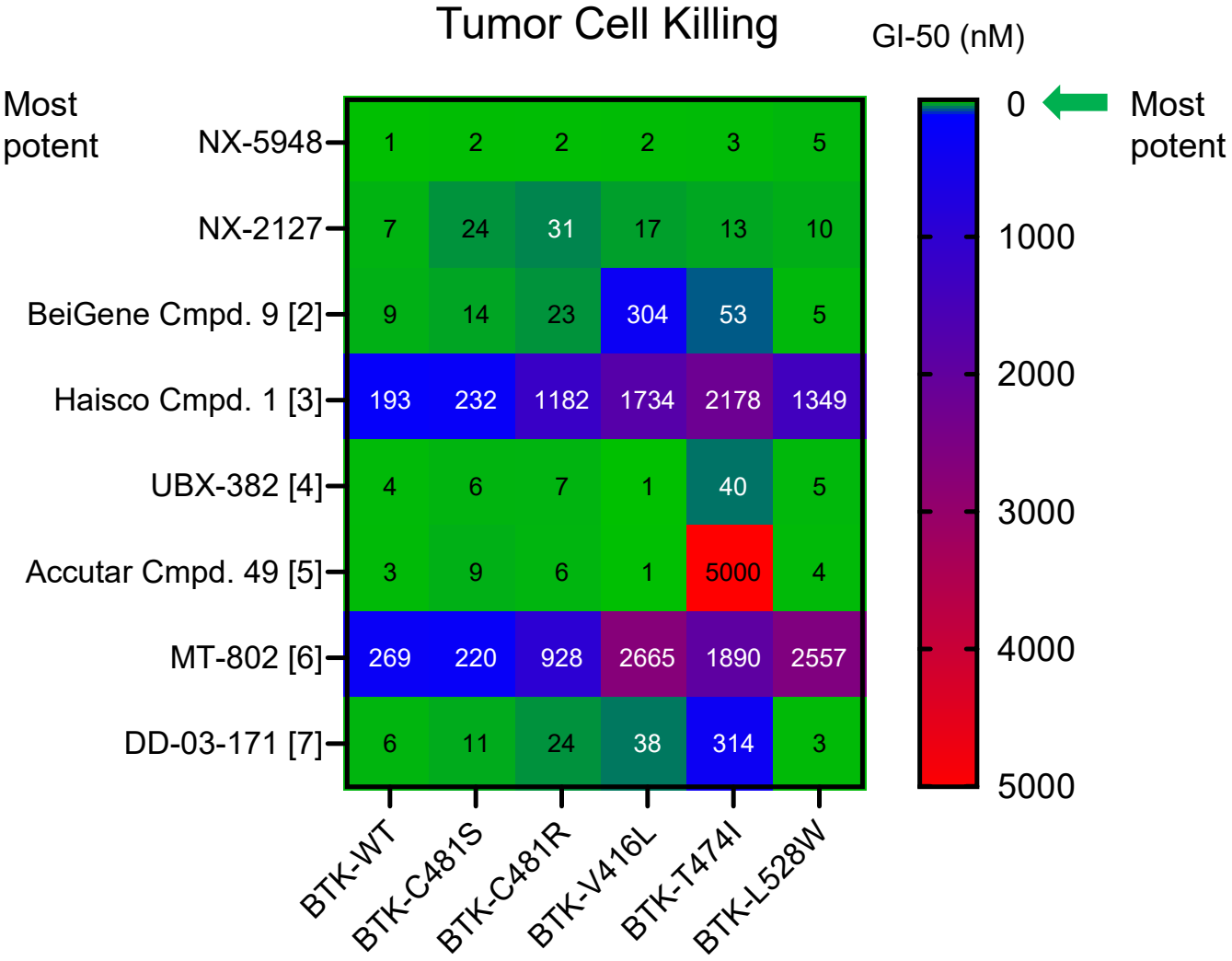


Average of n ≥ 3 independent experiments. 72 hr time point Top concentration 5000 nM

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

Not All BTK Degraders Are Created Equal



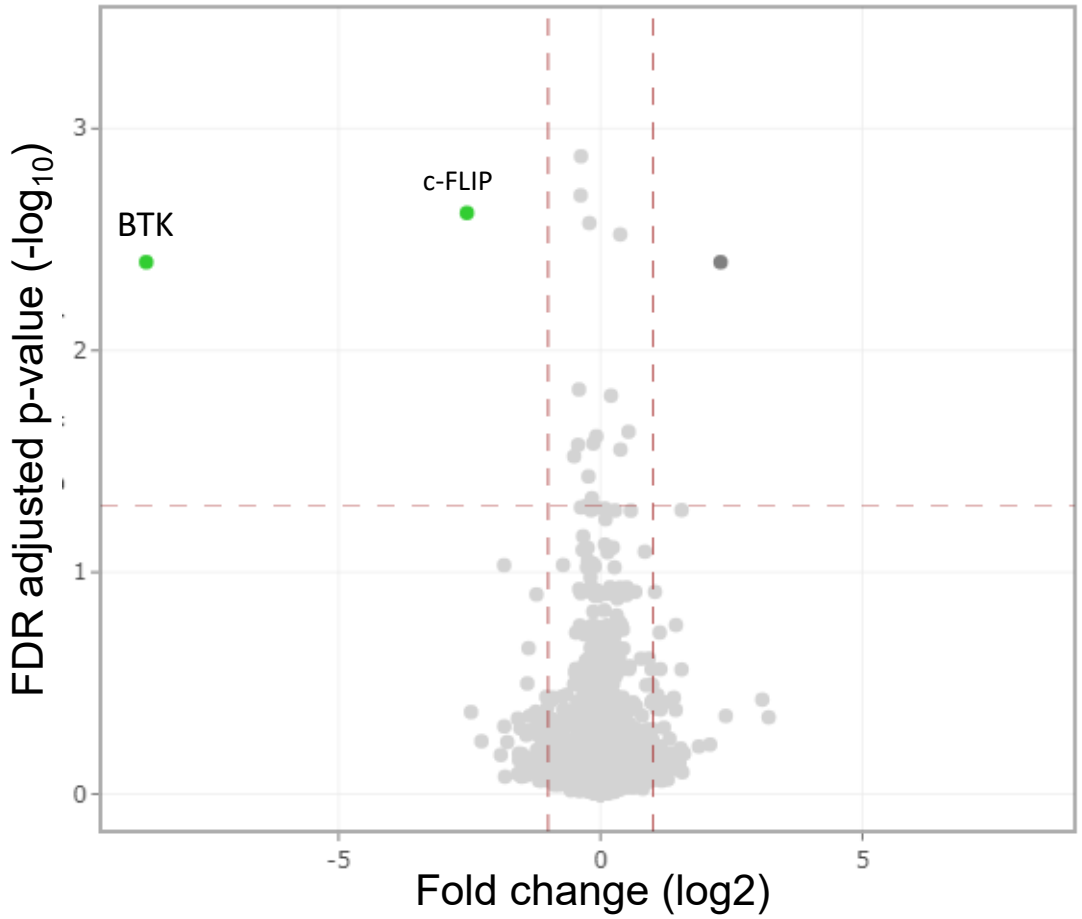


TMD8 cells with knock-in mutations
72 hr time point, 5000 nM top concentration
Average of n ≥ 4 independent experiments

[2] Example 9. WO 2021/219070 (BeiGene). [3] Example 1. WO 2022/111449 (Haisco).
[4] Lim et al. 2023. Blood Adv. 7(1): 92-105. [5] Example 49. WO 2022/169798 (Accutar)
[6] Buhimschi et al. 2018. Biochemistry 57(26): 3564-3575.[7] Dobrovolsky et al. 2019. Blood 133(9): 952-961.

Proteomics Study Demonstrates NX-5948 is Selective for BTK

Human TMD8 ABC DLBCL cells incubated for 6 h with 50 nM NX-5948

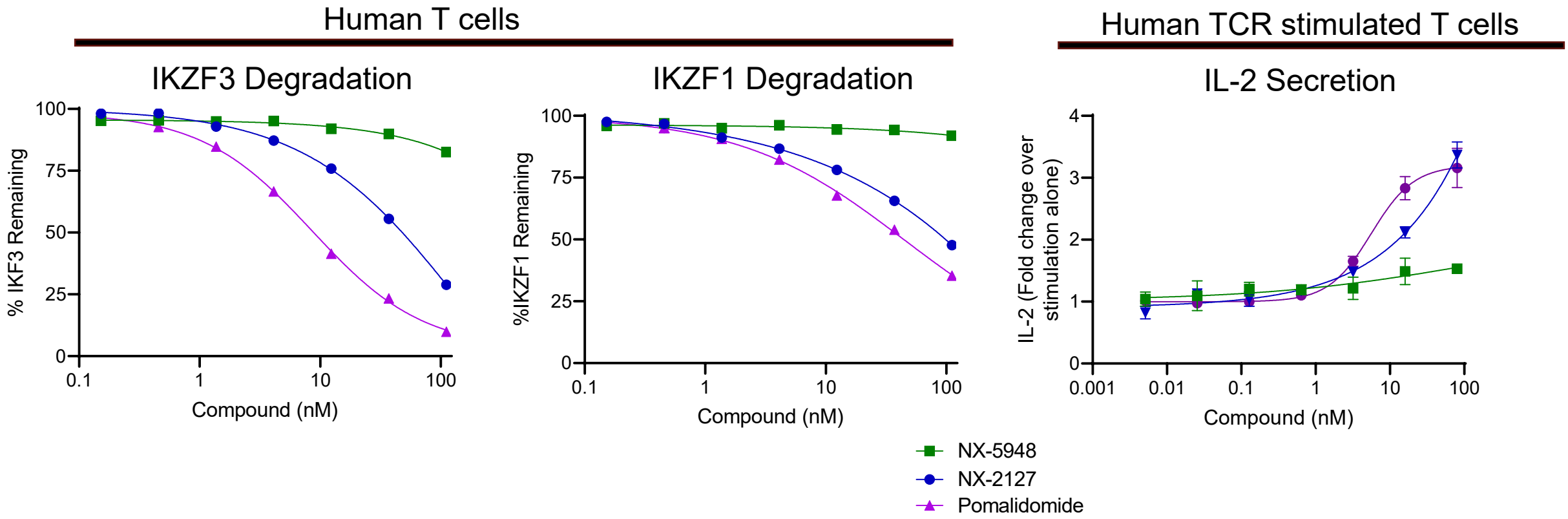


c-FLIP is an anti-apoptotic protein required to maintain survival of ABC DLBCL cells that is regulated by the BCR/NF-κB signaling axis

BTK inhibition by ibrutinib also downregulates c-FLIP in TMD8 cells (*Nurix data and Nagel; Onco Target; 2015*)

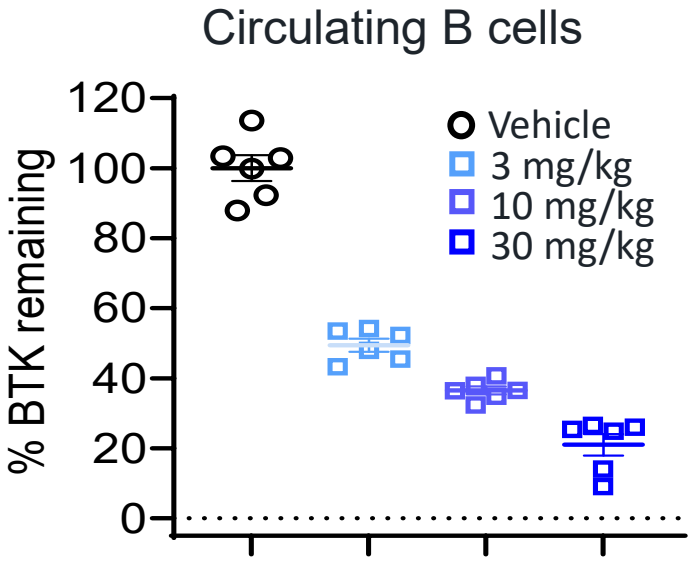
c-FLIP reduction is believed to be a secondary effect of BCR/BTK signaling loss

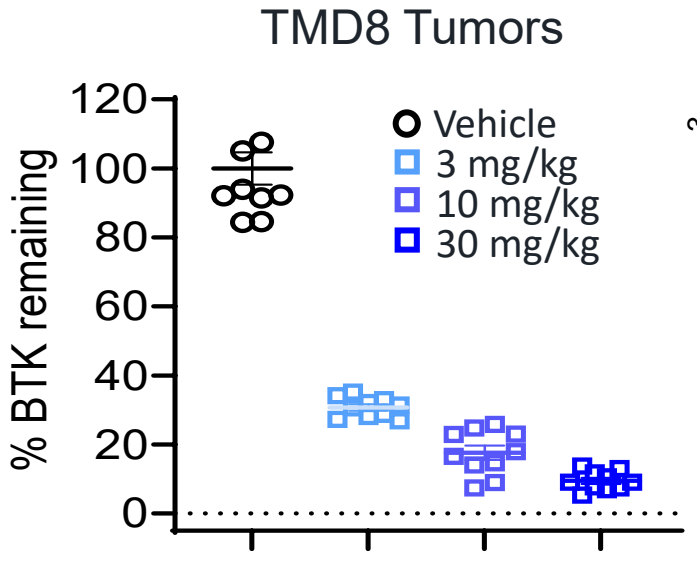
No Significant Degradation of IKZF1/3 with NX-5948 at Therapeutically Relevant Concentrations

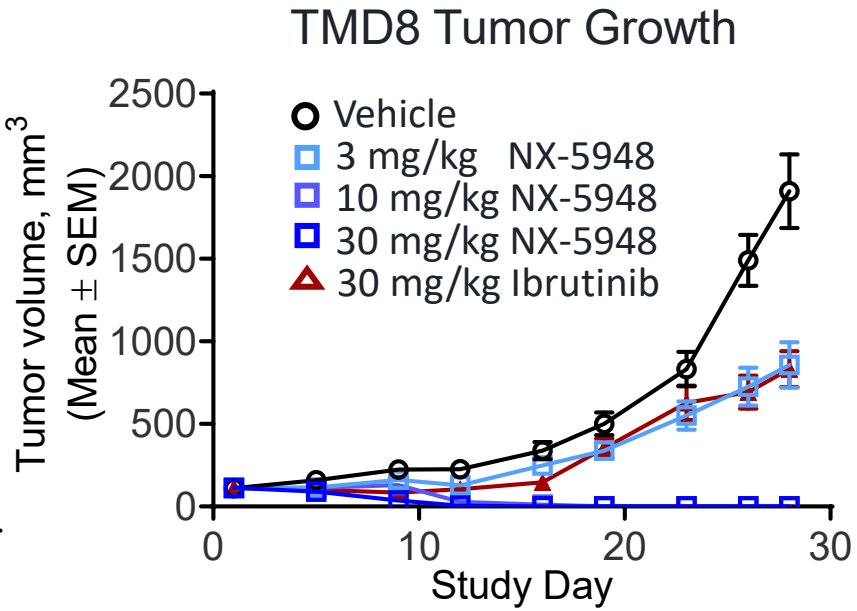


- IKZF1/3 degradation and IL-2 secretion were evaluated for both NX-2127 and NX-5948 using pomalidomide as a control
- NX-5948 showed no significant degradation of IKZF1/3 in primary human T cells and no modulation of IL-2 in TCR stimulated T cells

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

N/A: Not applicable; TGI: tumor growth inhibition.
P values determined on tumor volume by mixed-effect analysis with Dunnett's multiple comparisons test

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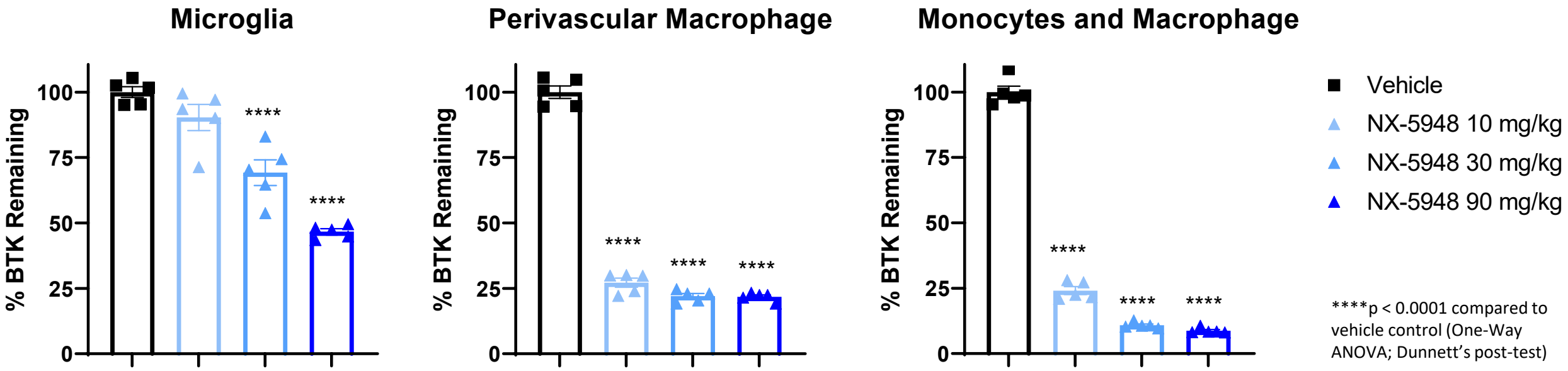
Rountree et al., TPD 2022

NX-5948 Degrades BTK in Brain Microglia of Naïve Mice

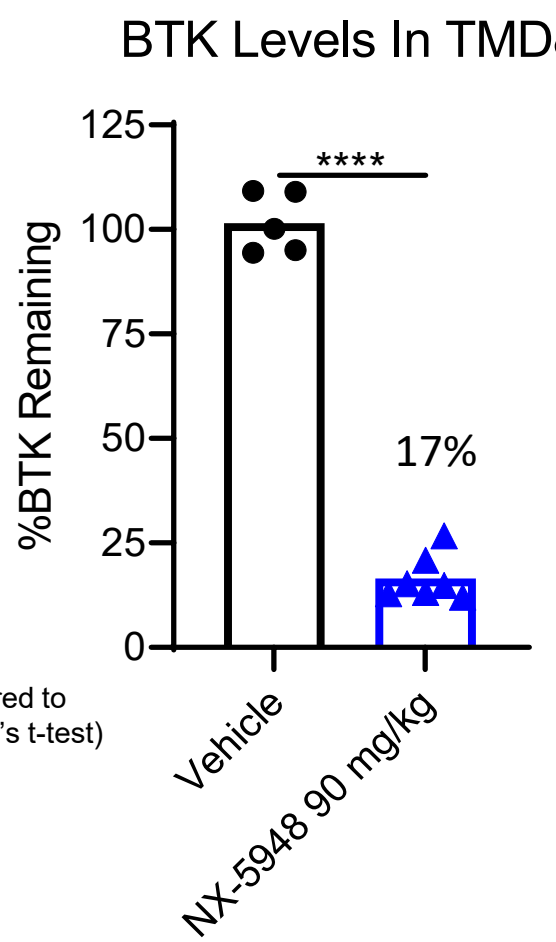
NX-5948 administered orally QD x 3 days to naïve C57BL/6J mice.
BTK levels assessed 8 h after 3rd dose by flow cytometry.



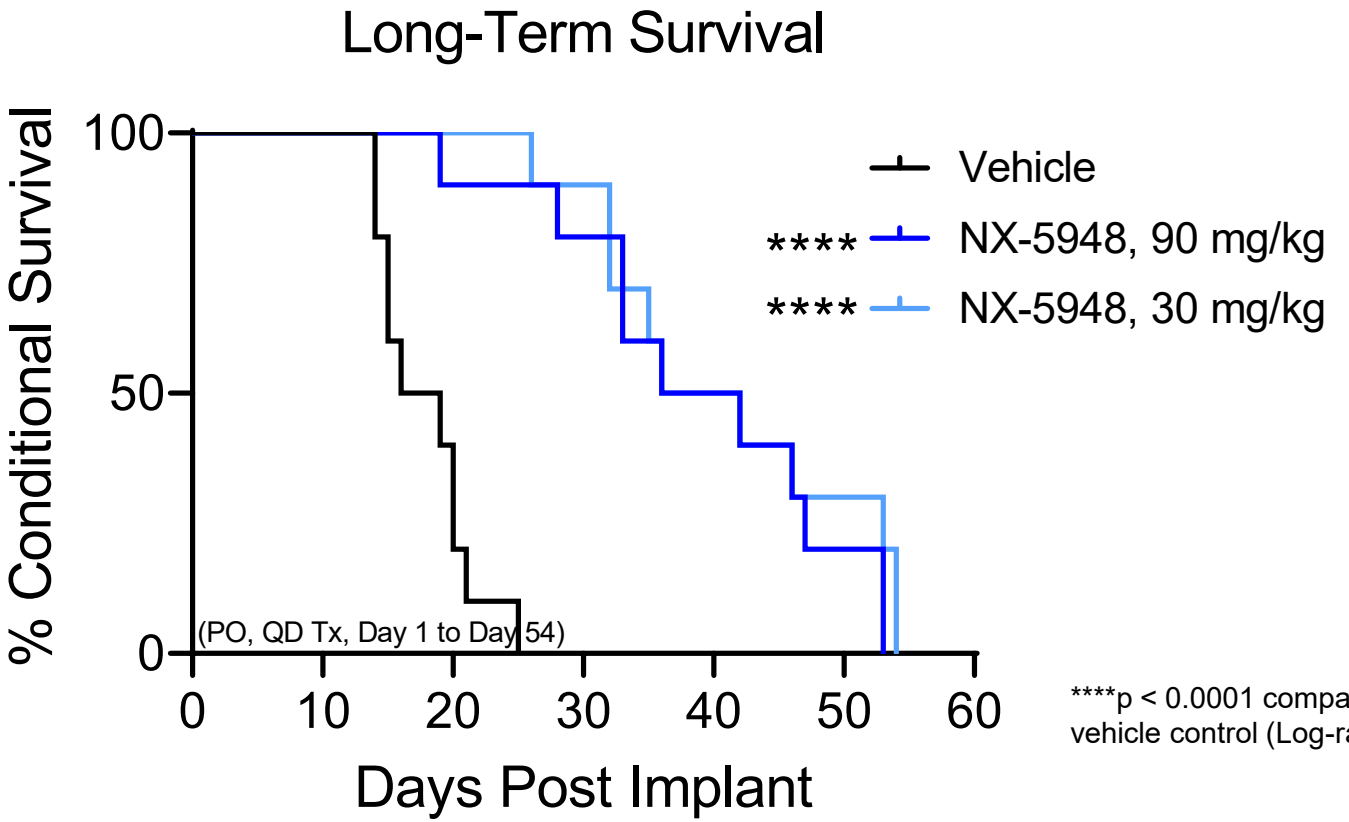
- NX-5948 drives dose-dependent BTK degradation in cells isolated from brains
- Magnitude of BTK degradation depends on dose and cell type

Oral Administration of NX-5948 Degrades BTK in Tumor Cells and Prolongs Survival in a Mouse Model of CNS Lymphoma

5 x 10^5 TMD8 cells implanted by intracranial injection on Day 0
NX-5948 administered orally QD Days 1-11 (left) or Days 1-54 (right)
BTK levels assessed 24 h after the 11^{th} dose by flow cytometry

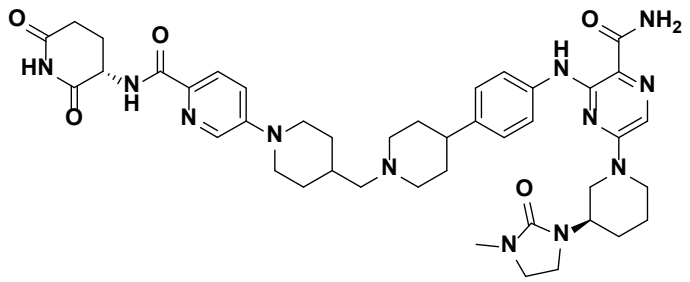


****p < 0.0001 compared to vehicle control (Welch's t-test)



****p < 0.0001 compared to vehicle control (Log-rank test)

NX-5948 Cellular Potency and Cross-species PK



	Degradation Results
BTK DC_{50} (Dmax): WT/C481S TMD8 cells @4h	0.32 nM (97%) / 0.21 nM (97%)
BTK DC_{50} Primary human B Cells	0.034 nM (98%)

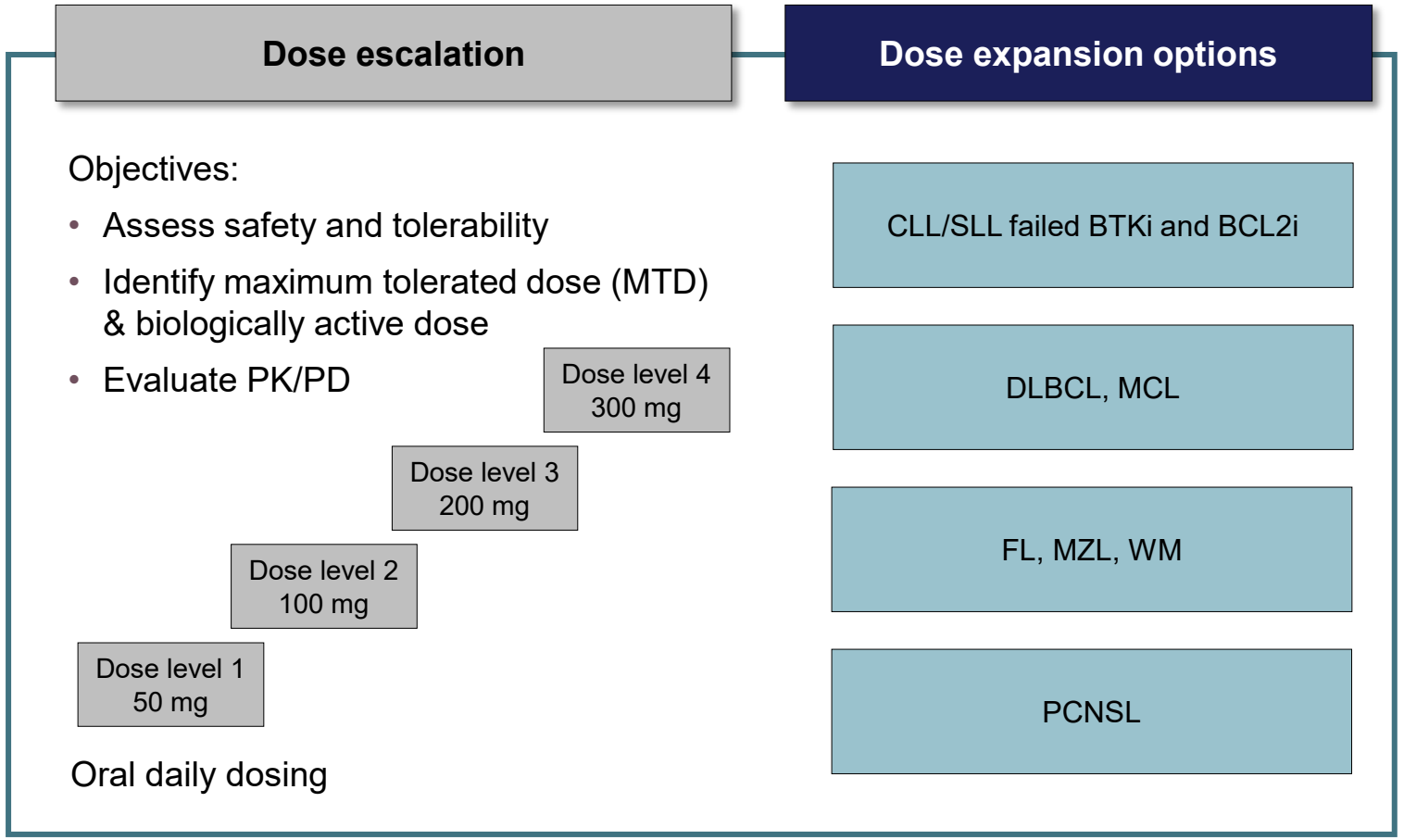
	Mouse	Rat	Dog	Cynomolgus Monkey
Cl_{obs} (mL/min/kg), 1 mpk IV bolus	6	31	68	39
AUC (hr*μM), 10 mpk PO	4.6	1.3	0.3*	0.18
C_{max} (μM), 10 mpk PO	0.891	0.098	0.014*	0.014
$V_{ss,obs}$ (L/kg), 1 mpk IV	1.18	8.0	44.3	19.2
F (%)	7-25	16	9	2
In Vitro Plasma Protein Binding (%)	99.6	98.4	97.6	92 (97.1 humans)

* normalized from 5 mg/kg PO dose

- No issues with *in vitro* ADME, *in vitro* tox assays were clean
- DRF and 28-day in rats/NHP supported advancement to clinic

NX-5948-301: Trial Design

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

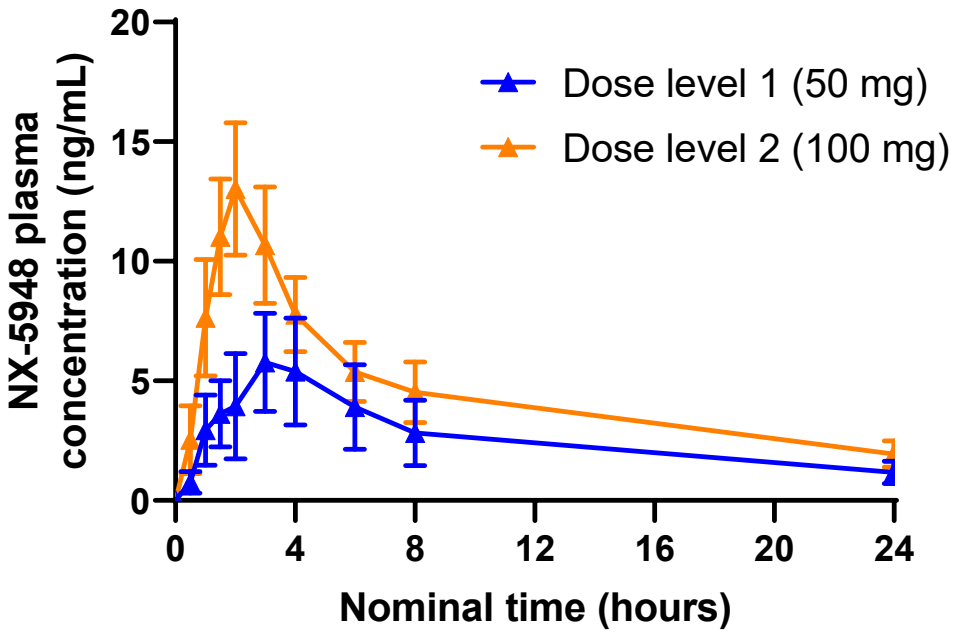


- Phase 1a dose escalation is ongoing at clinical sites in the U.S. and U.K.
- Anticipate initiating expansion cohort(s) in H2 2023

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

Preliminary Data Suggest that NX-5948 Exhibits Dose Proportional Pharmacokinetics

Mean (± SEM) Cycle 1 Day 1 pharmacokinetic profile of patients treated with NX-5948



Data cutoff: December 1, 2022

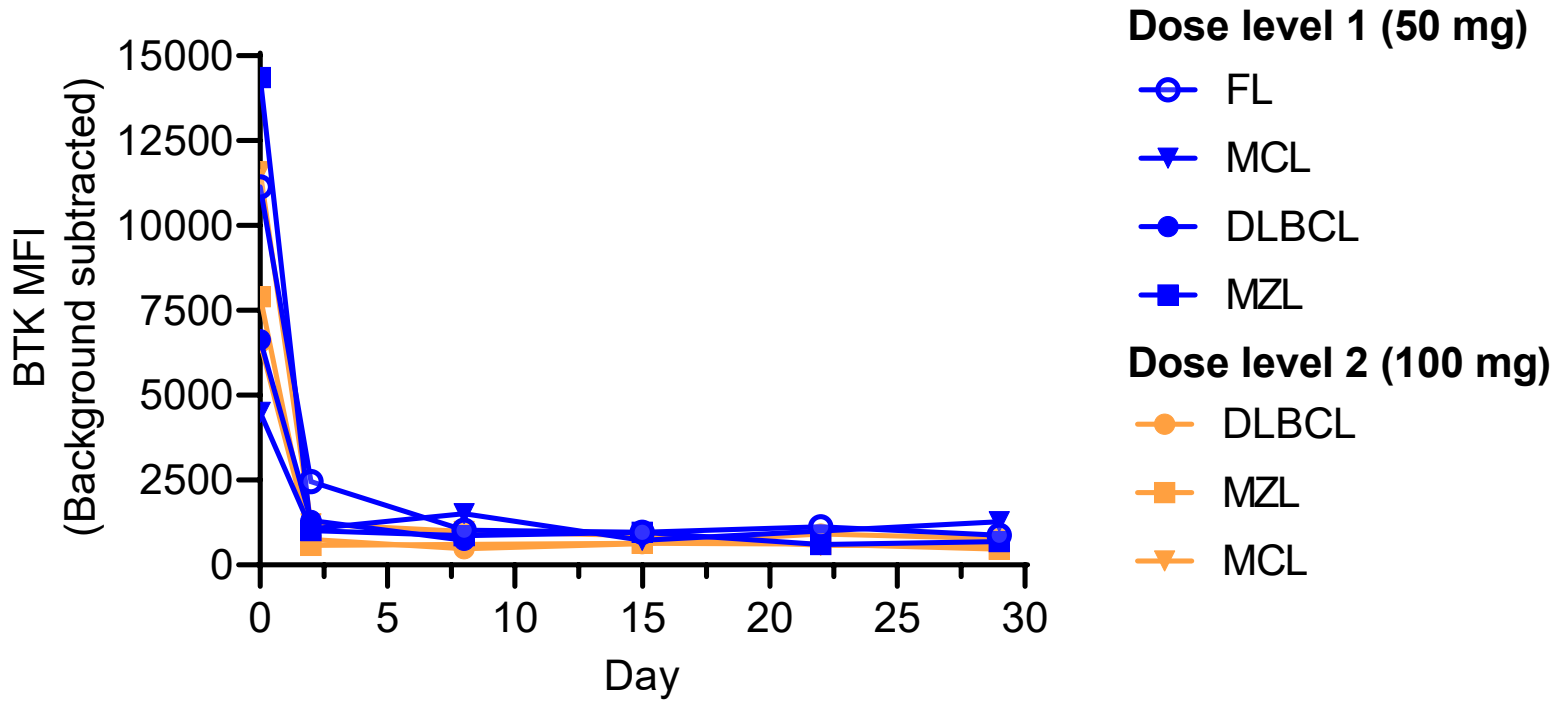
	Cycle 1, Day 1			
Dose	C_{max} (ng/mL)	AUC_{0-last} (h*ng/mL)	T_{max} (hours)	$t_{1/2}$ * (hours)
50 mg n=4	4.52 (102)	42.1 (152)	3.0	12.8 (19.9)
100 mg n=3	12.3 (45.3)	99.6 (50.2)	2.0	12.4 (9.39)

C_{max} and AUC_{0-last} are presented as geometric mean (geometric %CV); T_{max} is presented as median; $t_{1/2}$ is presented as mean (%CV); *AUC extrapolation >20%

- The half life of ~12.6 hours supports once daily dosing.
- The T_{max} of 2–3 hours suggests fast absorption.
- Exposures (both AUC and C_{max}) increase linearly with dose.

NX-5948 Resulted in Rapid, Robust and Sustained BTK Degradation in all Patients Dosed

- NX-5948 induced sustained BTK degradation of 89±4% at Cycle 2 Day 1 across dose levels

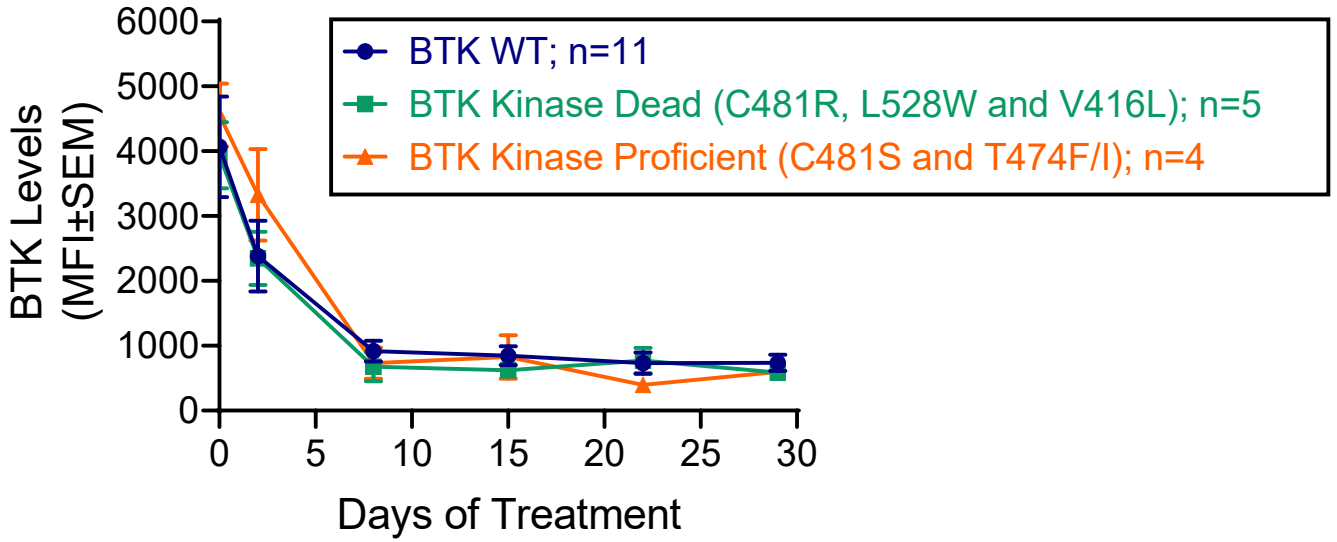


FL (follicular lymphoma), DLBCL (diffuse large B cell lymphoma), MCL (mantle cell lymphoma), MZL (marginal zone lymphoma)

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

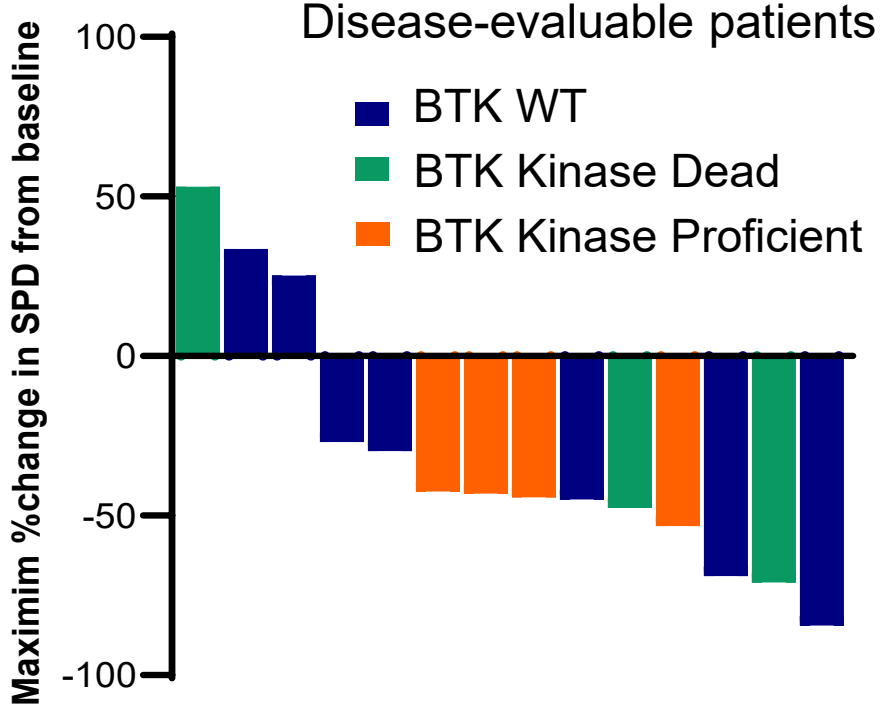
NX-2127 Preliminary Efficacy in Patients with CLL

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

Disease-evaluable patients



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

Montoya, Dec. 2022 ASH

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

NX-5948
for BTK inhibitor resistance mutations in CLL with potential for early lines of therapy

NX-2127
for aggressive NHL and advanced CLL including BTK inhibitor resistance mutations

B-Cell Malignancies Annual Incidence (US & EU)

NX-5948

NX-5948 potential in combination

NX-2127 in 3L+

NX-2127

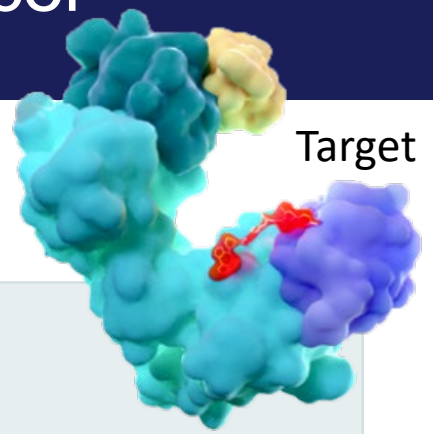
Goal: Displace BTKi in indications where single-agent BTKi is standard of care and address BTKi resistance mutations

Goal: Expand role for BTK target therapy

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

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

Targeted Protein Degradation Has the Potential to Address Significant Limitations of Current Targeted Therapies for Cancer



Emergent BTKi-Resistant Mutations

- The use of BTK inhibitors for treating B-cell malignancies has led to the development of acquired mutations that confer resistance to both covalent and noncovalent BTK inhibitors

Scaffolding Functions of BTK

- Multiple mutant variants of BTK are kinase-dead but retain the ability to propagate BCR signaling in TMD8 cells
- Scaffolding functions of BTK in oncogenic setting can pose additional challenges for the application of BTK inhibitors

Targeted Degraders as "Next-Generation" Therapeutics

- Unlike an inhibitor, a degrader can address both the enzymatic and scaffolding functions of a protein
- Degraders can target known and novel clinical resistance mutations
- Exciting applications in the emerging class of Degrader Antibody Conjugates

Thank you

nurix