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Leader in Targeted Protein Modulation

Targeted Protein Degradation of BTK Overcomes Clinically-Relevant Resistance Mutations and Its Oncogenic Scaffolding Functions

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Discovery on Target – Small Molecules for Cancer Targets
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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

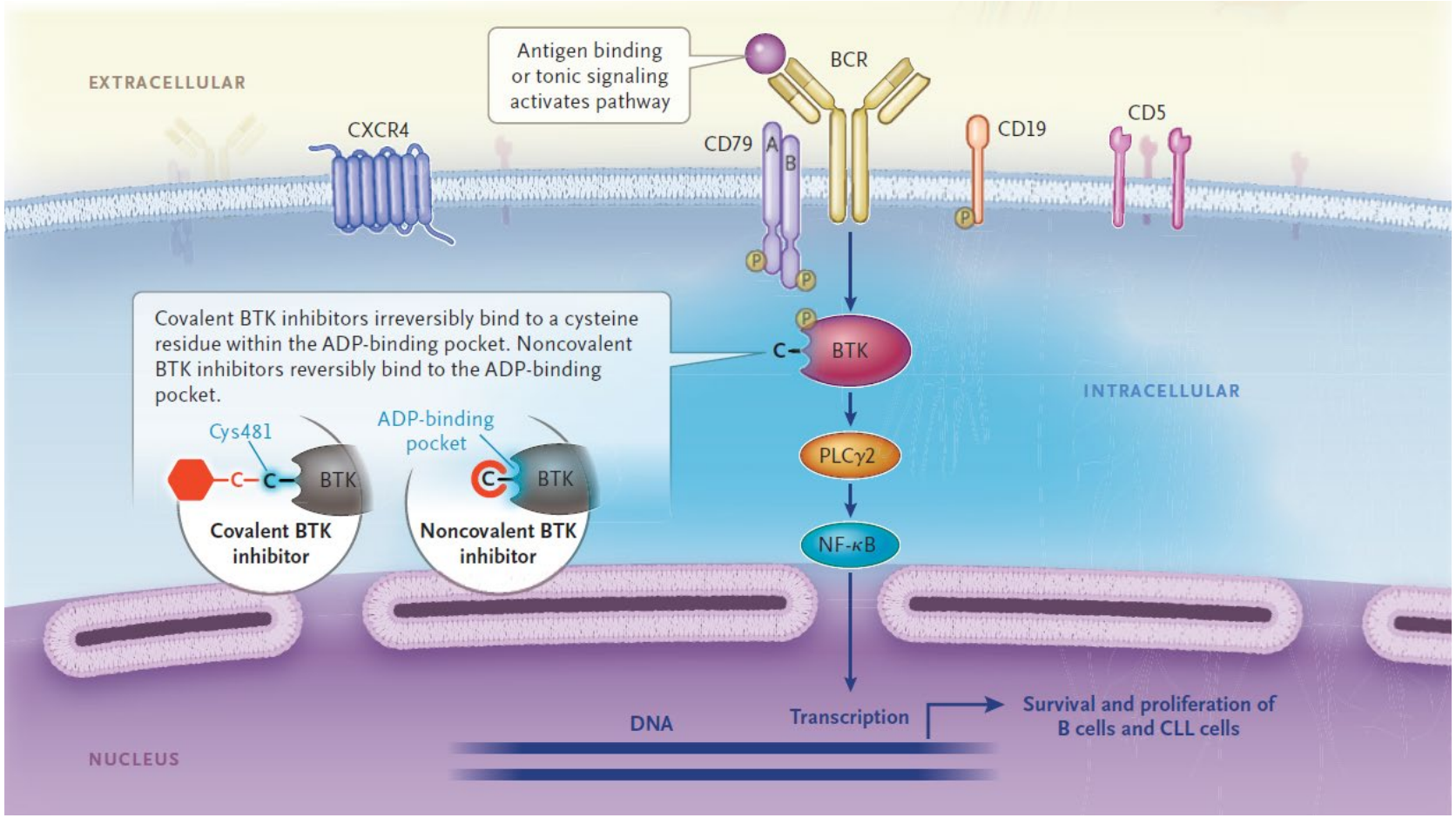
Targeted Protein Degradation (TPD)

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

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				
TPD	**NX-5948**	BTK	B-cell malignancies				
TPE	**NX-1607**	CBL-B	Immuno-Oncology				
TPD	**NX-0479 / GS-6791**	IRAK4	Rheumatoid arthritis and other inflammatory diseases				GILEAD
TPM	5 programs	Undisclosed	Oncology / autoimmune disease				
TPD	4 programs	Undisclosed	Undisclosed				GILEAD
TPD	5 programs	Undisclosed	Undisclosed				sanofi
DAC	Multiple programs	Undisclosed	Oncology				Seagen

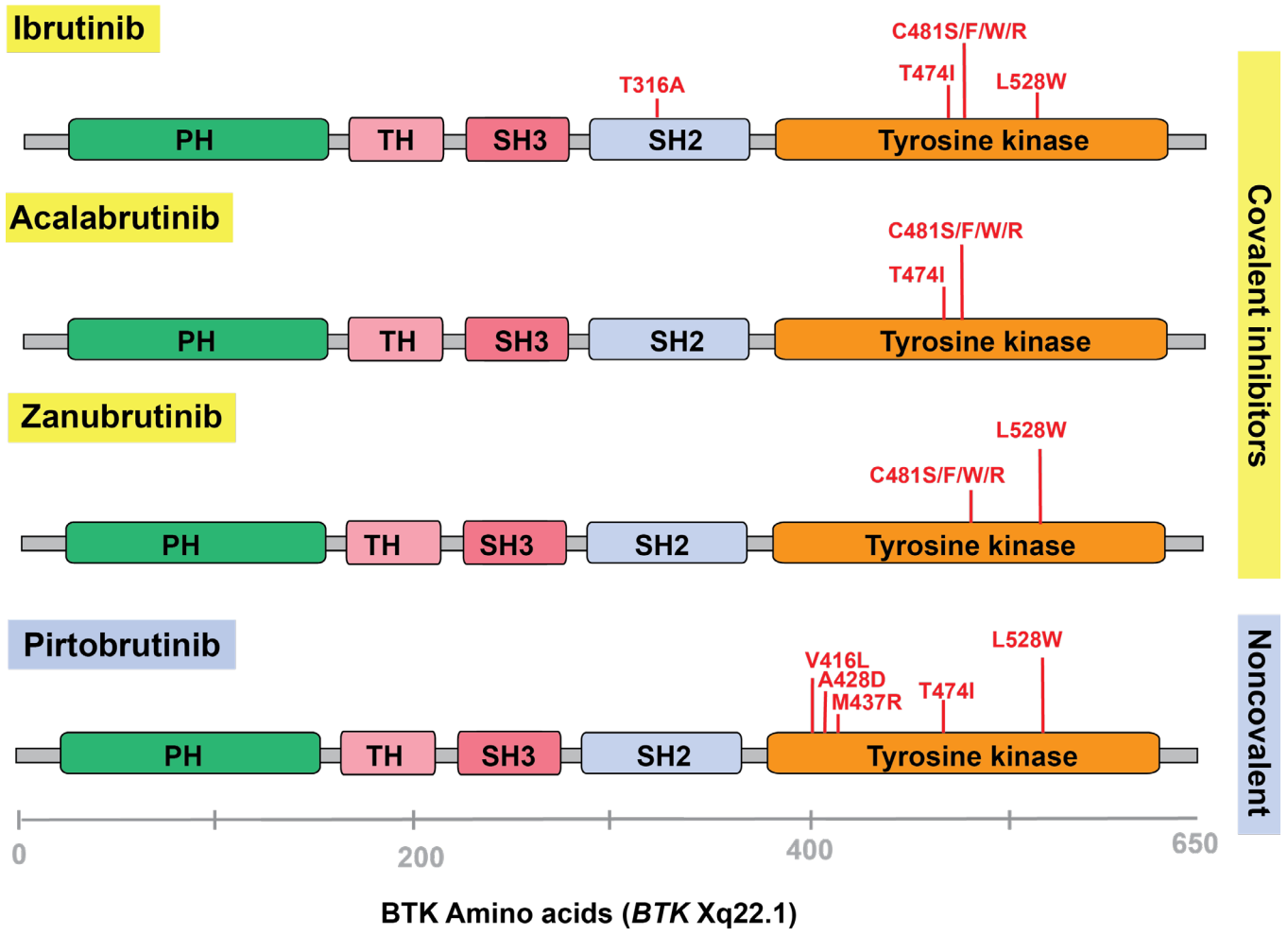
Inhibiting BTK for B-cell Malignancies Is Effective but Also Leads to The Emergence of Clinical Resistance Mutations

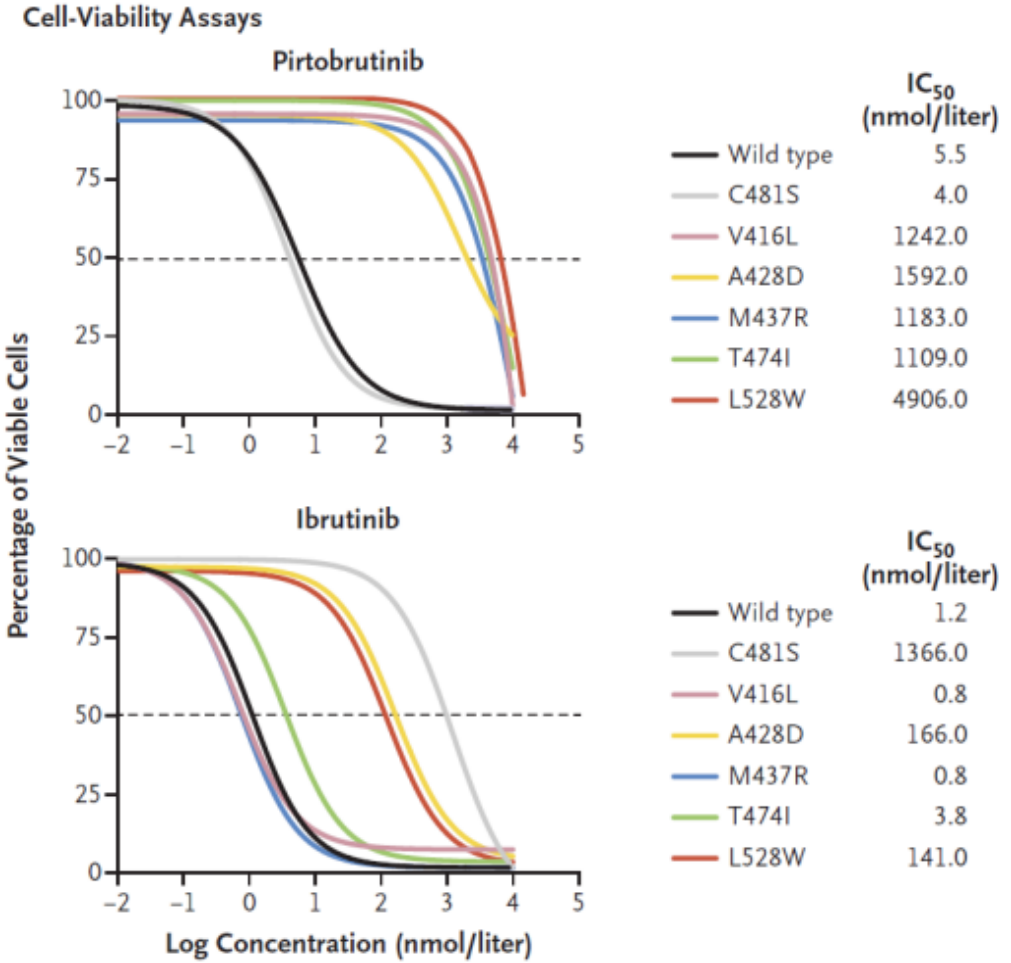


- BTK is a nonreceptor tyrosine kinase and plays a crucial role in the B-cell receptor (BCR) signaling pathway
- Inhibition of BTK enzymatic activity has been established as an effective therapeutic strategy
- Examples of covalent BTK inhibitors - Ibrutinib, Acalabrutinib, Tirabrutinib and Zanubrutinib
  - ❑ Resistance mutations arise during treatment with covalent inhibitors, with BTK C481 mutations being a primary mechanism of resistance
- Examples of noncovalent BTK inhibitors – Pirtobrutinib, Fenebrutinib and Vecabrutinib.

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

Clinical Landscape of Treatment-Emergent Resistance to Inhibitors Is Evolving

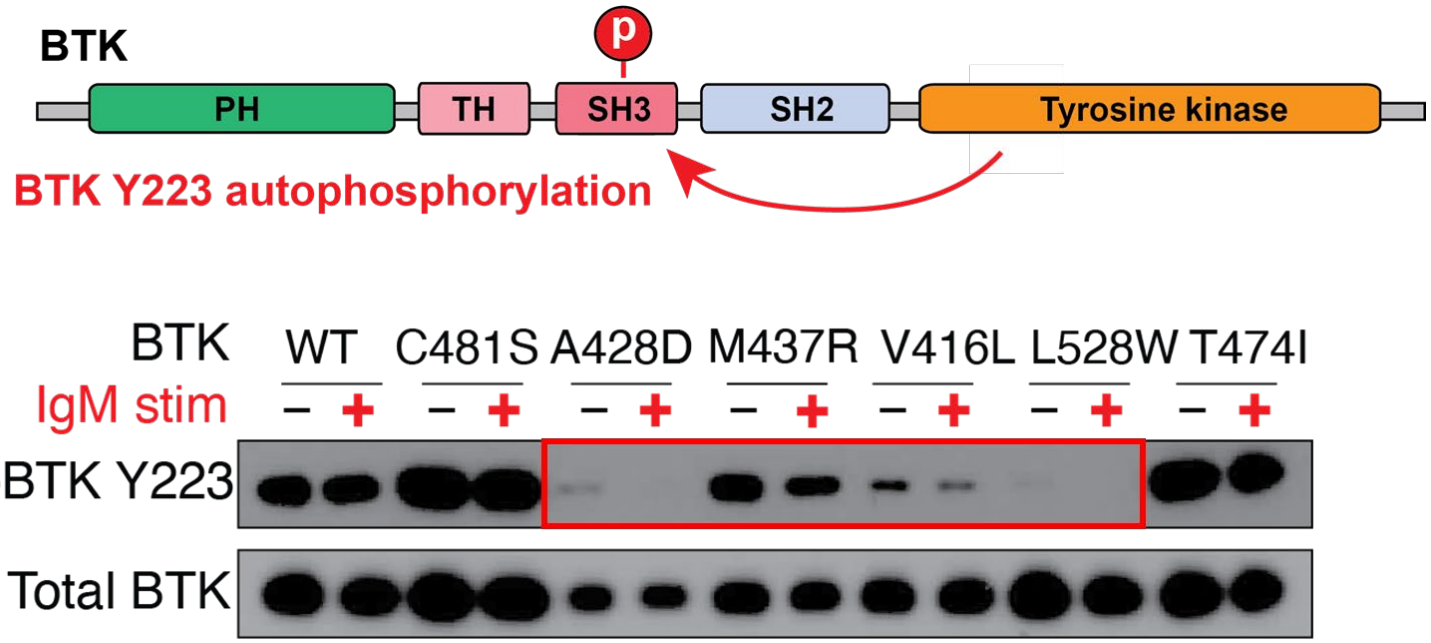




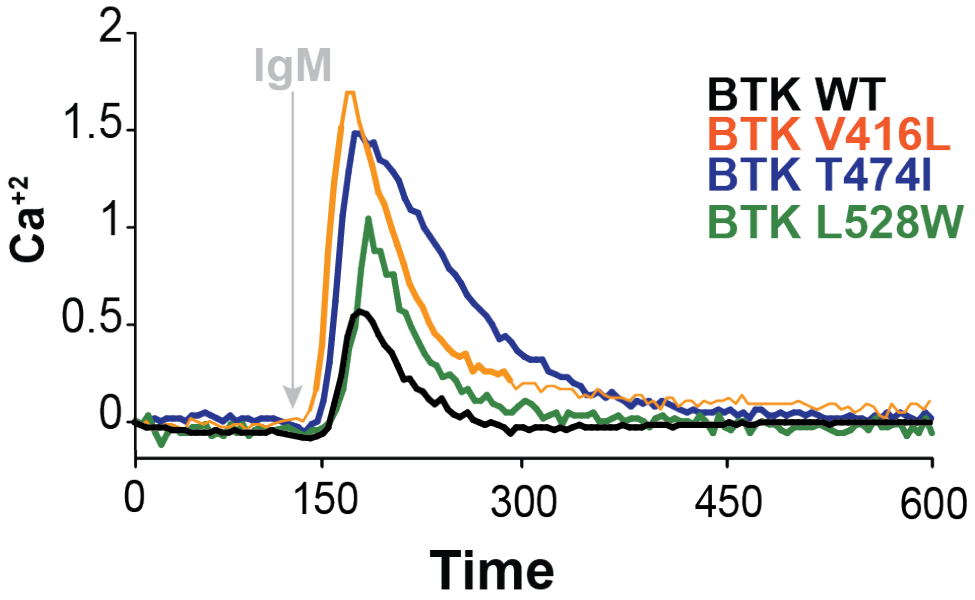
Montoya et al., ASH 2022 and Wang et al., NEJM 2022

Several BTK Mutations Abrogate BTK Phosphorylation yet Continue to Propagate Downstream BCR Signaling

BTK Y223 Phosphorylation in TMD8 Cell



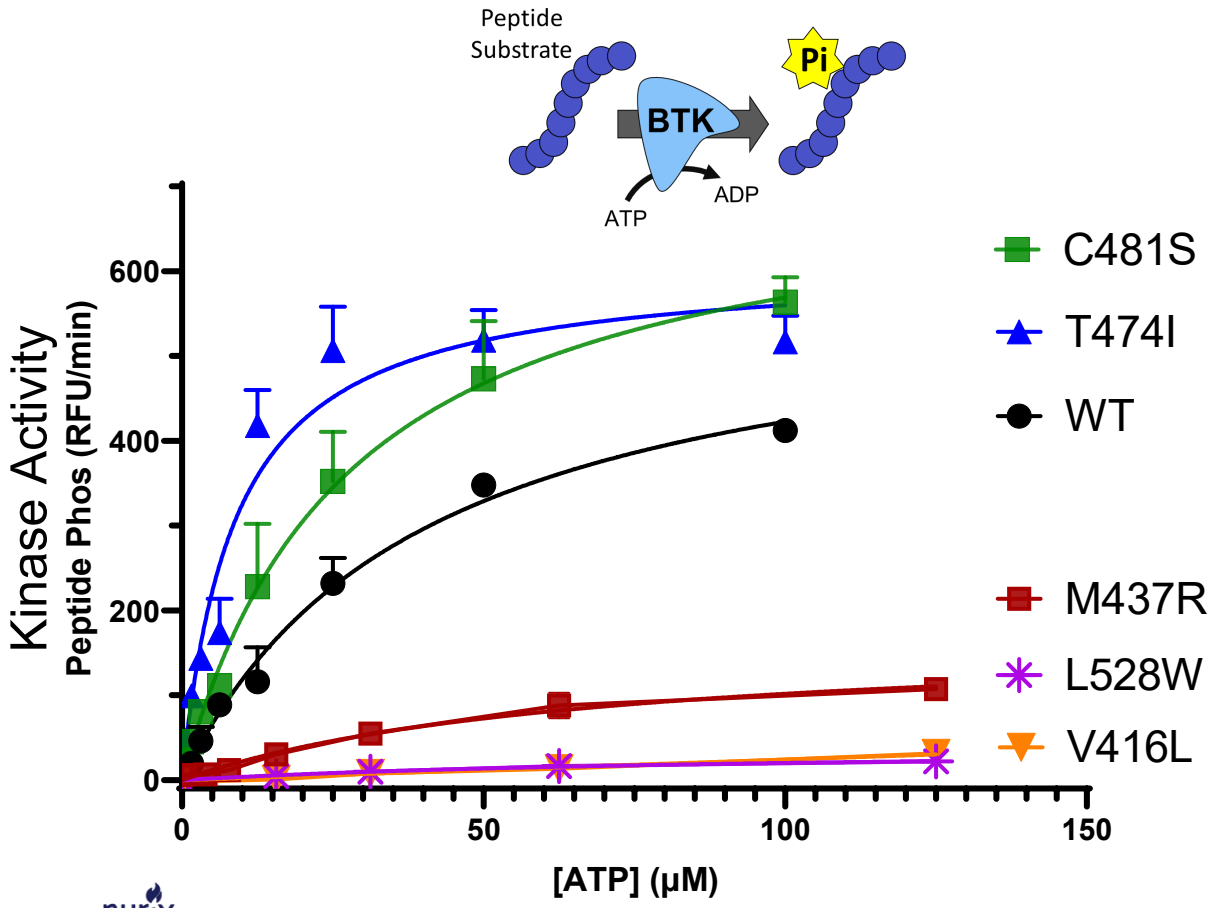
Calcium Ion Flux in TMD8 Cell



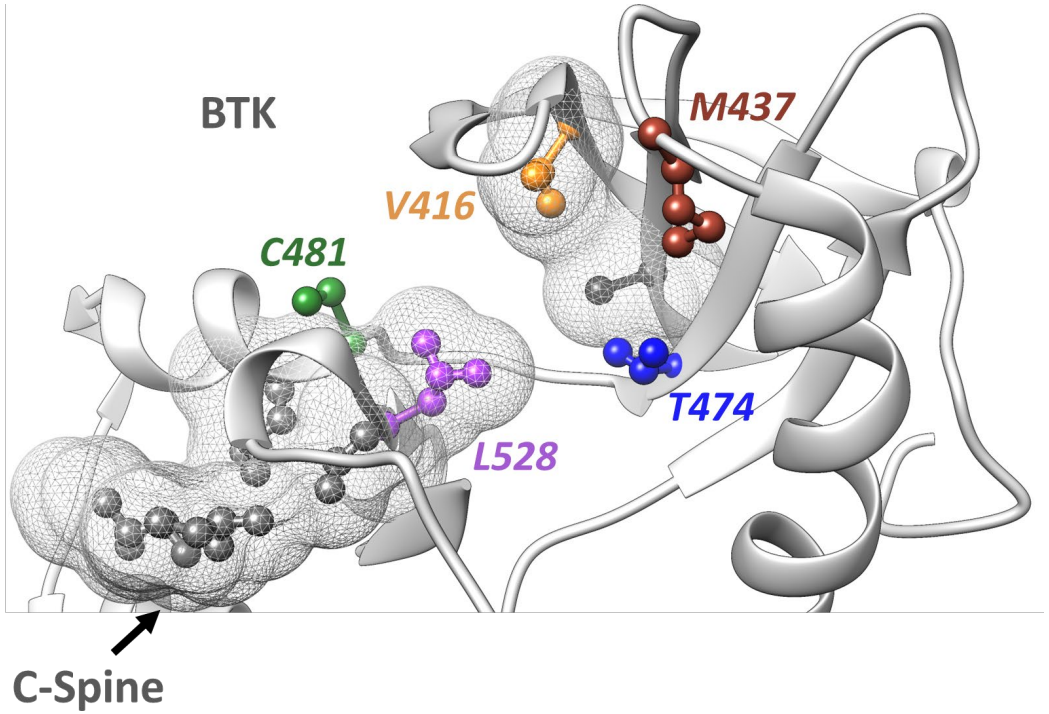
Montoya et al., ASH 2022

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

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

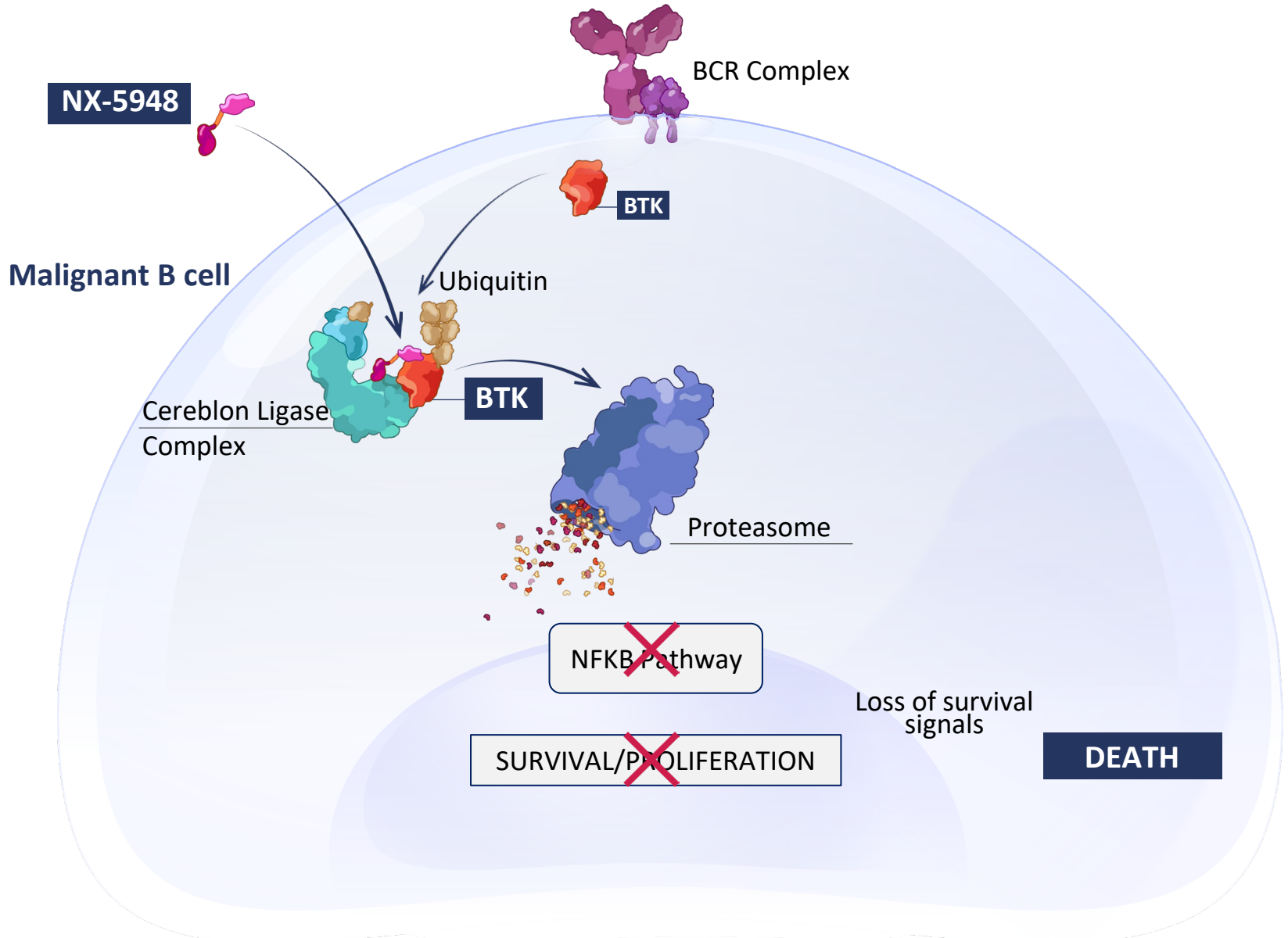


Mutations revealed by non-covalent inhibitors interrupt the catalytic C-spine of kinase domain



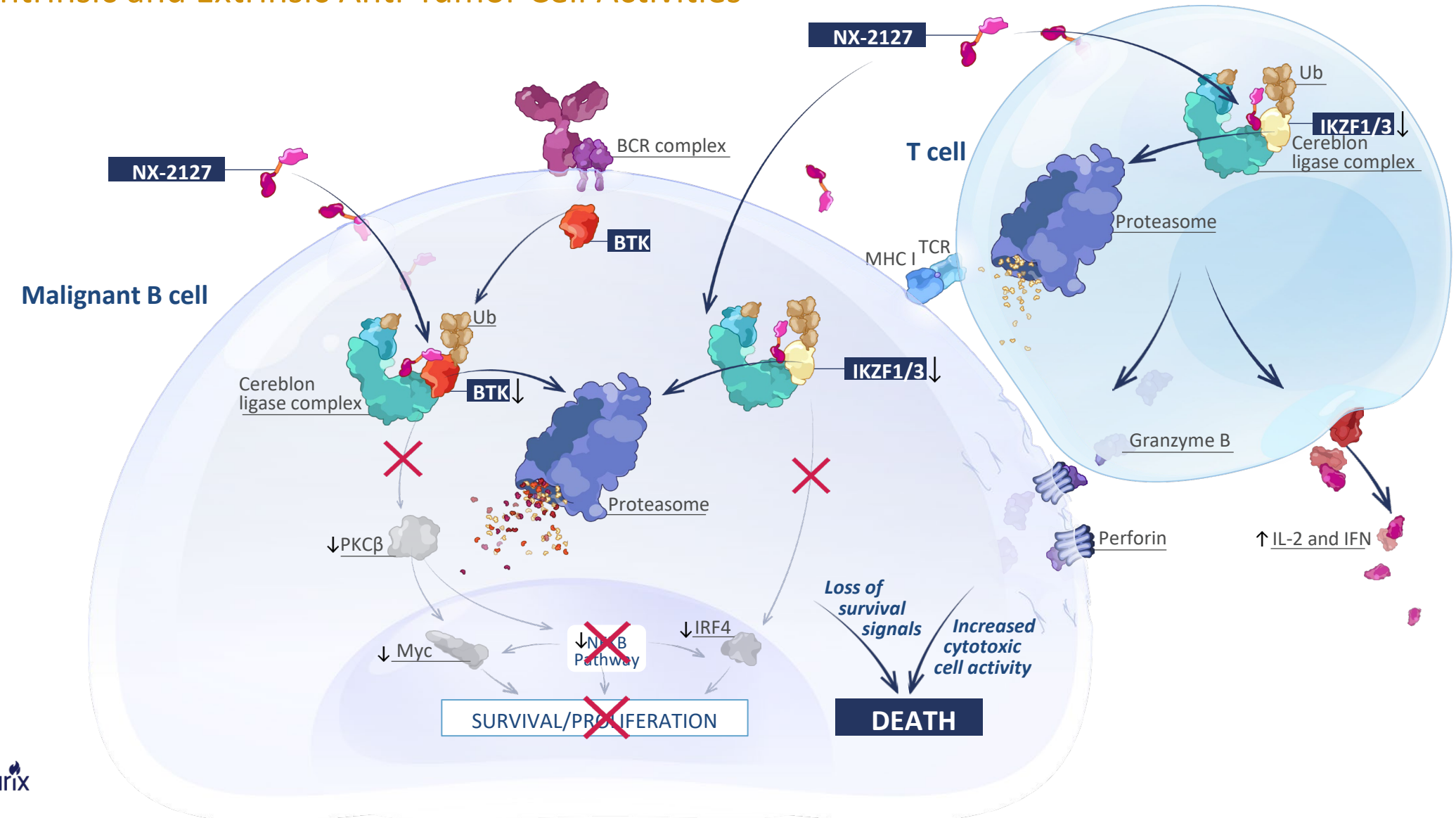
Montoya et al., ASH 2022 and unpublished data

NX-5948 Is a Potent and Selective Degrader of BTK

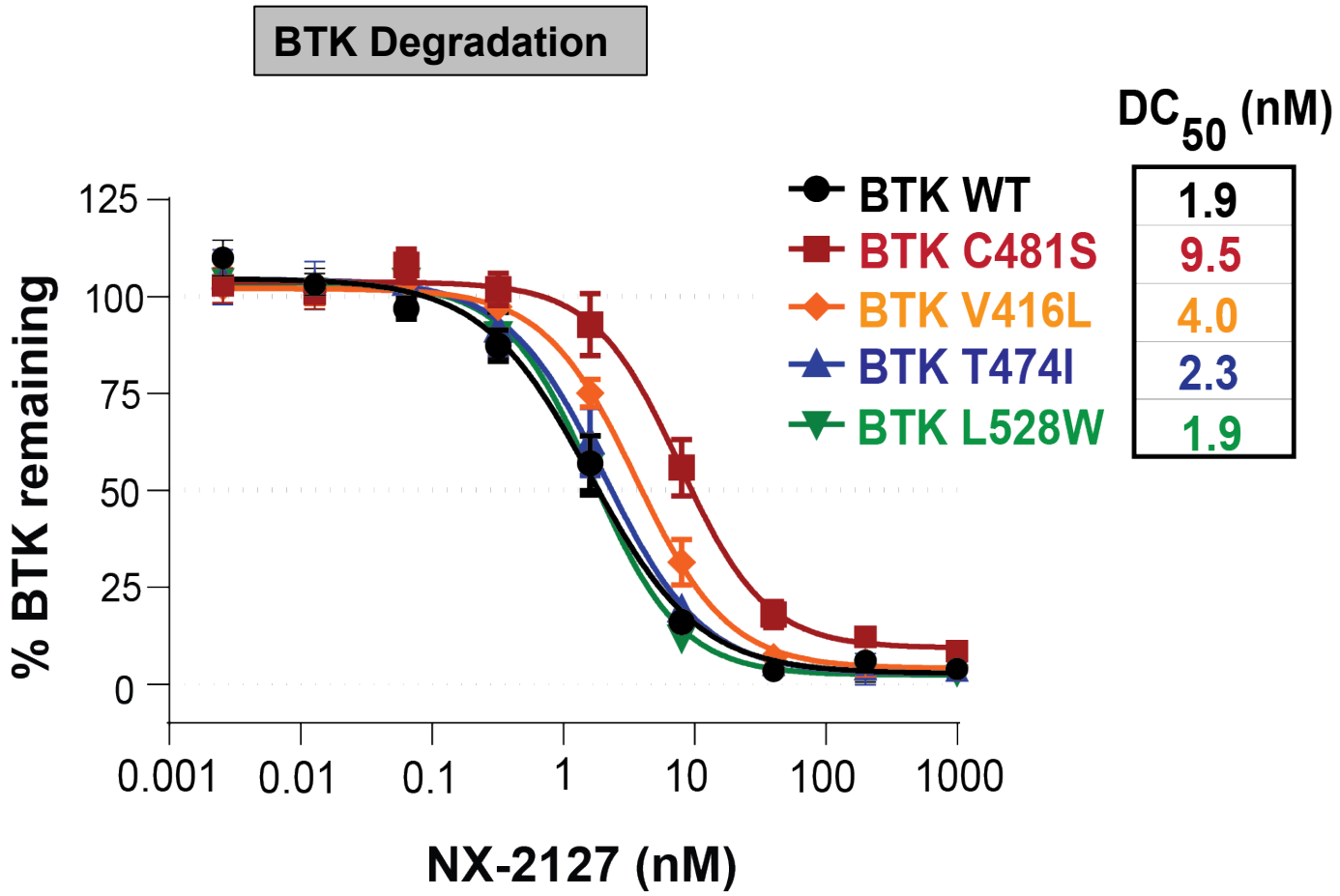


NX-2127 Dual Mechanism of Action

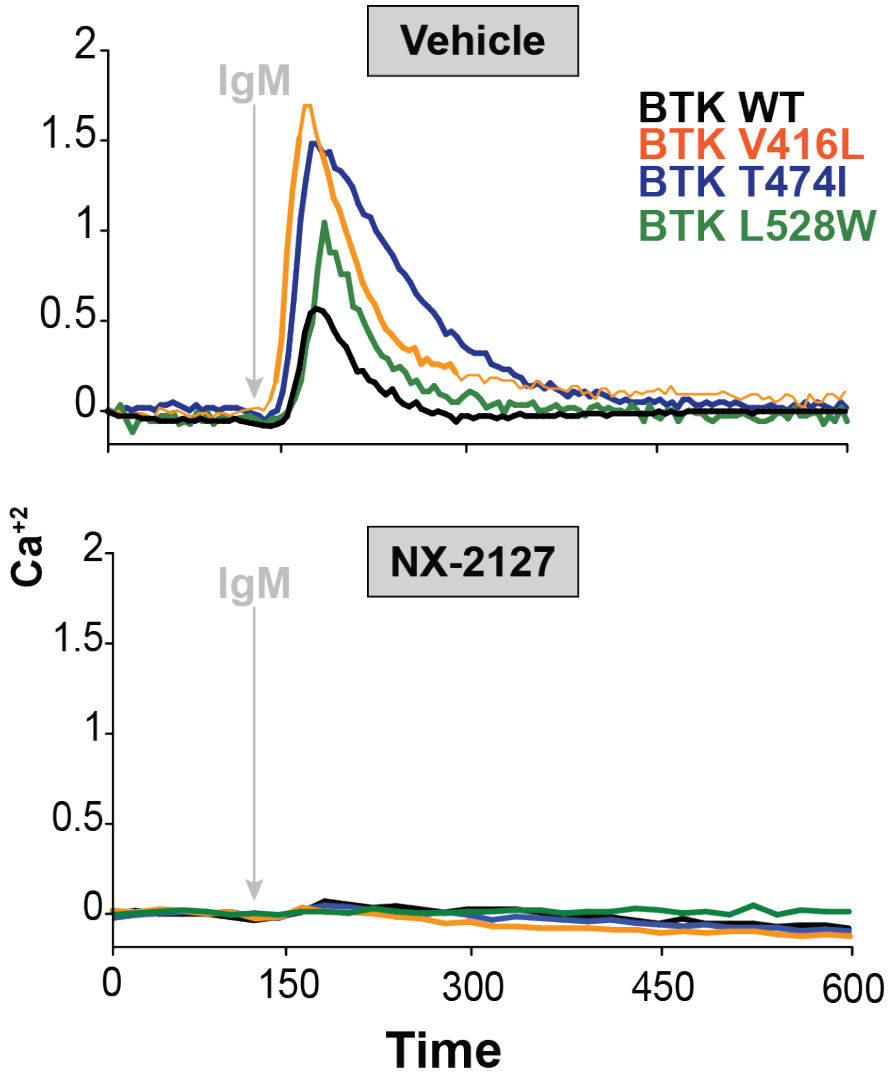
Targeted Degradation of BTK and IKZF1/3 Provides Both Intrinsic and Extrinsic Anti-Tumor Cell Activities



NX-2127 Degrades Both Wild-Type and Mutant BTK and Suppresses Ca^{++} Signaling



DC_{50} (nM)
1.9
9.5
4.0
2.3
1.9



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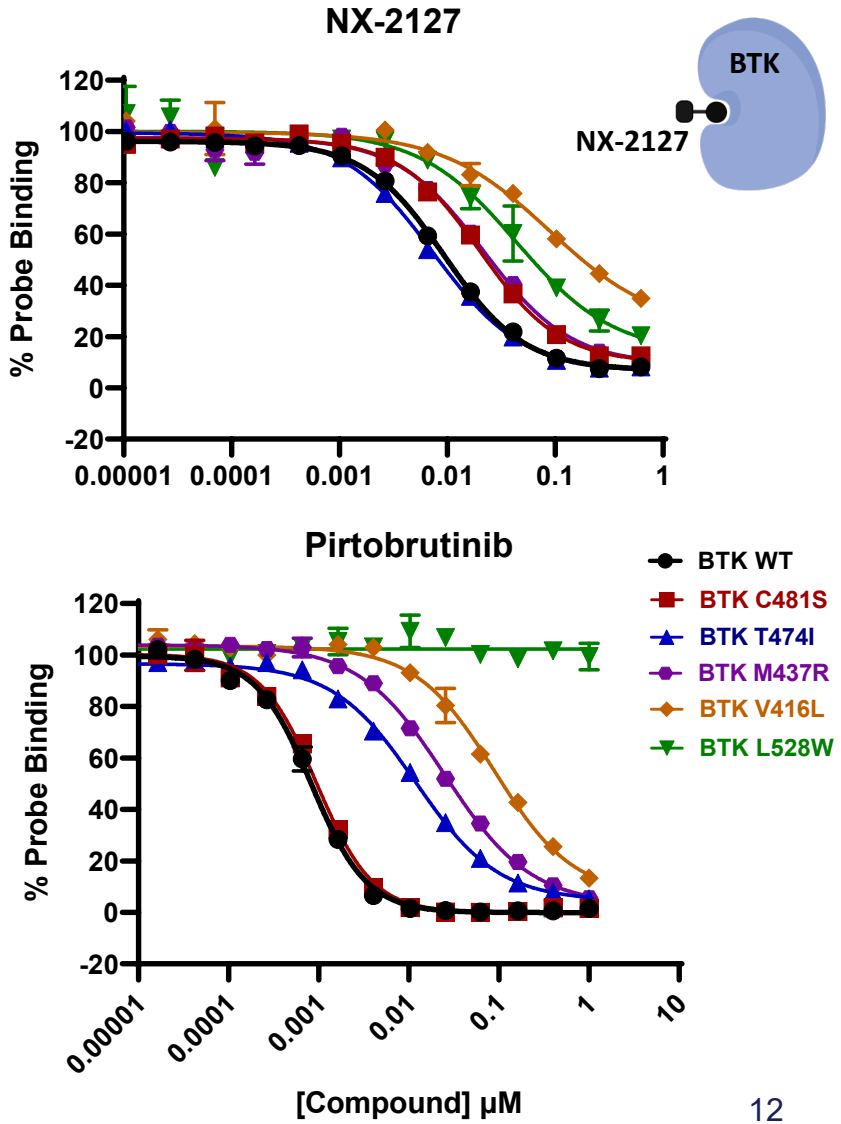
Montoya et al., ASH 2022

NX-2127 Demonstrates Binding to Recurrent Acquired Resistant BTK Mutant Variants

BTK Protein	Binding of **NX-2127** Determined by SPR K_d (nM)	Binding Determined by FRET Displacement Assay IC_{50} (nM)		
		NX-2127	Pirtobrutinib	Ibrutinib
WT	18	10	0.76	1.4
C481S	45	22	0.77	6.2
T474I	18	8.6	12	1.8
M437R	44	23	30	0.28
V416L	97	165	98	3.8
L528W	88	70	>1000	>1000

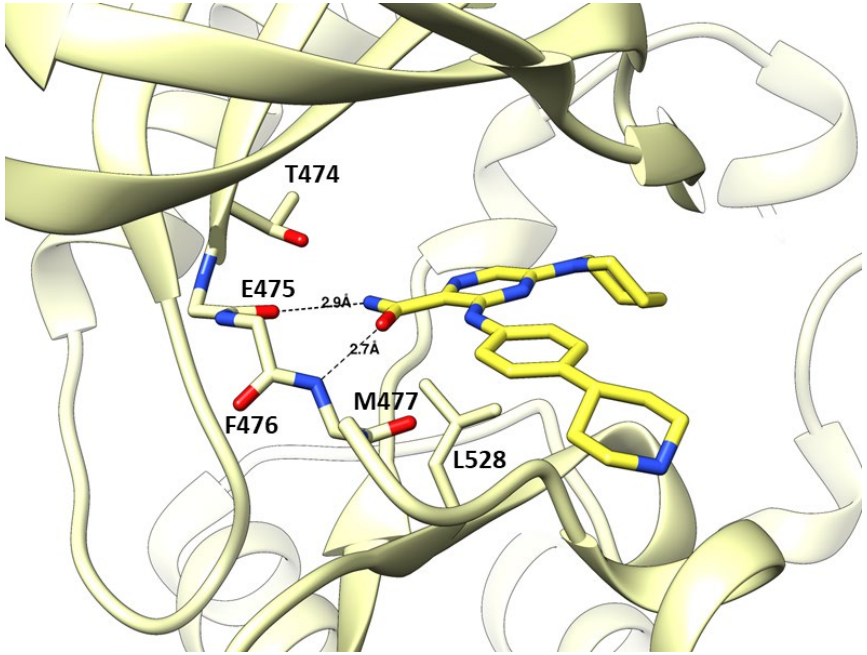
*IC_{50} determined at 60 min for Ibrutinib
IC_{50}s reported here are mean of at least 3 experiments



unpublished data

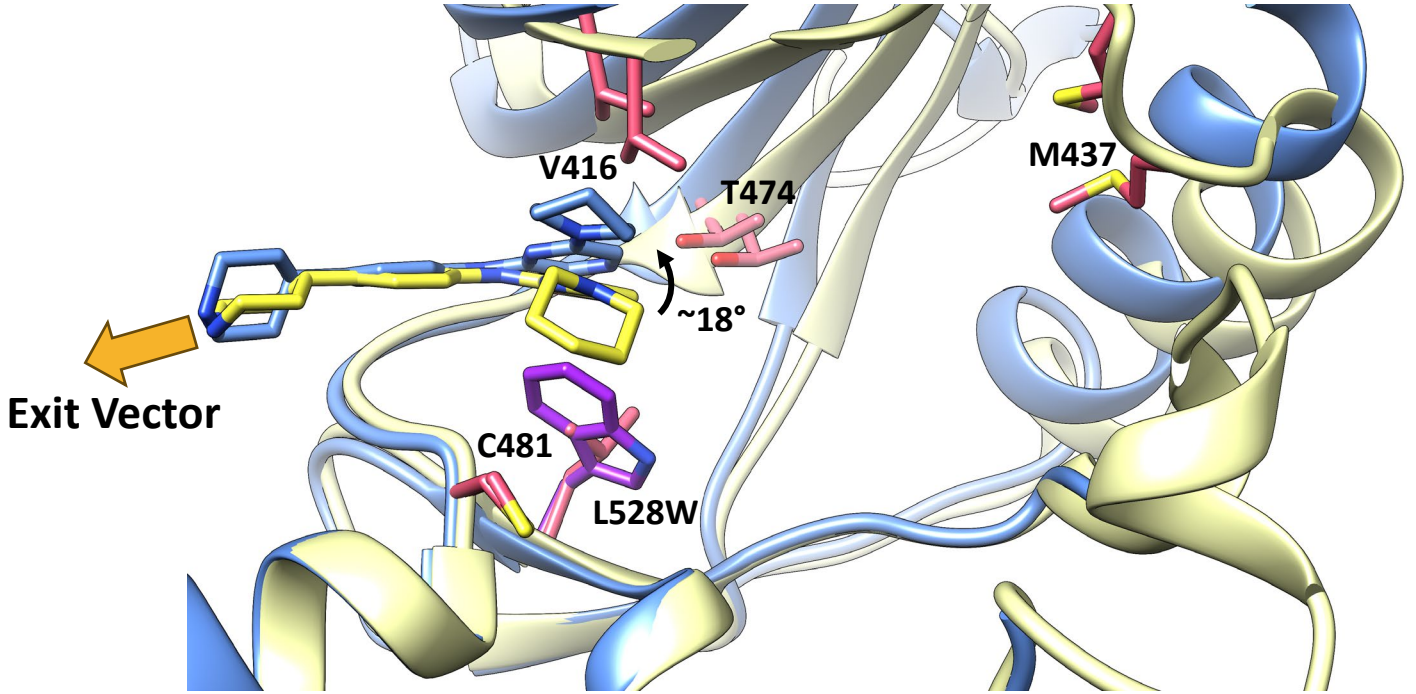
Crystal Structure of NX-2127 Bound to BTK WT and L528W

BTK-binding ligand of NX-2127 bound to WT BTK Kinase Domain



- Interacts with the ATP binding pocket
- Forms hydrogen bonds with residue E475 and M477 in the hinge region

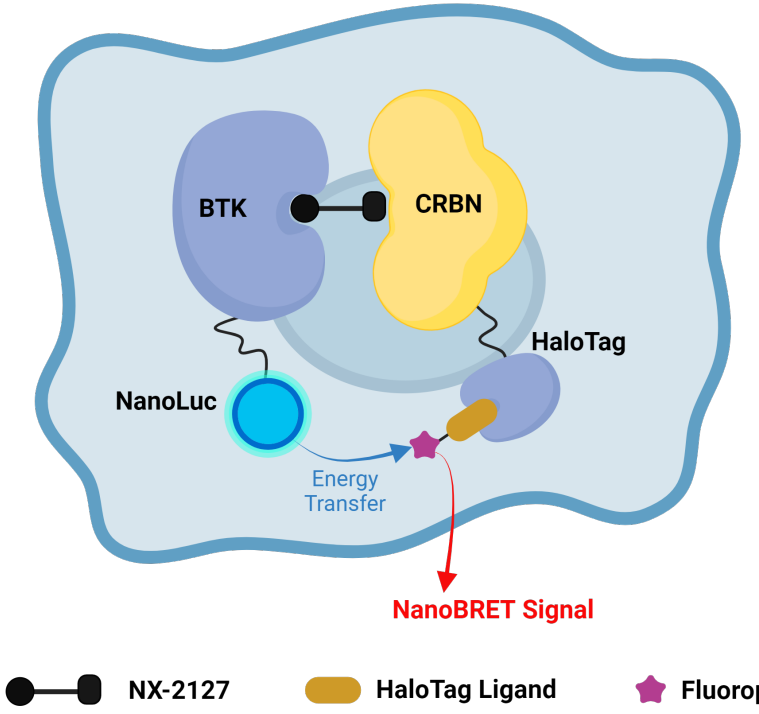
Overlay of BTK WT (yellow) and L528W (blue) Kinase Domains

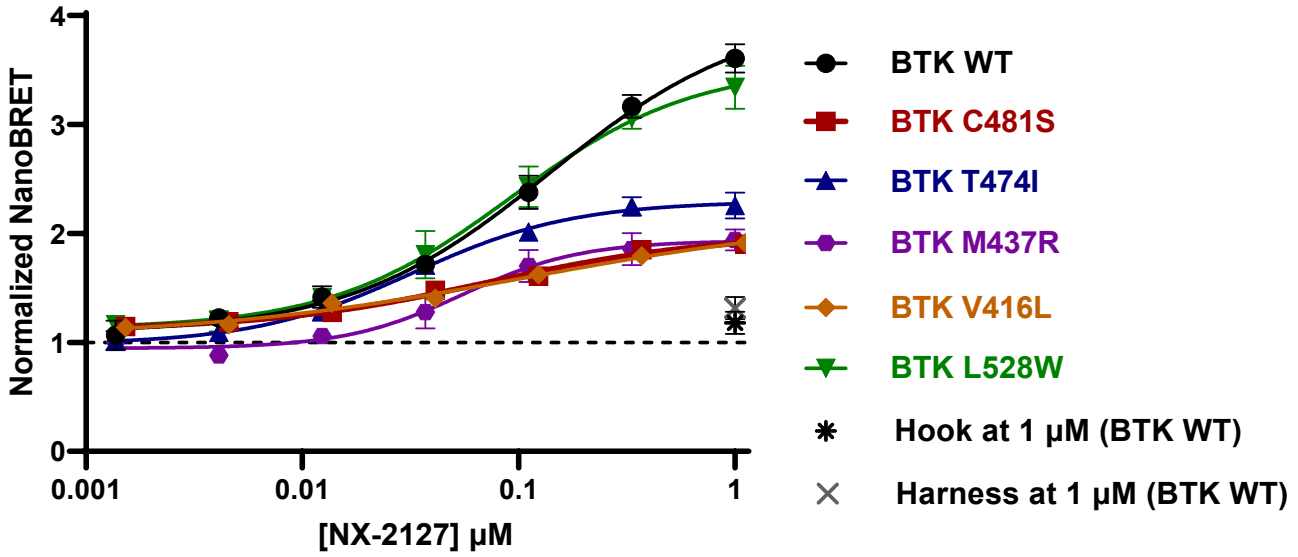


- Steric repulsion between the ligand and the tryptophan side chain in the L528W mutant
- The piperidine moiety of the ligand undergoes an 18-degree shift toward the P loop to accommodate binding

unpublished data

NX-2127 Induces Robust and Dose-dependent Ternary Complex Formation In Cell



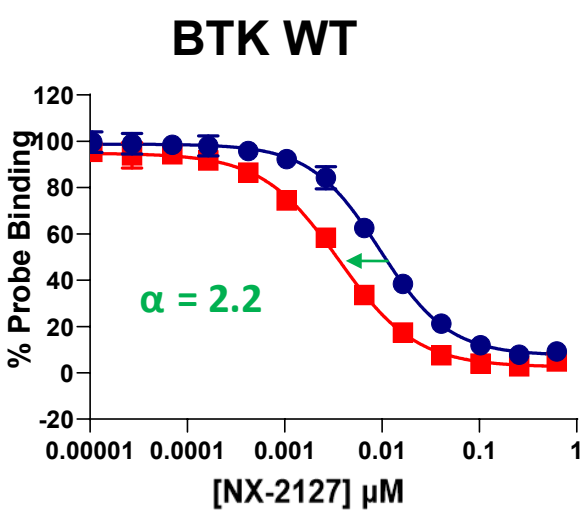


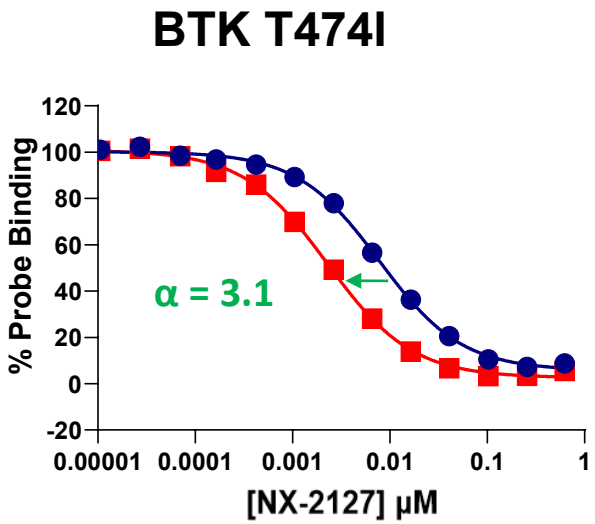
Ternary complex formation measured by NanoBRET signal in HEK293 cells co-expressing NanoLuc-BTK (WT or mutant) and Halo-tag cereblon at 6h

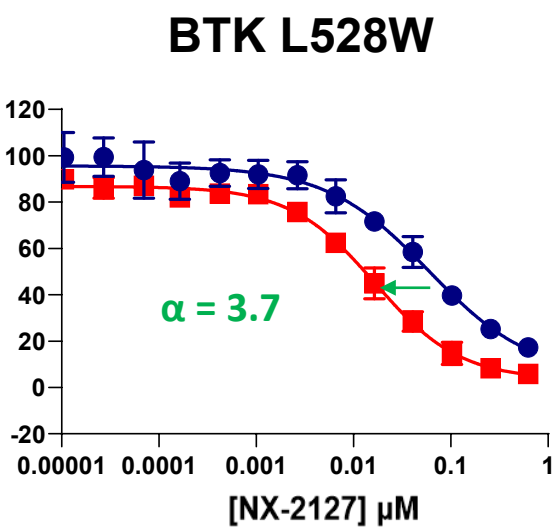
BTK Form	NanoBRET Ternary Complex EC_{50} (nM)
BTK-WT	139
BTK-C481S	73
BTK-T474I	32
BTK-M437R	55
BTK-V416L	109
BTK-L528W	92

unpublished data

NX-2127 Forms Stable Ternary Complexes Between BTK and CRBN Irrespective of Mutation Status



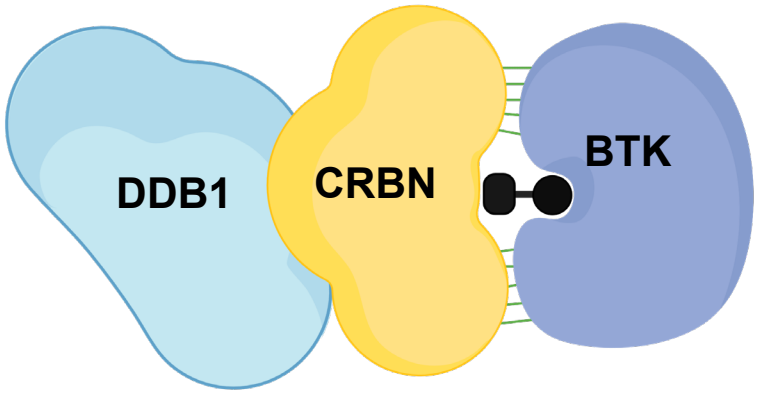




No CRBN

⊕ CRBN (1 μM)

$$\alpha = \frac{IC_{50}\ \text{No CRBN}}{IC_{50}\ \text{with CRBN (1 μM)}}$$

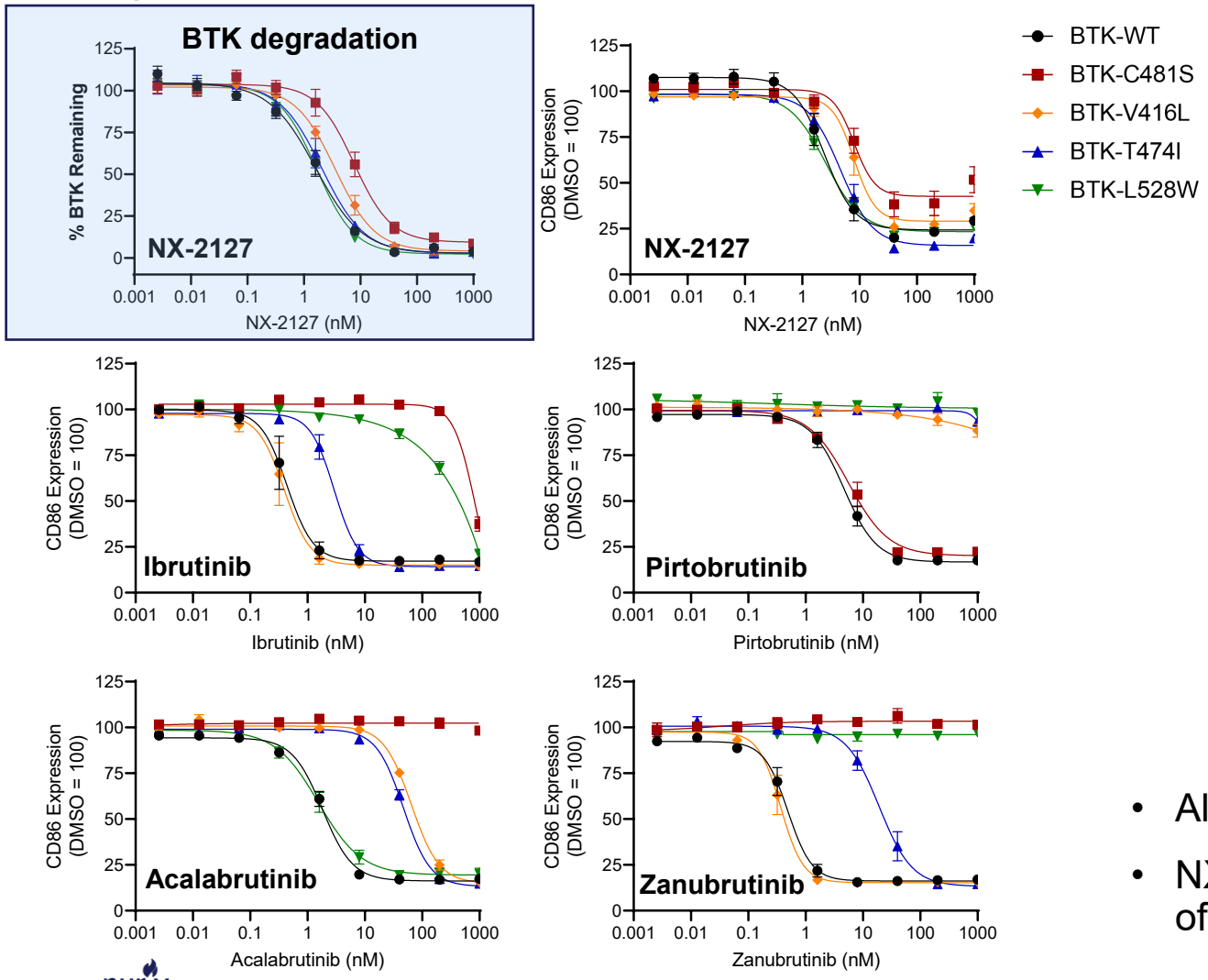


- Positive Cooperativity (α>1)
- Stable ternary complex
- Induced protein-protein interactions
- Greater tolerance for reduced binary affinity

CRBN, cereblon; **DDB1**, DNA damage binding protein 1.

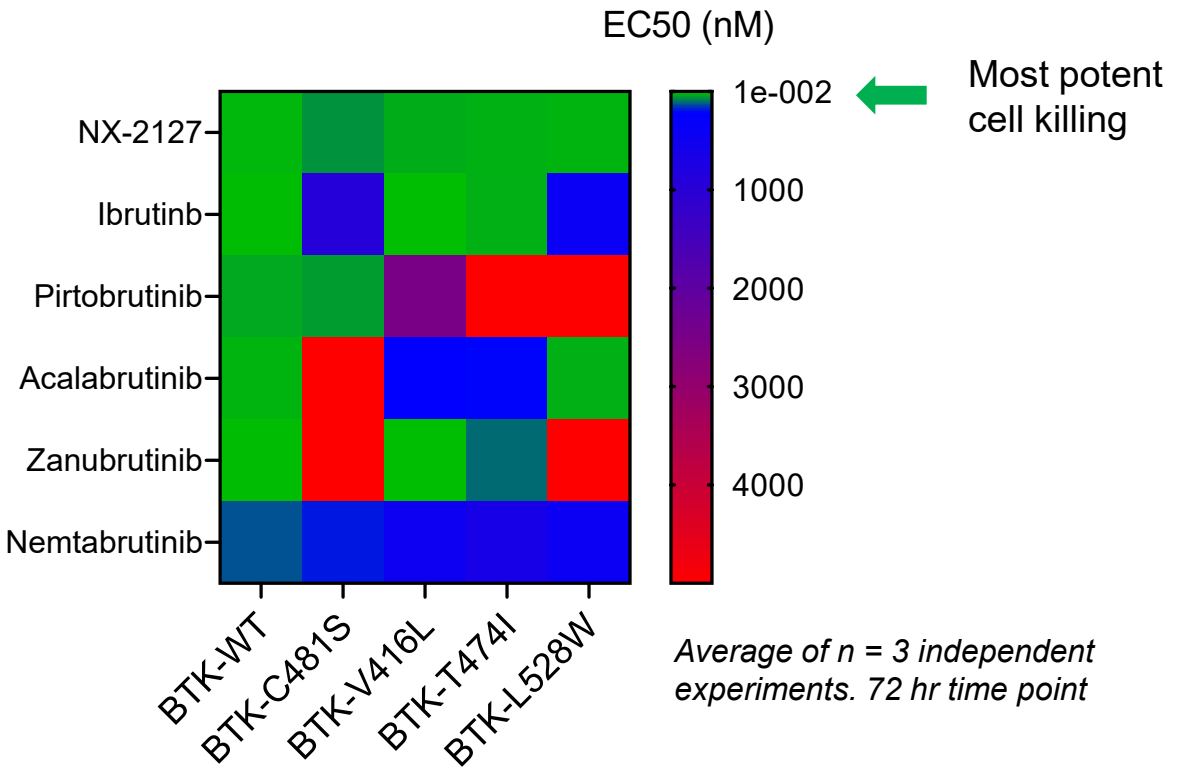
NX-2127 Is Potent and More Broadly Active Than All BTK Inhibitors Tested

BTK degradation and activation marker suppression in TMD8 tumor cells



Average of n = 3 independent experiments +/- SEM

TMD8 tumor cell killing

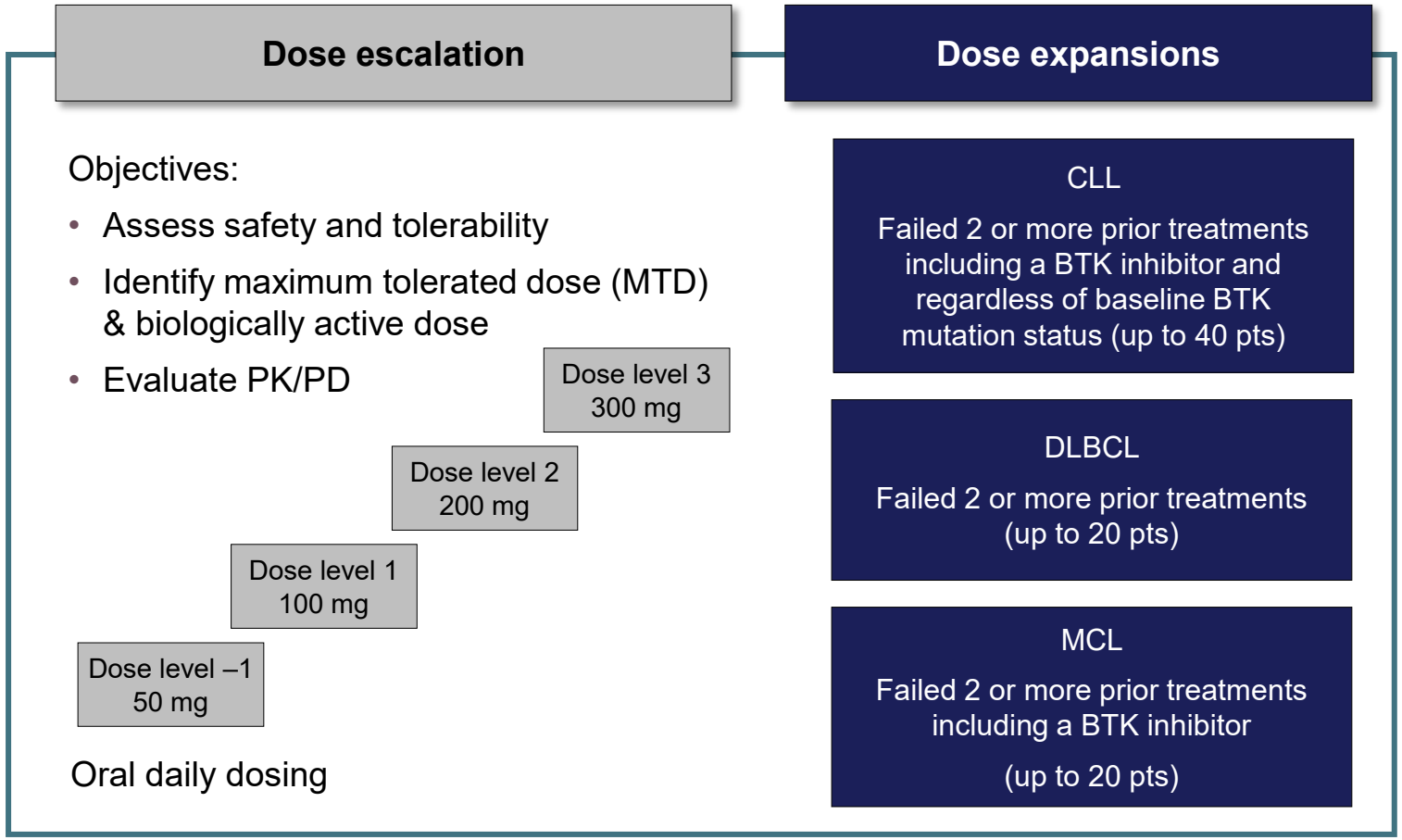


Average of n = 3 independent experiments. 72 hr time point

- 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-2127-001: Trial Design

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



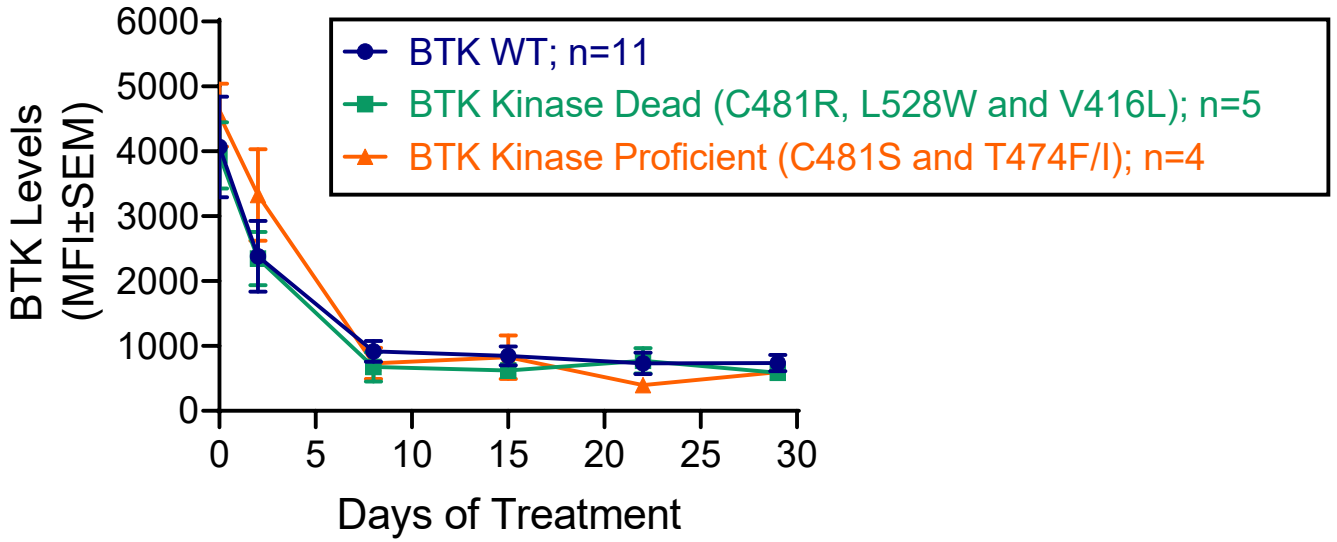
- CLL Phase 1b expansion cohort ongoing at 100 mg dose
- DLBCL Phase 1b expansion cohort ongoing at 300 mg
- MCL Phase 1b expansion cohort ongoing at 300 mg
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL

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

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

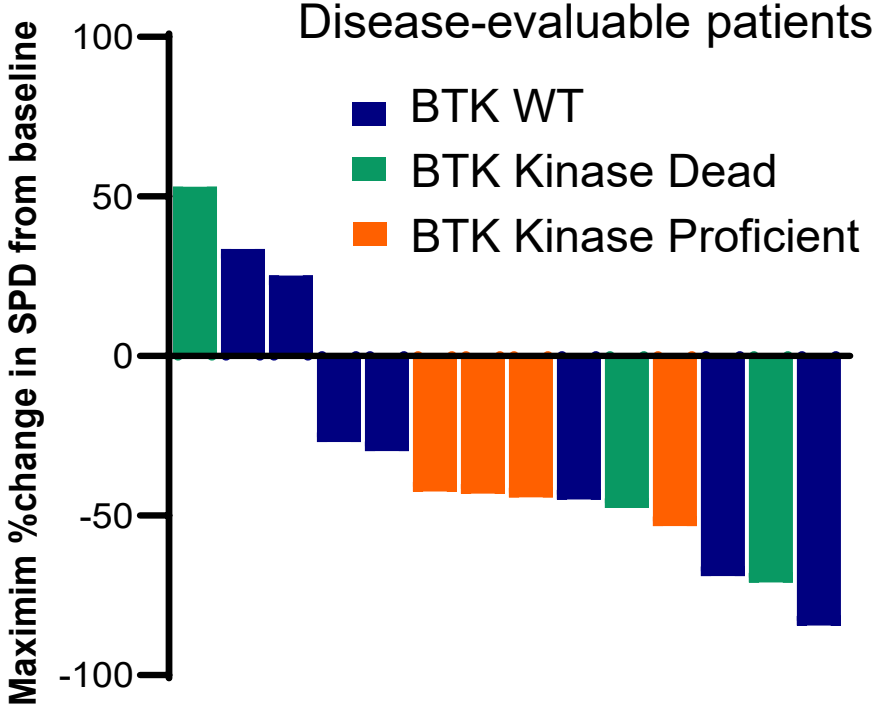
NX-2127 Preliminary Efficacy in Patients with CLL

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

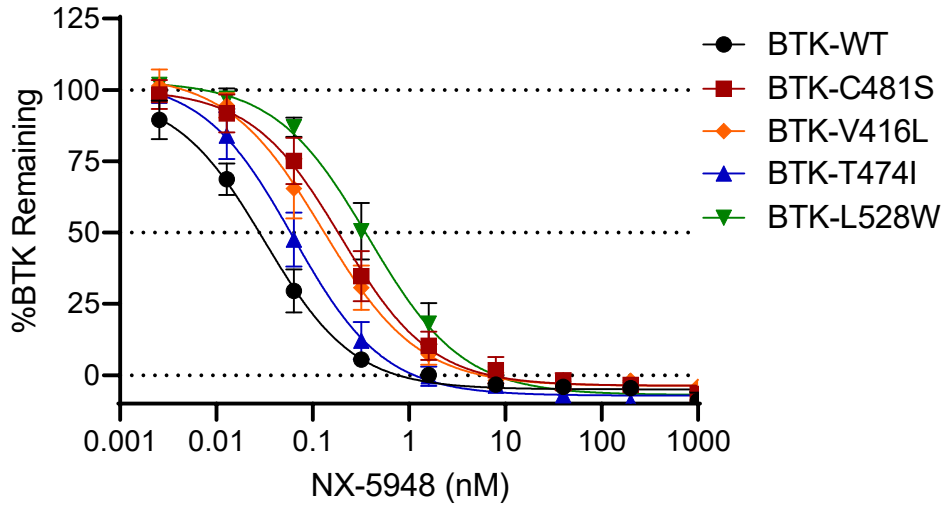
Disease-evaluable patients



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

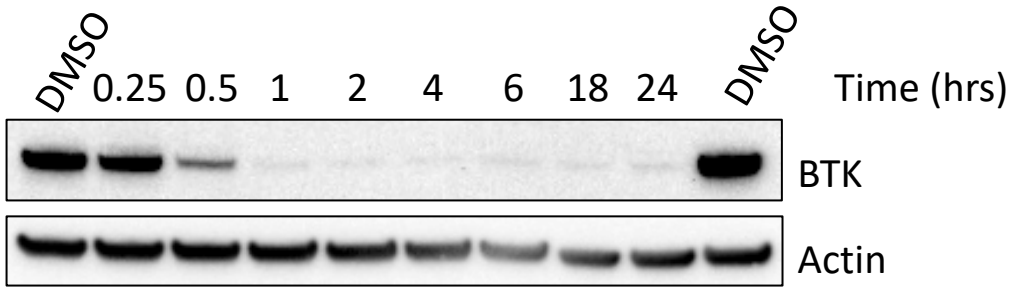
NX-5948 Demonstrates High Degradation Potency Against Both WT and Mutant BTK

BTK Degradation in TMD8



	BTK DC_{50} (nM) @ 24 hr
BTK-WT	0.03
BTK-C481S	0.21
BTK-V416L	0.15
BTK-T474I	0.07
BTK-L528W	0.41

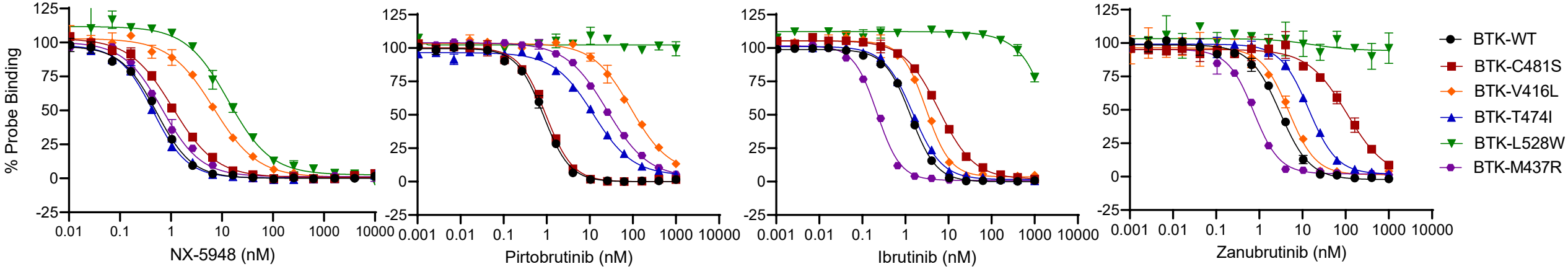
Degradation Time-Course



Ramos human Burkitt's lymphoma B cells incubated with 10 nM NX-5948

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

NX-5948 Exhibits High-Affinity Binding to WT BTK and Maintains Strong Binding with BTK Resistant Mutants



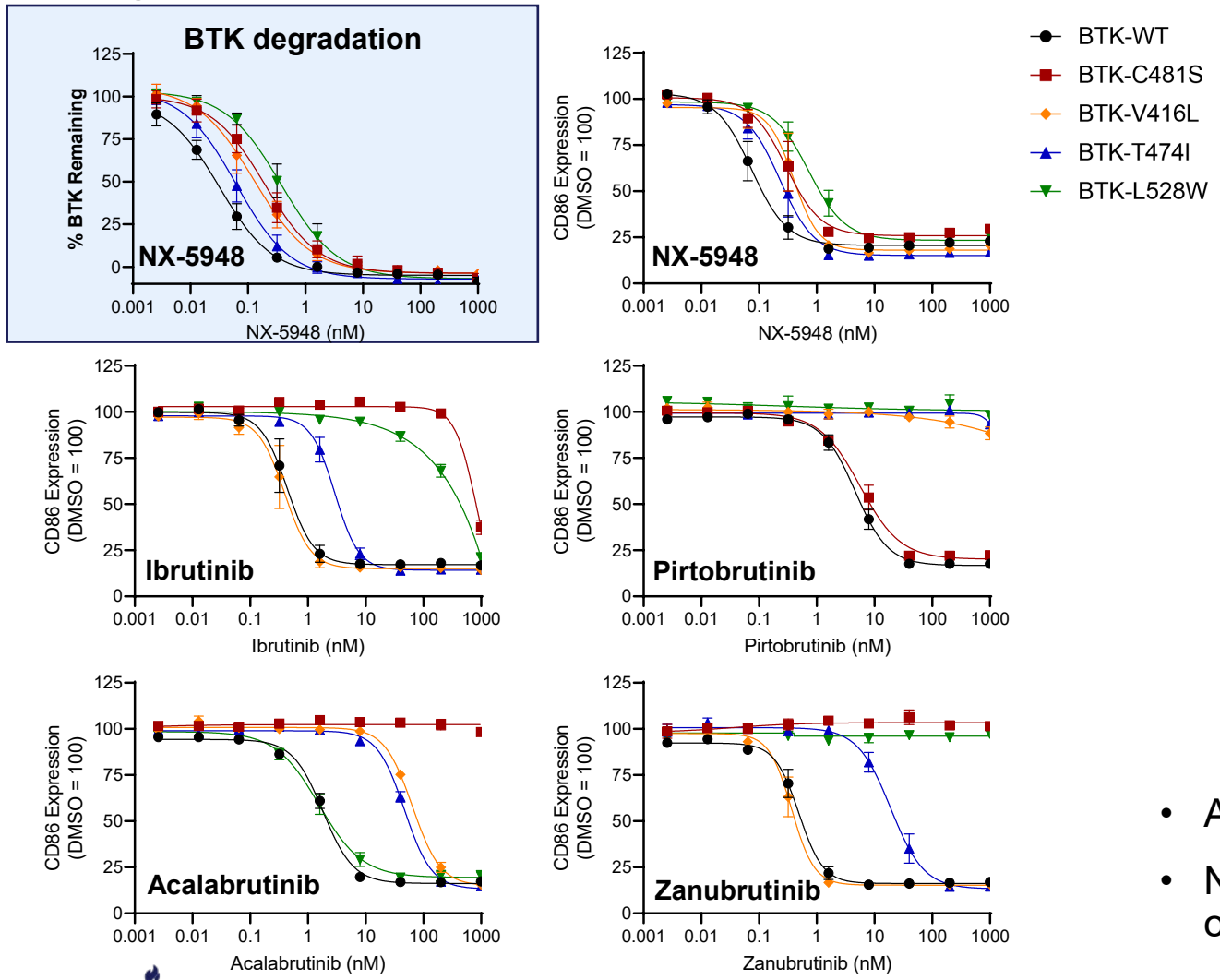
	Binding Determined by FRET Displacement Assay, IC_{50} (nM)						
	NX-5948	Pirtobrutinib	Vecabrutinib	Fenebrutinib	Ibrutinib*	Acalabrutinib*	Zanubrutinib*
BTK-WT	0.77	0.76	0.38	0.68	1.4	27	2.7
BTK-C481S	1.7	0.83	0.44	0.69	6.2	467	101
BTK-V416L	17	130	144	21	3.8	4101	4.7
BTK-T474I	0.67	13	2.7	2.7	1.8	189	12
BTK-L528W	20	>1000	84	7.6	>1000	240	>1000
BTK-M437R	1.2	47	1.0	114	0.28	53	0.61

*IC_{50} determined at 60 min for Ibrutinib, Acalabrutinib and Zanubrutinib
IC_{50}s reported here are mean of at least 3 experiments

Acquired resistance mutations reduce the binding of covalent and non-covalent BTK inhibitors to BTK

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

BTK degradation and activation marker suppression in TMD8 tumor cells



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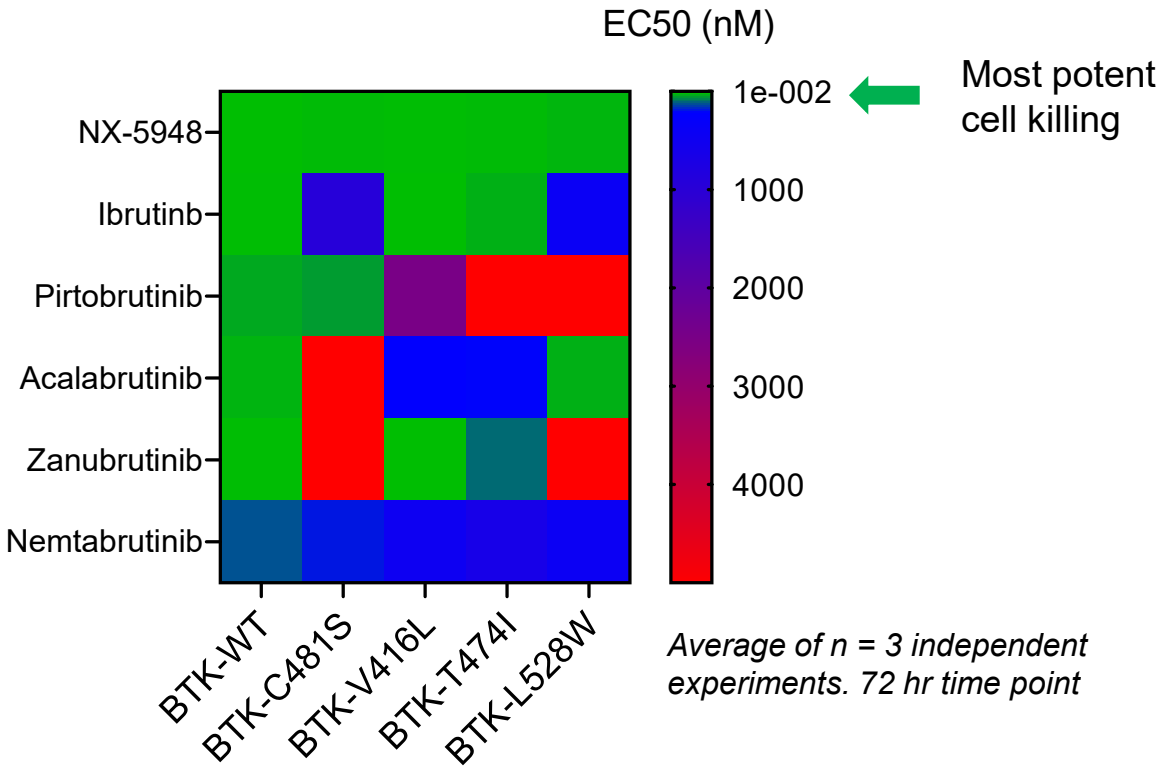
TMD8 tumor cell killing

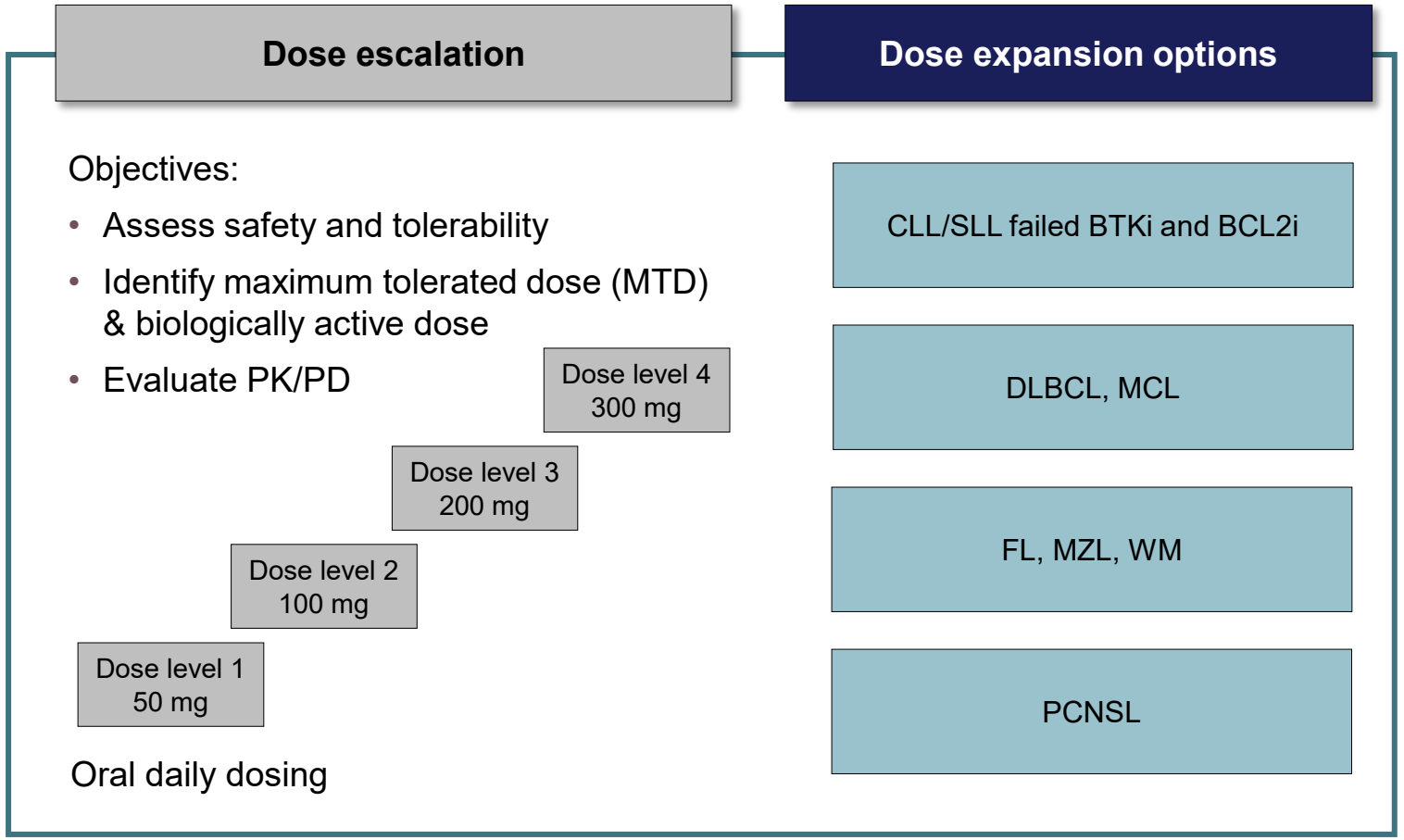


Average of n = 3 independent experiments. 72 hr time point

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

NX-5948-301: Trial Design

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

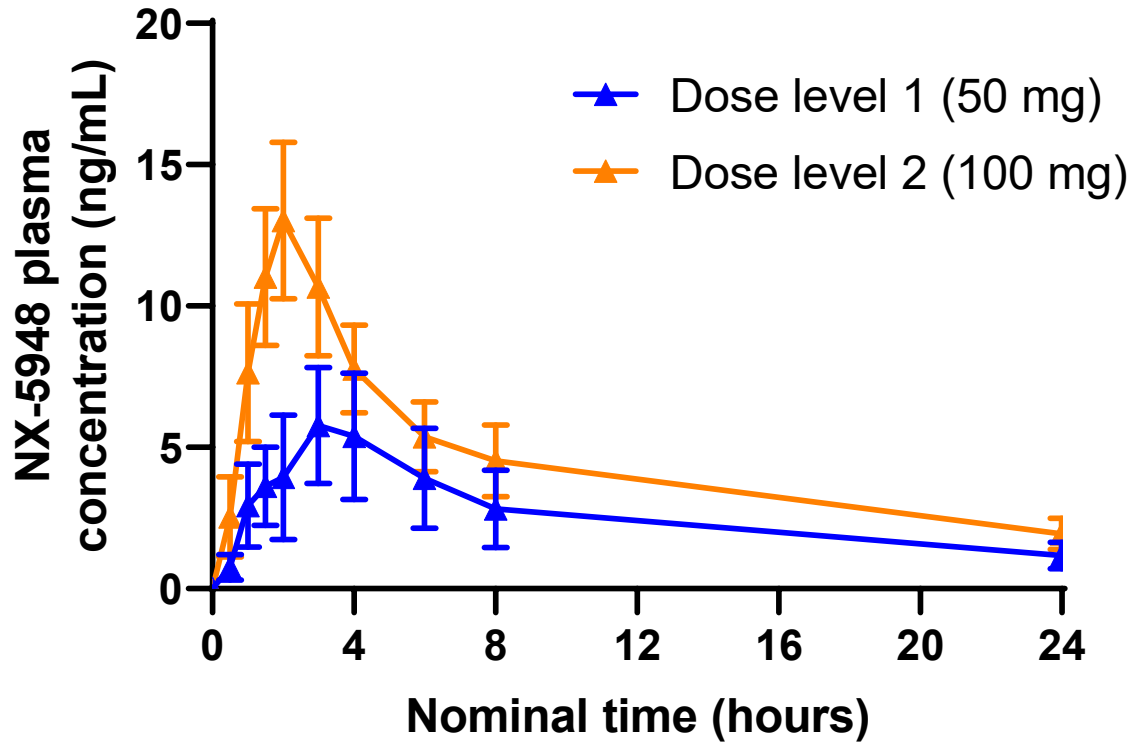


- Phase 1a dose escalation is ongoing at clinical sites in the U.S. and U.K.
- Anticipate initiating expansion cohort(s) in H2 2023

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 Suggests NX-5948 Exhibits Linear PK and Supports Daily Dosing

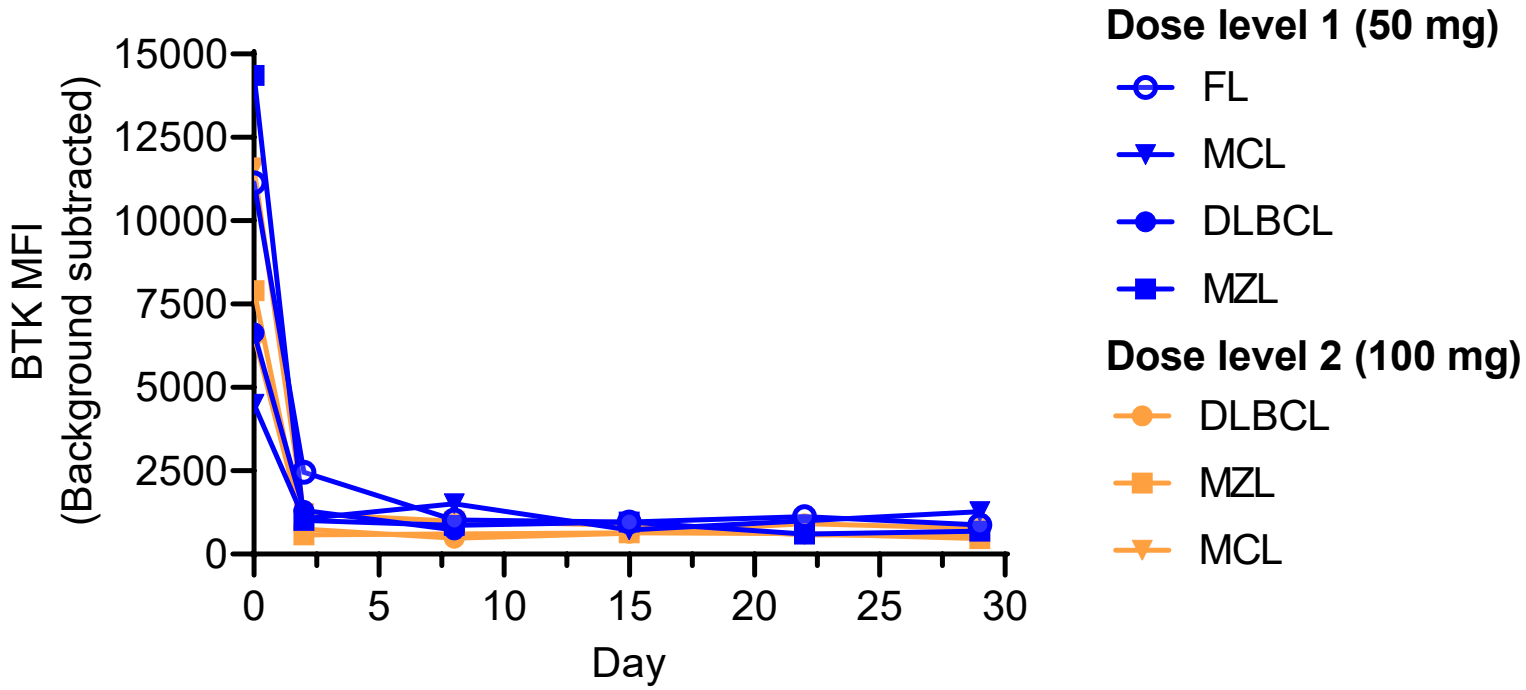
Mean (± SEM) Cycle 1 Day 1 pharmacokinetic profile of patients treated with NX-5948



Data cutoff: December 1, 2022

- Half-life ~12.6 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



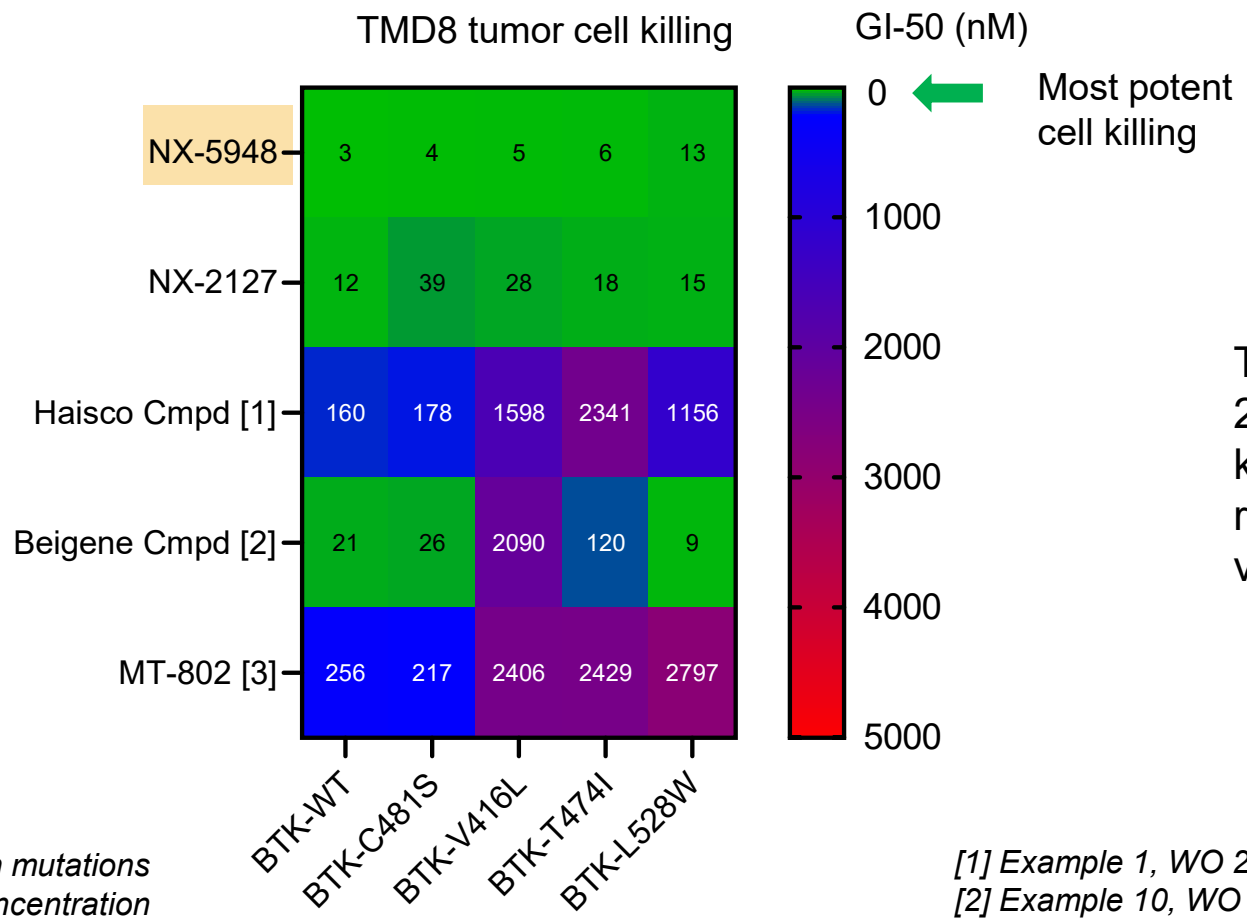
FL (follicular lymphoma), DLBCL (diffuse large B cell lymphoma), MCL (mantle cell lymphoma), MZL (marginal zone lymphoma)

Data cutoff: December 1, 2022

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

Not All BTK Degraders Are Created Equal

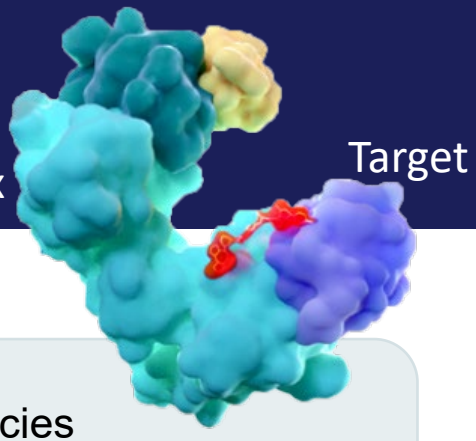


The ability of NX-5948 and NX-2127 to induce TMD8 tumor-cell killing was compared to other reported degraders in a 72-hour viability assay

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

[1] Example 1, WO 2022/111449 (Haisco)
[2] Example 10, WO 2021/219070 (BeiGene)
[3] Buhimschi et al. 2018. Biochemistry 57(26): 3564-3575.

Summary



Emergent BTKi-Resistant Mutations

- The use of BTK inhibition 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 BTK Degraders as "Next-Generation" Therapeutics

- Unlike an inhibitor, a degrader can address both the enzymatic and non-enzymatic scaffolding functions of a protein
- Degraders that display positive cooperativity are more resilient to resistance mutations
- Nurix's BTK degraders, NX-2127 and NX-5948, are potent against known and novel clinically relevant BTK inhibitor resistance mutations

Thank you!