nurix

Leader in Targeted Protein Modulation

Targeted Protein Degradation for Treatment of Hematologic Malignancies Addressing Both the Enzymatic and Scaffolding Functions of BTK Using NX-5948 and NX-2127 in the Clinic

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2nd Targeted Protein Degradation in Japan
Kanagawa, Japan
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Nurix Drugs Engage Ligases for the Treatment of Cancer

Targeted Protein Modulation: TPM = TPD + TPE

A Powerful Cellular System

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

Harness ligases to decrease specific protein levels

Targeted Protein Degradation (TPD)

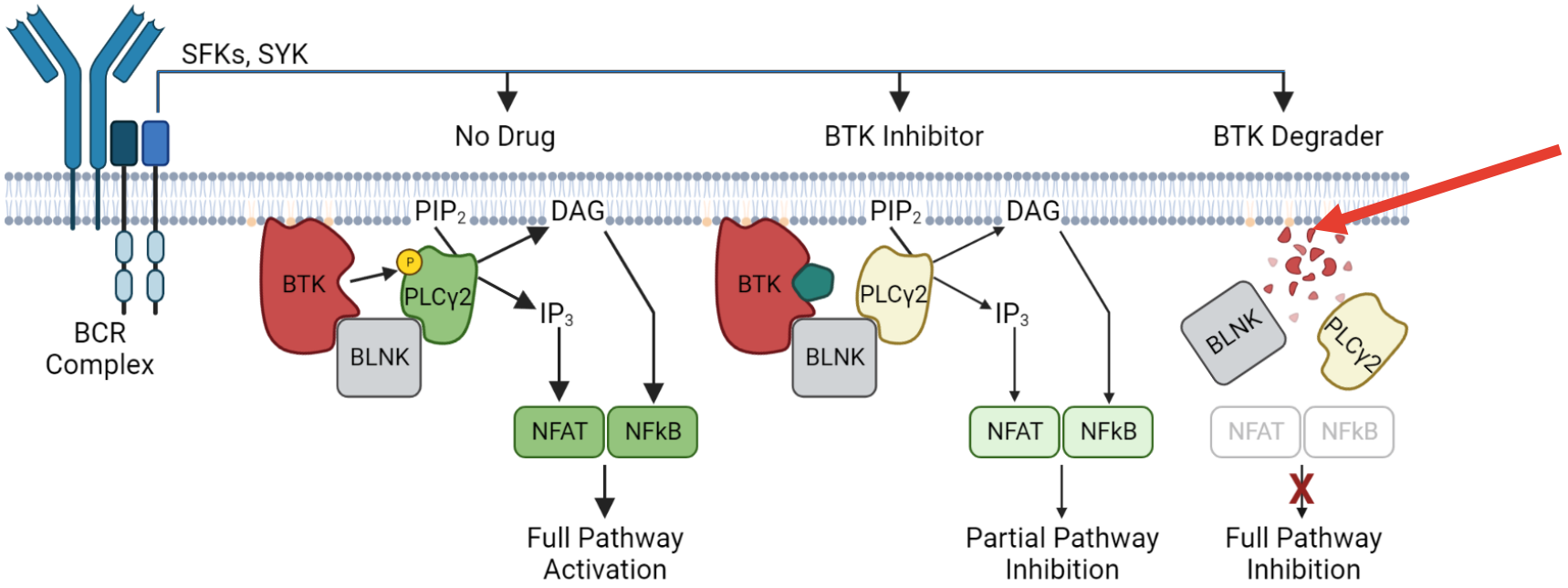
Targeted Protein Elevation (TPE)

Inhibit ligases to increase specific protein levels

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** Degrader	BTK-IKZF *Oral*	B-cell malignancies				
TPD	**NX-5948** Degrader	BTK *Oral*	B-cell malignancies				
TPD	**NX-0479 / GS-6791** Degrader	IRAK4 *Oral*	Rheumatoid arthritis and other inflammatory diseases			GILEAD	
TPE	**NX-1607** Inhibitor	CBL-B *Oral*	Immuno-Oncology				
TPM	Wholly owned & partnered	14 targets	Multiple				

Degraders Disrupt BCR Signaling More Effectively Than Inhibitors



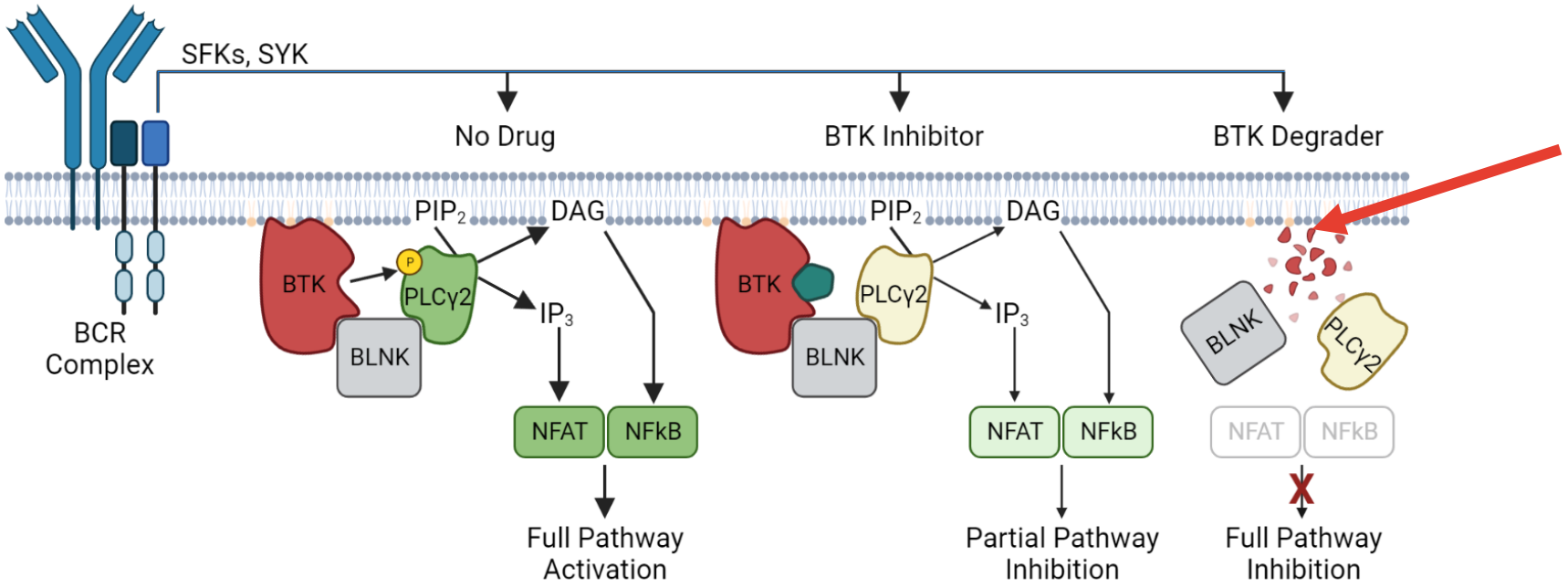
Removal of BTK disrupts the signaling complex effectively destroying the scaffolding function of the protein

Middendorp et al. Blood 2005
Woyach et al. NEJM 2014
Dhami et al. Sci.Signal 2022
Wang et al. NEJM 2022

Degraders Disrupt BCR Signaling More Effectively Than Inhibitors

Nurix Degraders:

1) Eliminate the scaffolding function of BTK oncogenic signals
2) Are effective against resistance mutations



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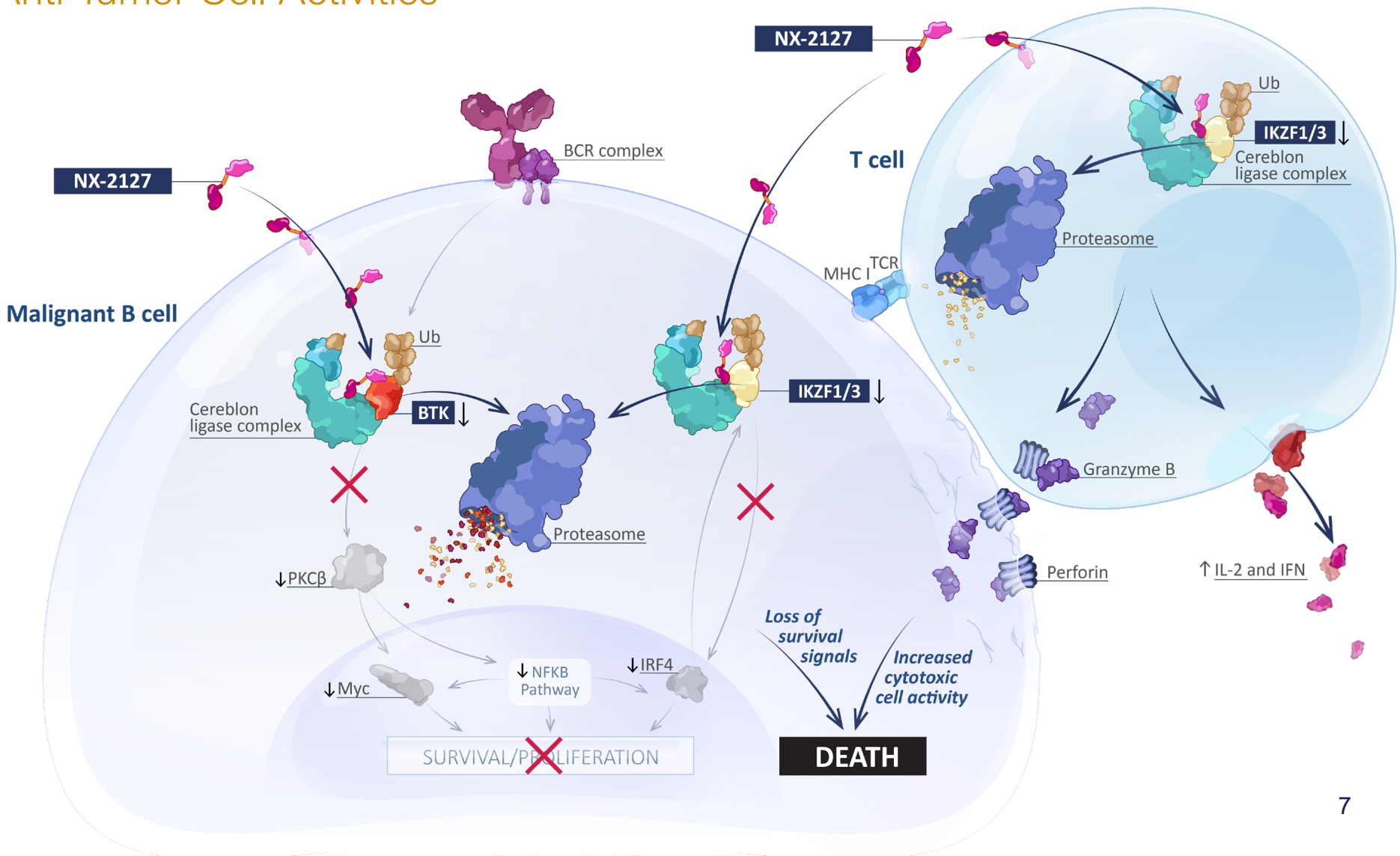
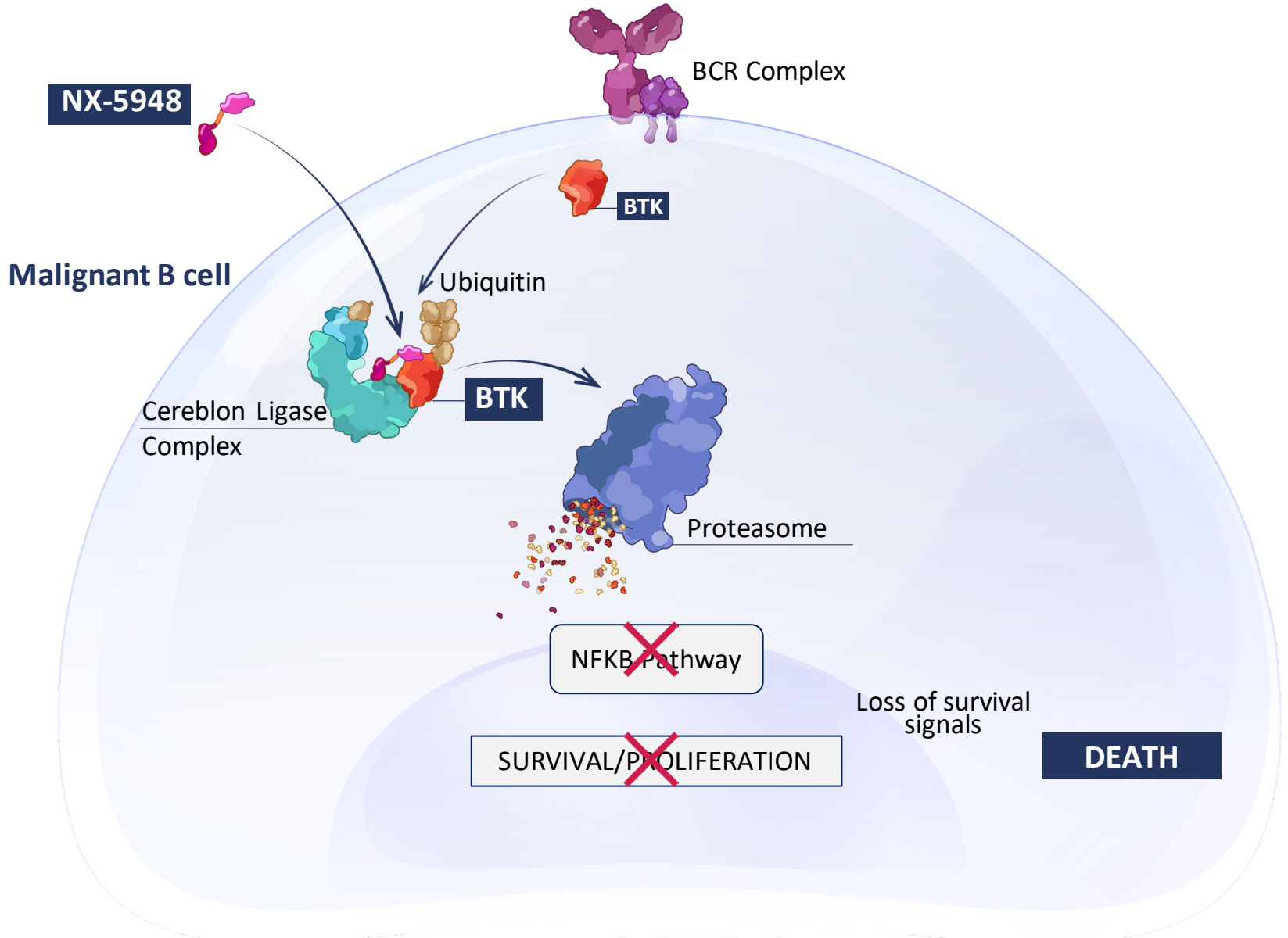
NX-2127 Dual Mechanism of Action

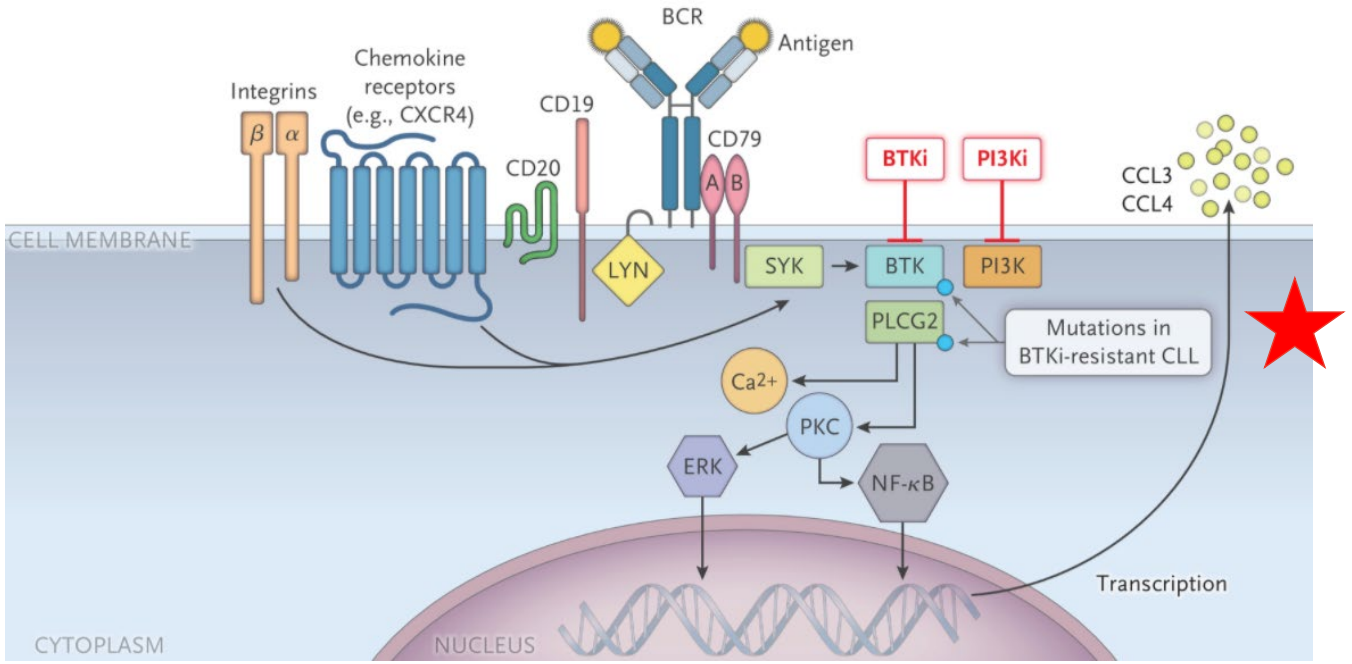
Targeted Degradation of BTK and IKZF1/3 Provides Both Intrinsic and Extrinsic Anti-Tumor Cell Activities



NX-5948 Is a Potent and Selective Degrader of BTK



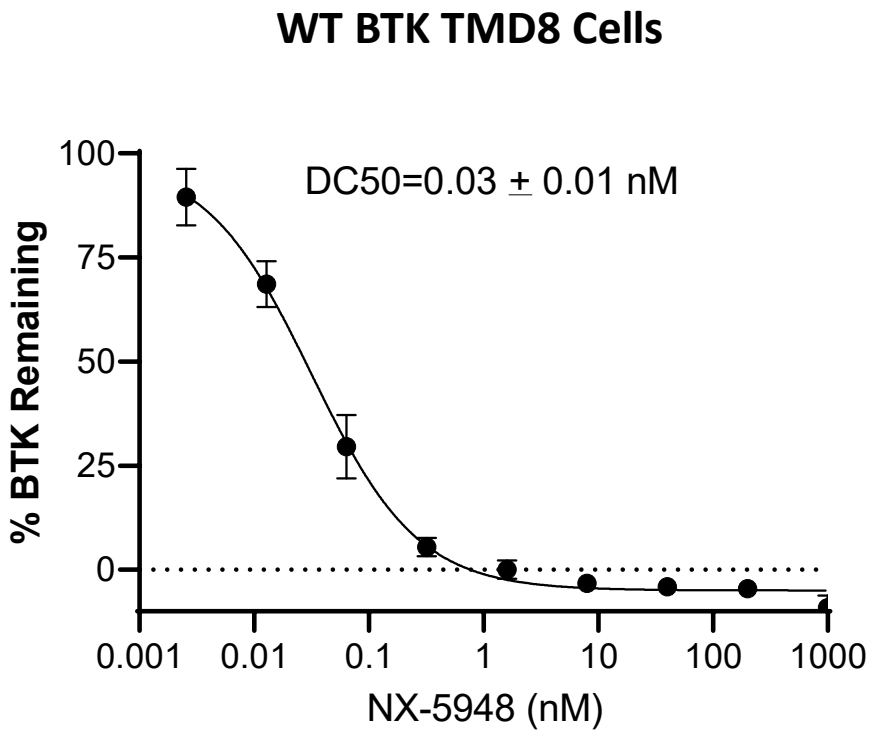
Treatment-Acquired Resistance to BTK Inhibitors Are an Increasing Clinical Challenge

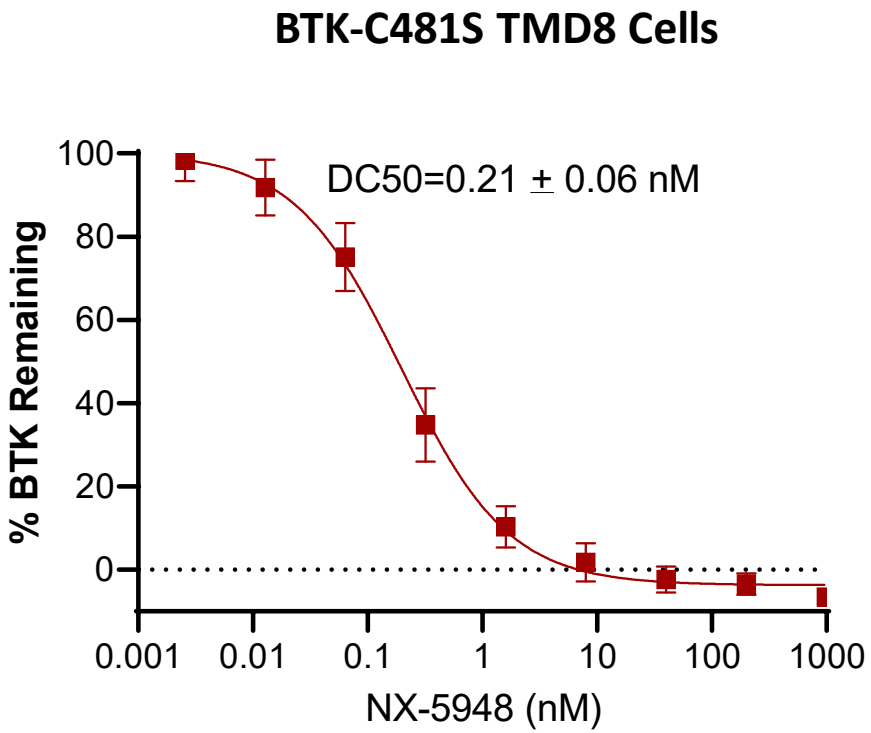


- Majority of patients have identified mutations in *BTK* C481 at the time of disease progression on ibrutinib; ~53-87% of patients
- Mutations also identified in PLCG2, immediately downstream of BTK
- *BTK* C481 mutations are also the main mechanism of resistance for acalabrutinib; 69% of patients

Figure from Burger et al NEJM 2020
Woyach et al. NEJM 2014; Burger Nature Communications 2016
Ahn et al. Blood 2017; Woyach et al. JCO 2017;
Woyach et al. ASH 2019; Scarfo et al. EHA 2020;
Wang et al. NEJM 2022

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

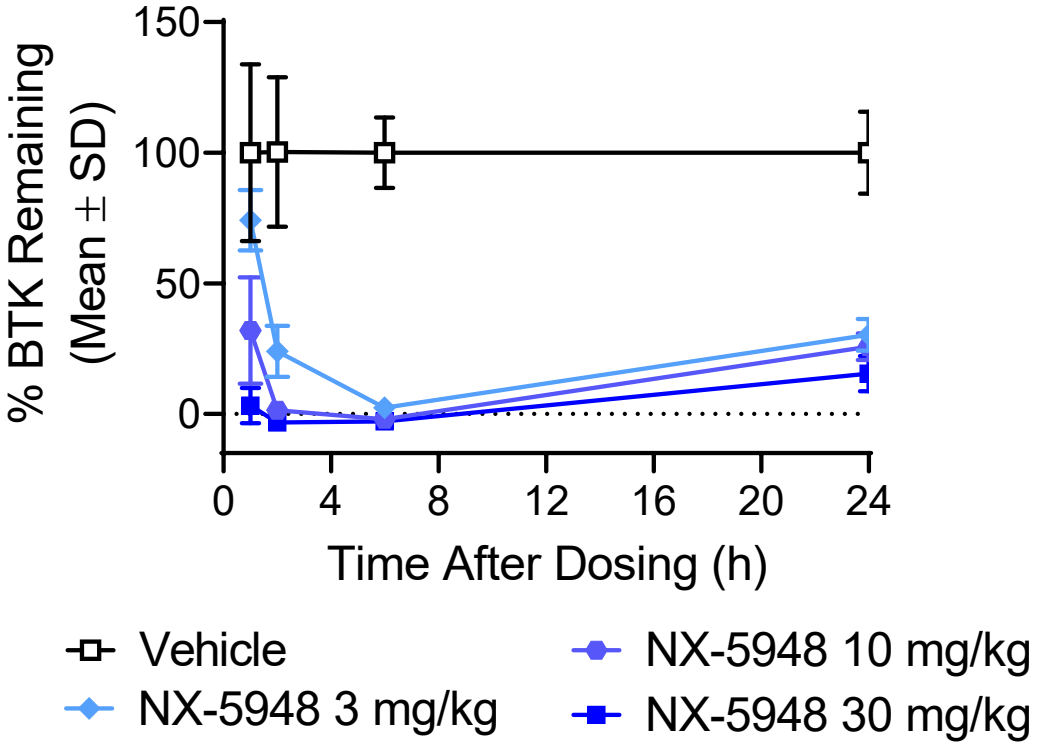




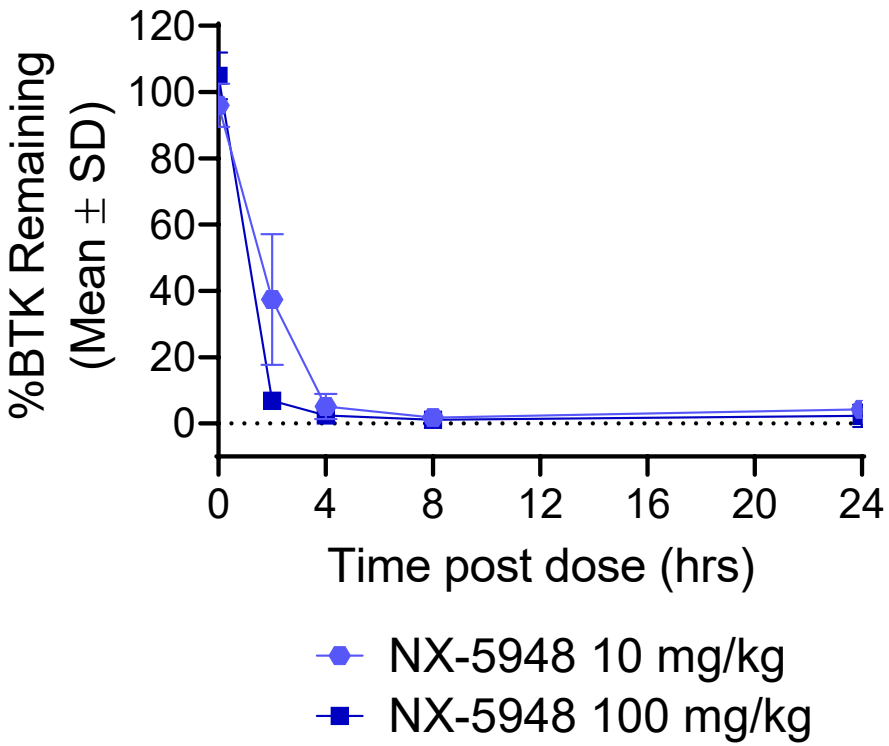
TMD8 cells harboring WT BTK or a knock-in BTK mutation (C481S) were incubated with NX-5948 for 24 hours, and BTK degradation was assessed by flow cytometry.

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



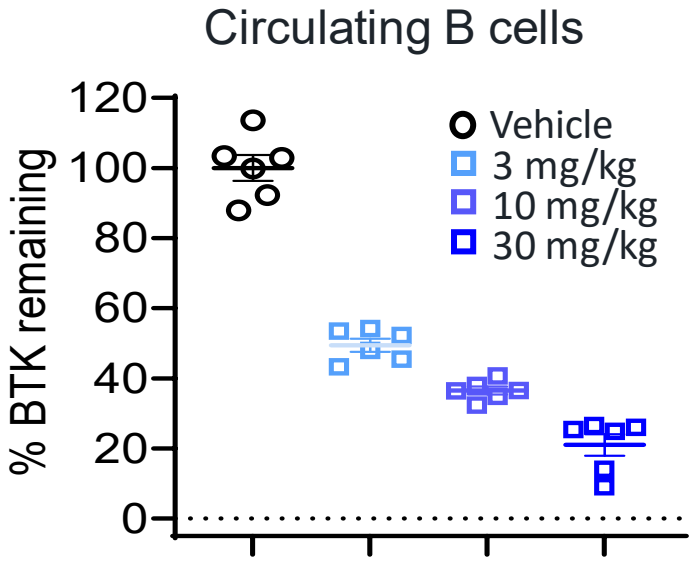
BTK Levels in Cyno Circulating B Cells

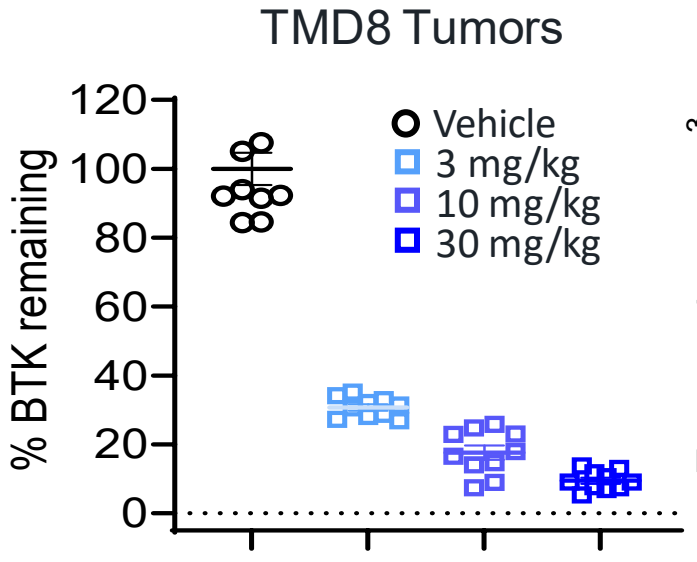


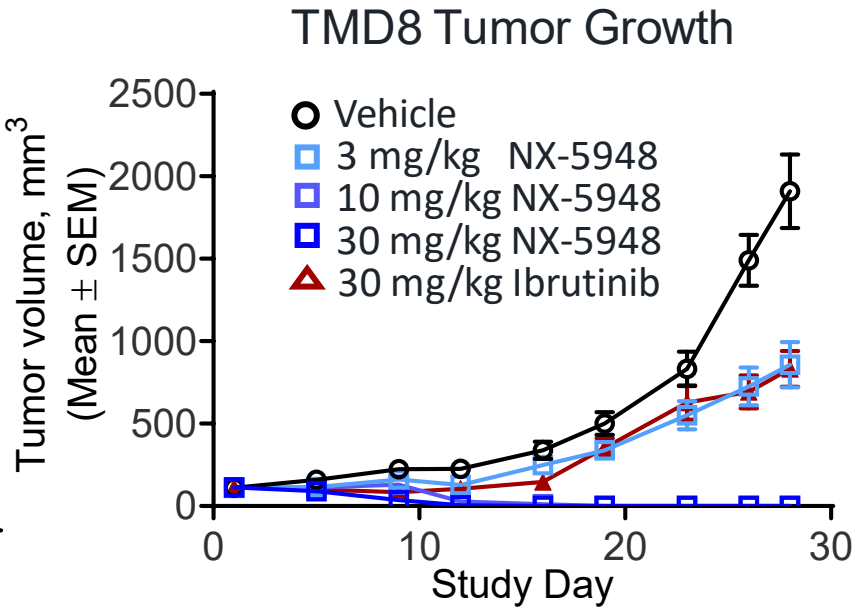
- In mice, BTK levels increased 24 hours after dosing from BTK resynthesis
- In cynomolgus monkeys, BTK levels remained suppressed at 24h

Rountree et al., TPD 2022

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







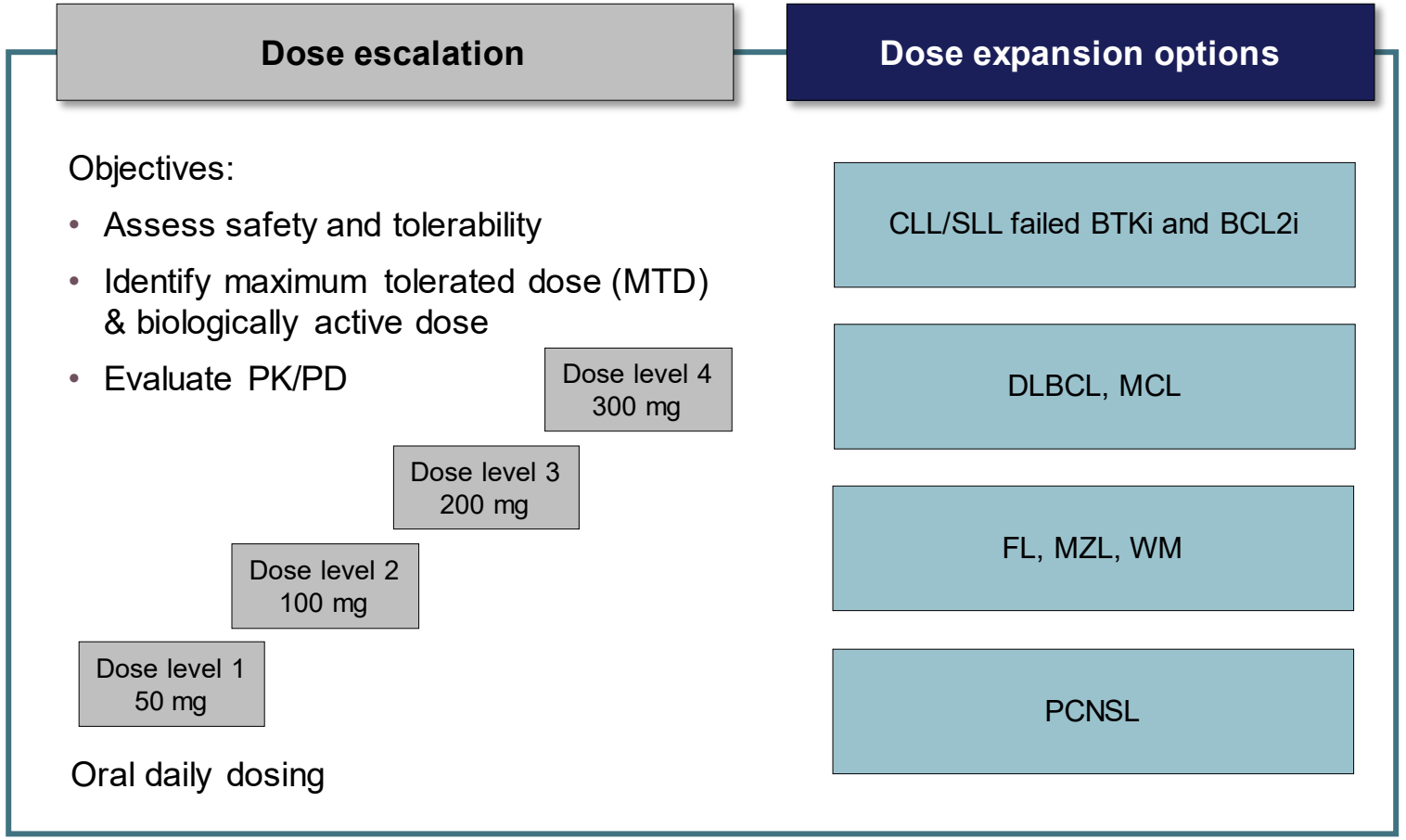
Treatment	Oral gavage dose (mg/kg)	% BTK degradation in circulating B cells	% BTK degradation in TMD8 tumor tissue	% TGI vs Vehicle (Day 26)	*P* value vs Vehicle
Vehicle	0	0.0±3.7	0.0±4.7	N/A	N/A
NX-5948	3	50.5±1.9	69.2±0.9	54%	0.0025
	10	63.5±1.1	82.4±2.1	100%	<0.0001
	30	79.0±3.1	90.5±0.5	100%	<0.0001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

Rountree et al., TPD 2022

NX-5948-301: Trial Design

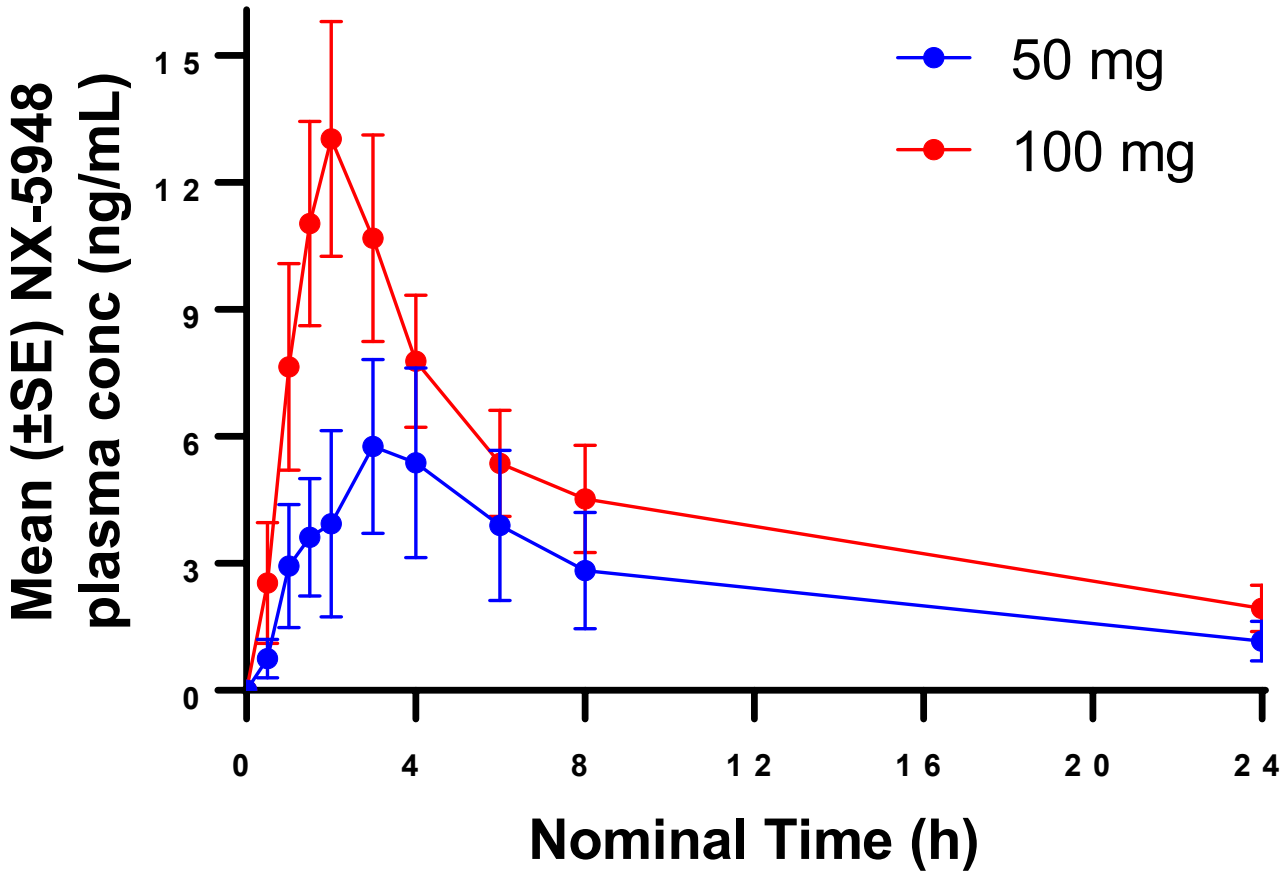
Phase 1 trial in adults with relapsed/refractory B-cell malignancies



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

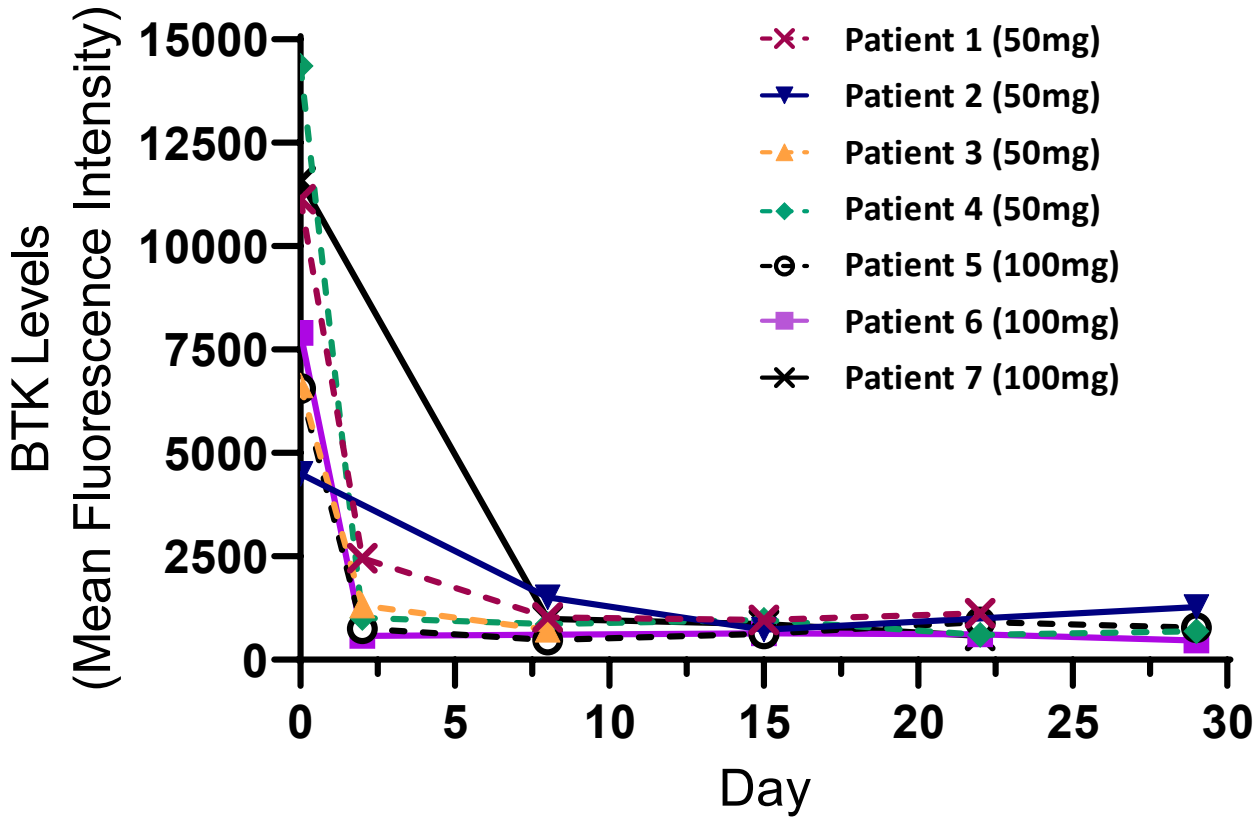
BTK, Bruton tyrosine kinase; **CLL**, chronic lymphocytic leukemia; **DLBCL**, diffuse large B-cell lymphoma; **FL**, follicular lymphoma; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **PCNSL**, primary CNS lymphoma; **PD,** pharmacodynamics; **PK,** pharmacokinetics; **WM**, Waldenstrom's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

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



- 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

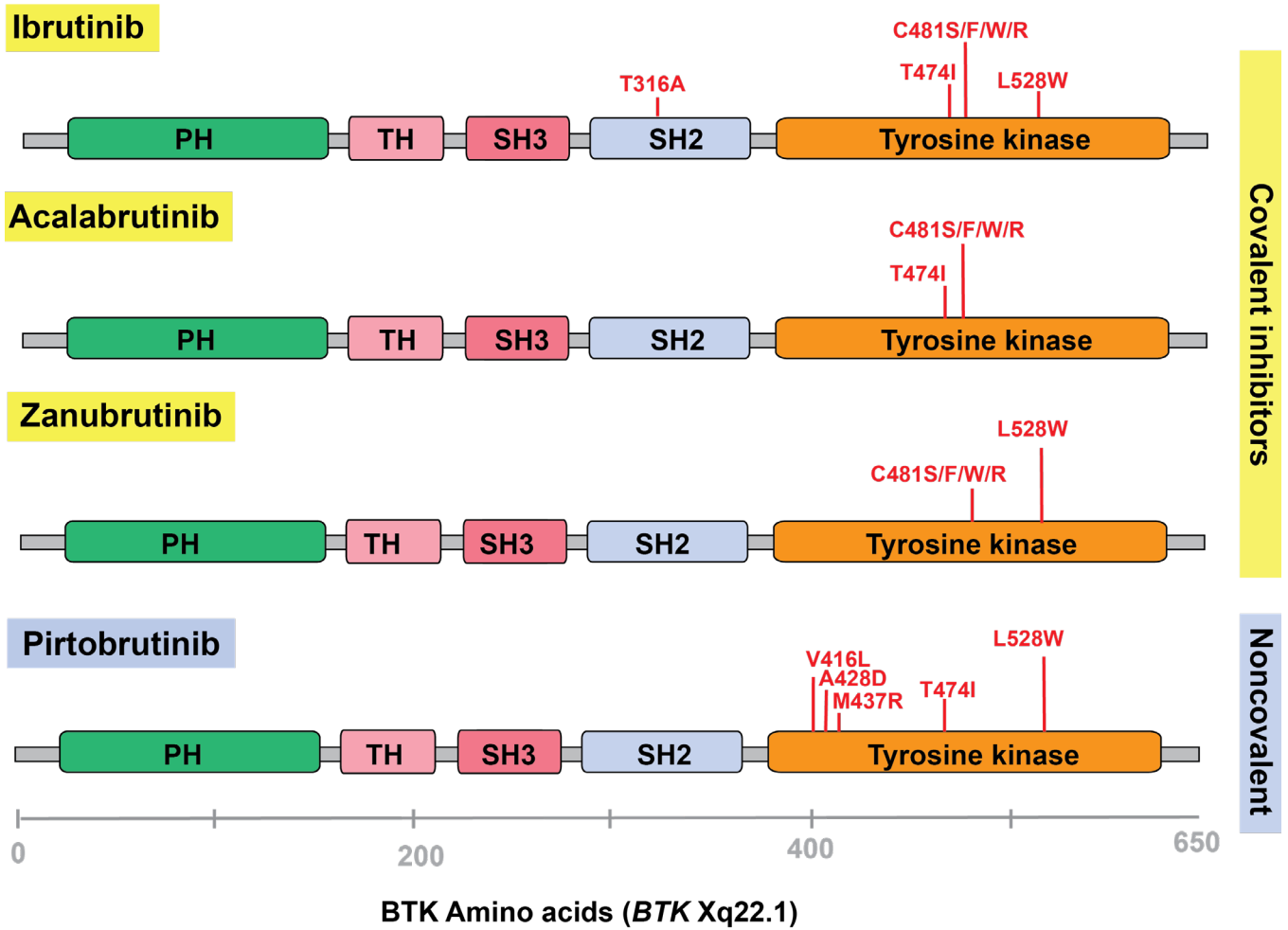


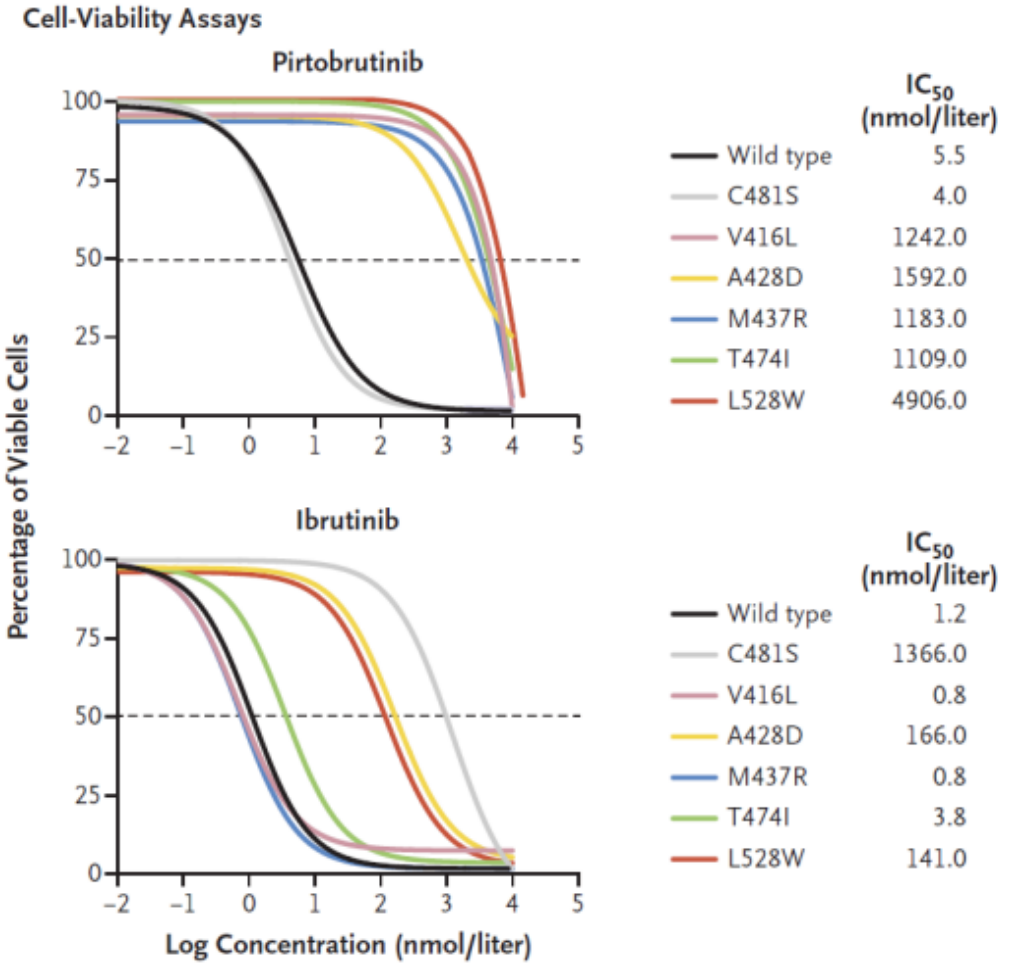
BTK levels are evaluated in real time in a FACS-based assay on whole blood from patients treated with NX-5948

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





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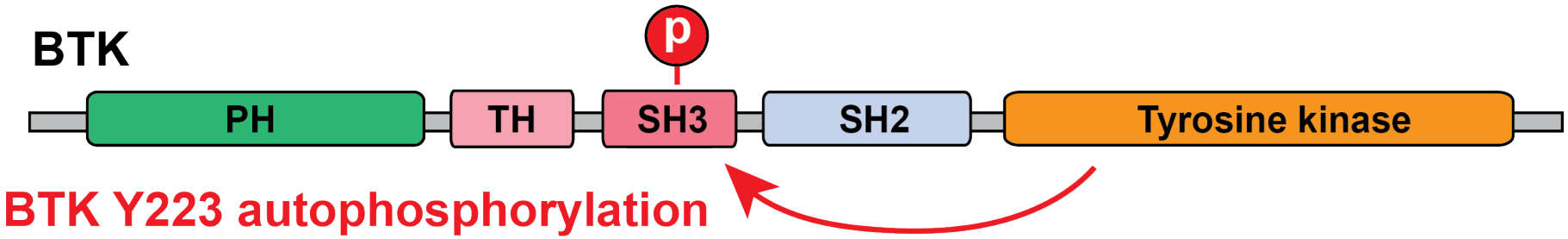
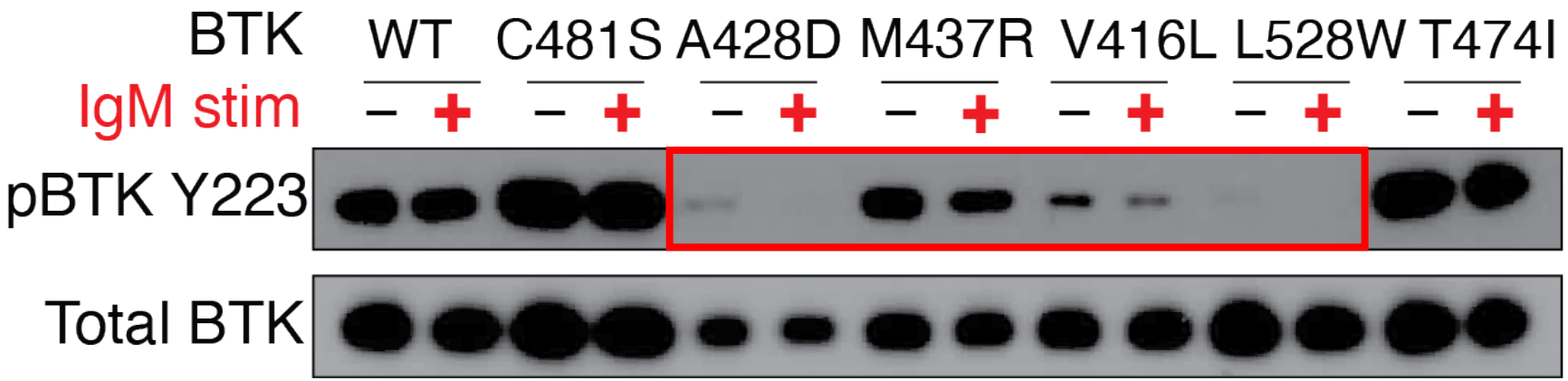
Montoya et al., ASH 2022

Wang, Mi, Thompson, et al. NEJM 2022

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

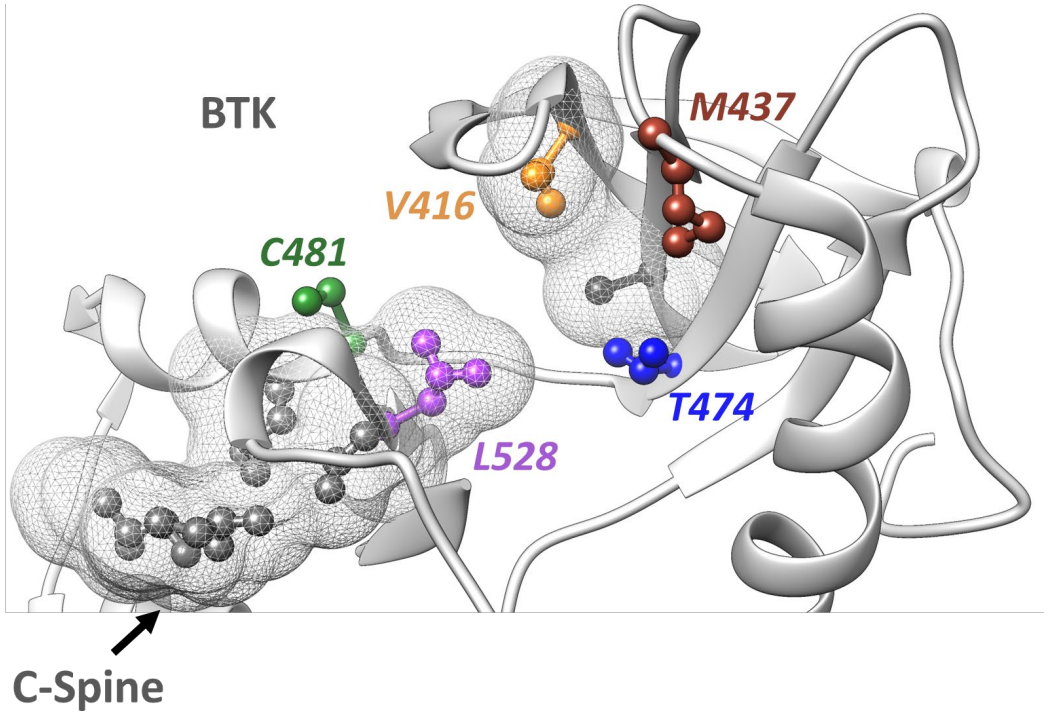




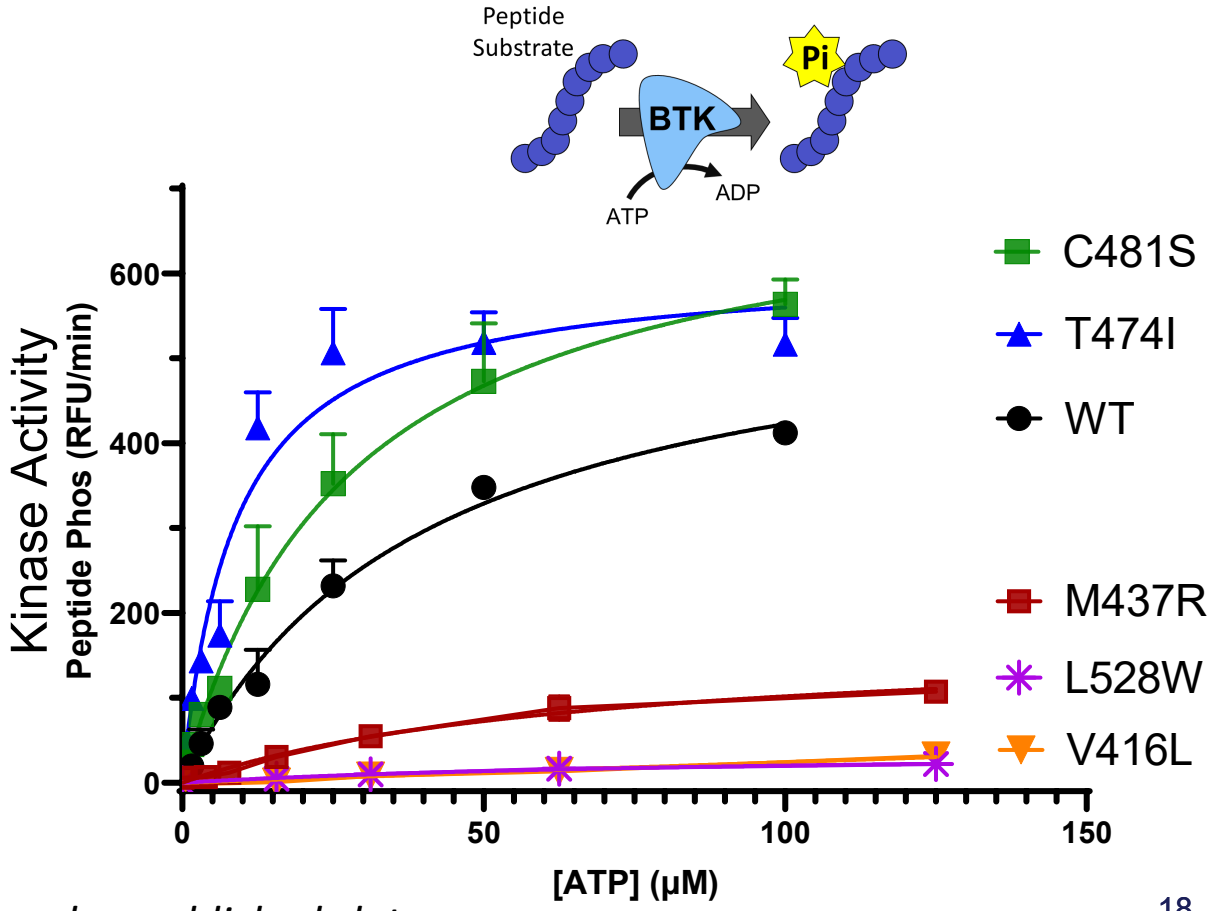
Wang, Mi, Thompson, et al. NEJM 2022

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

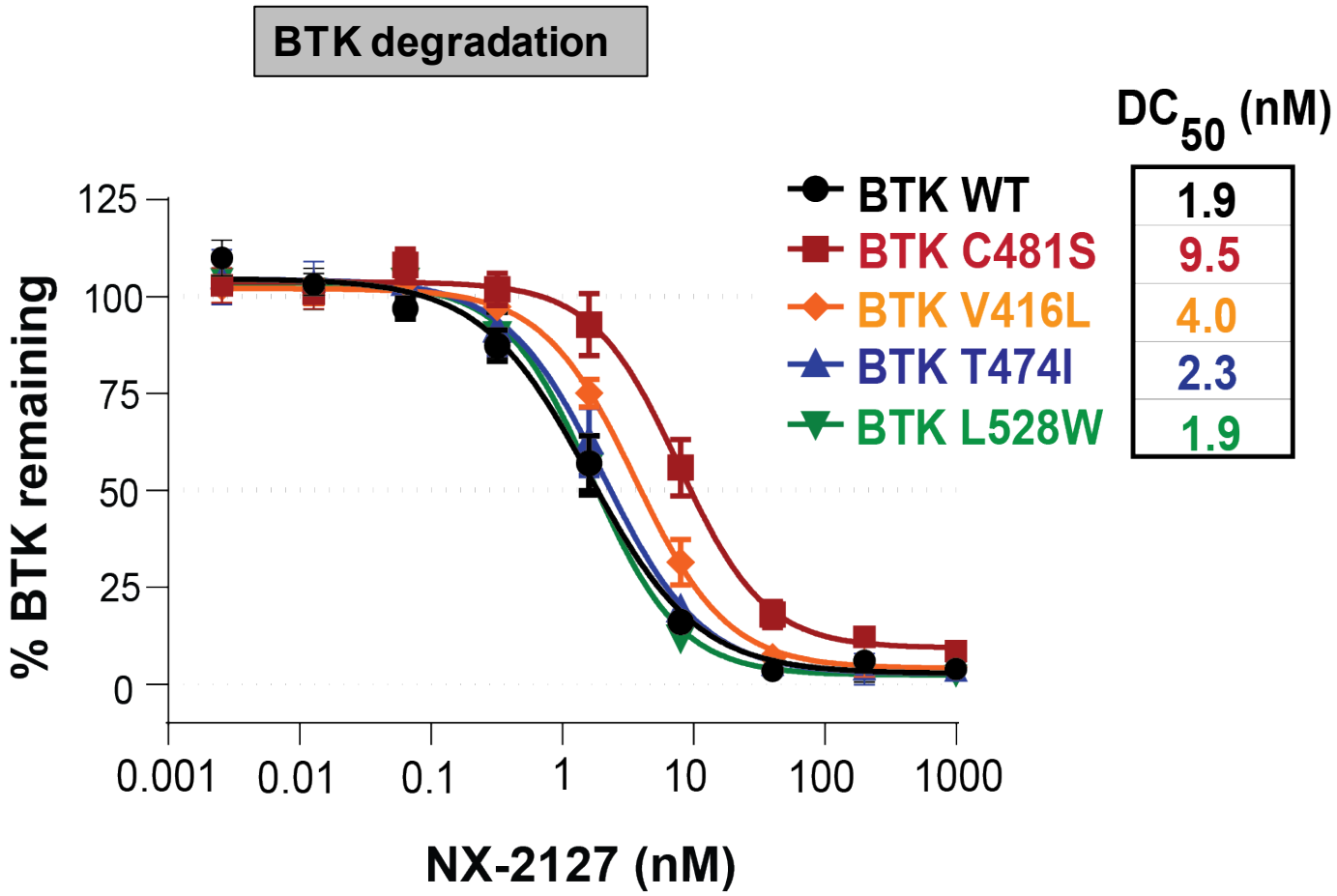


Some mutations that confer resistance to BTK lack kinase activity yet still potentiate BCR signaling

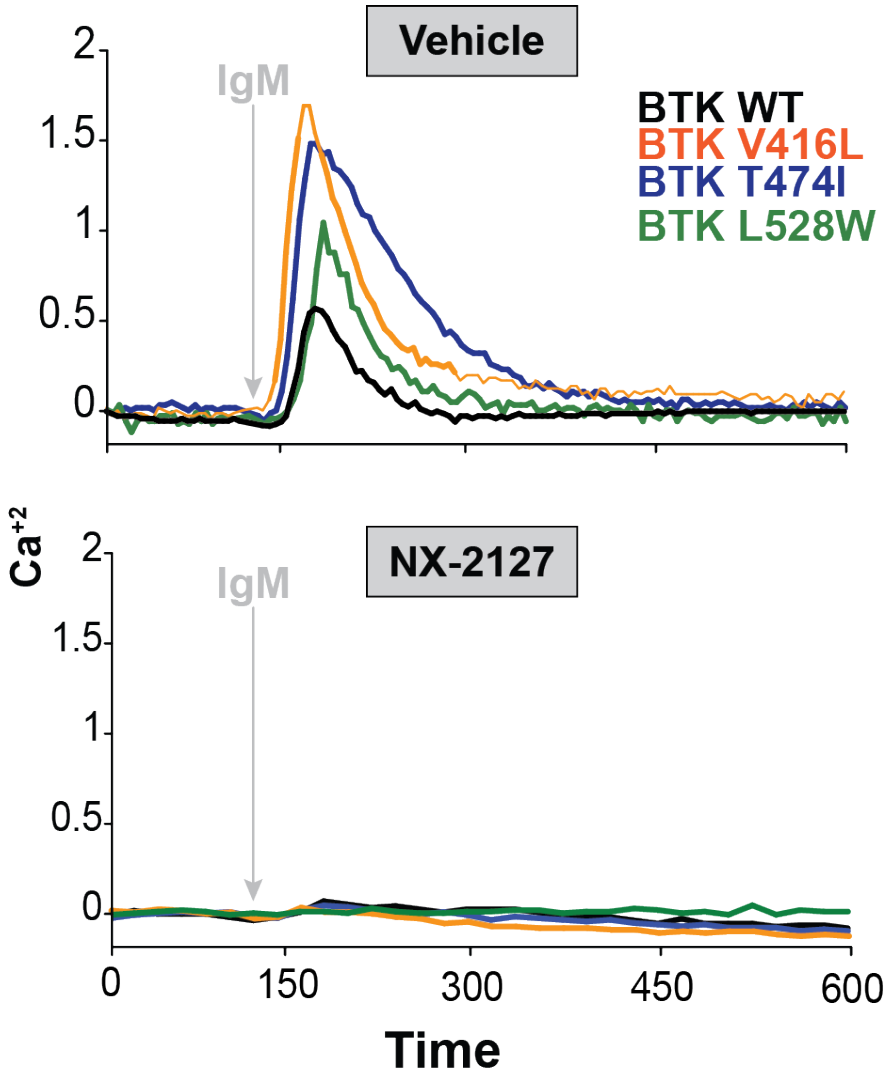


Montoya et al., ASH 2022 and unpublished data

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

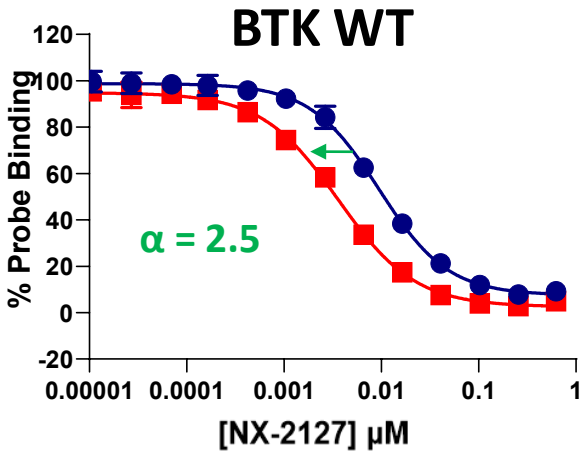


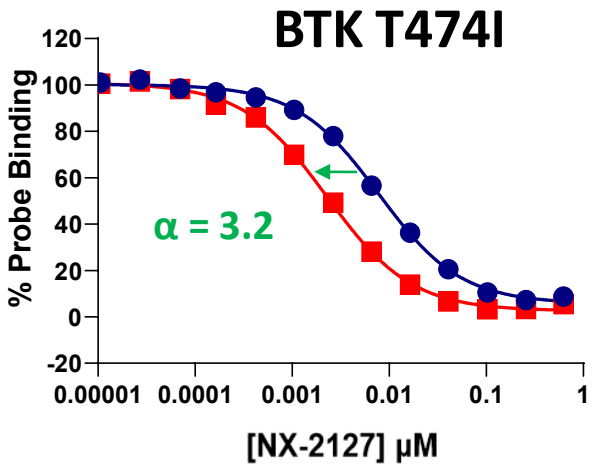
DC_{50} (nM)
1.9
9.5
4.0
2.3
1.9

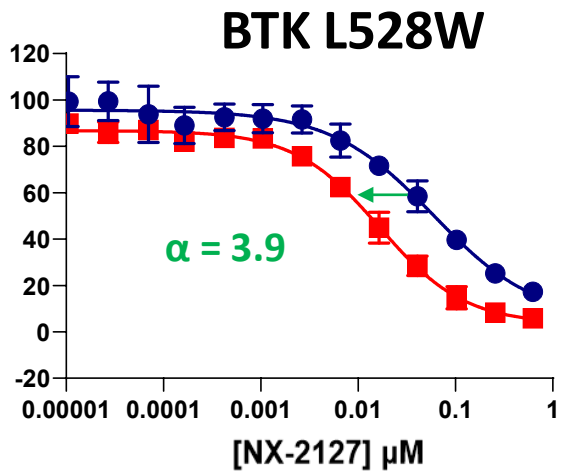


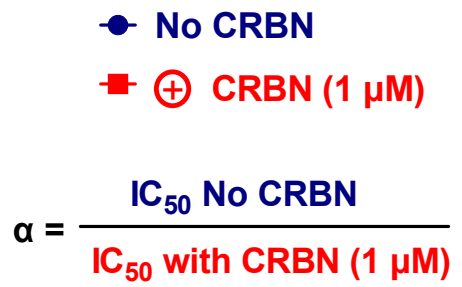
Montoya et al., ASH 2022

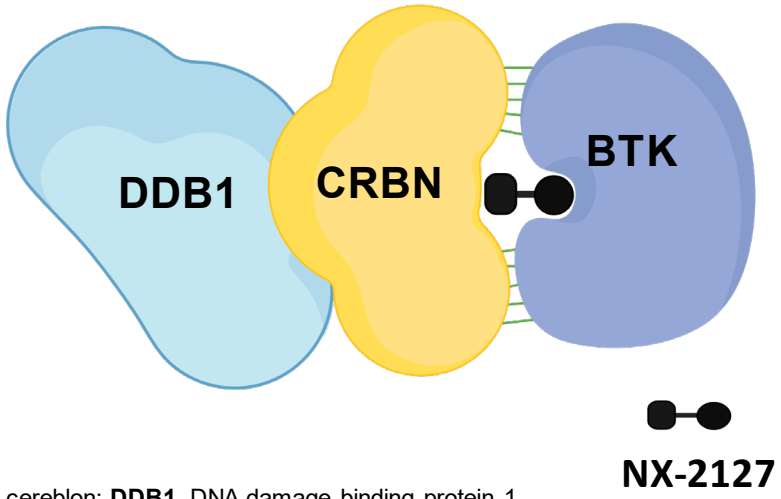
Nurix BTK Degraders Form Stable Ternary Complexes Between BTK and CRBN Irrespective of Mutation Status











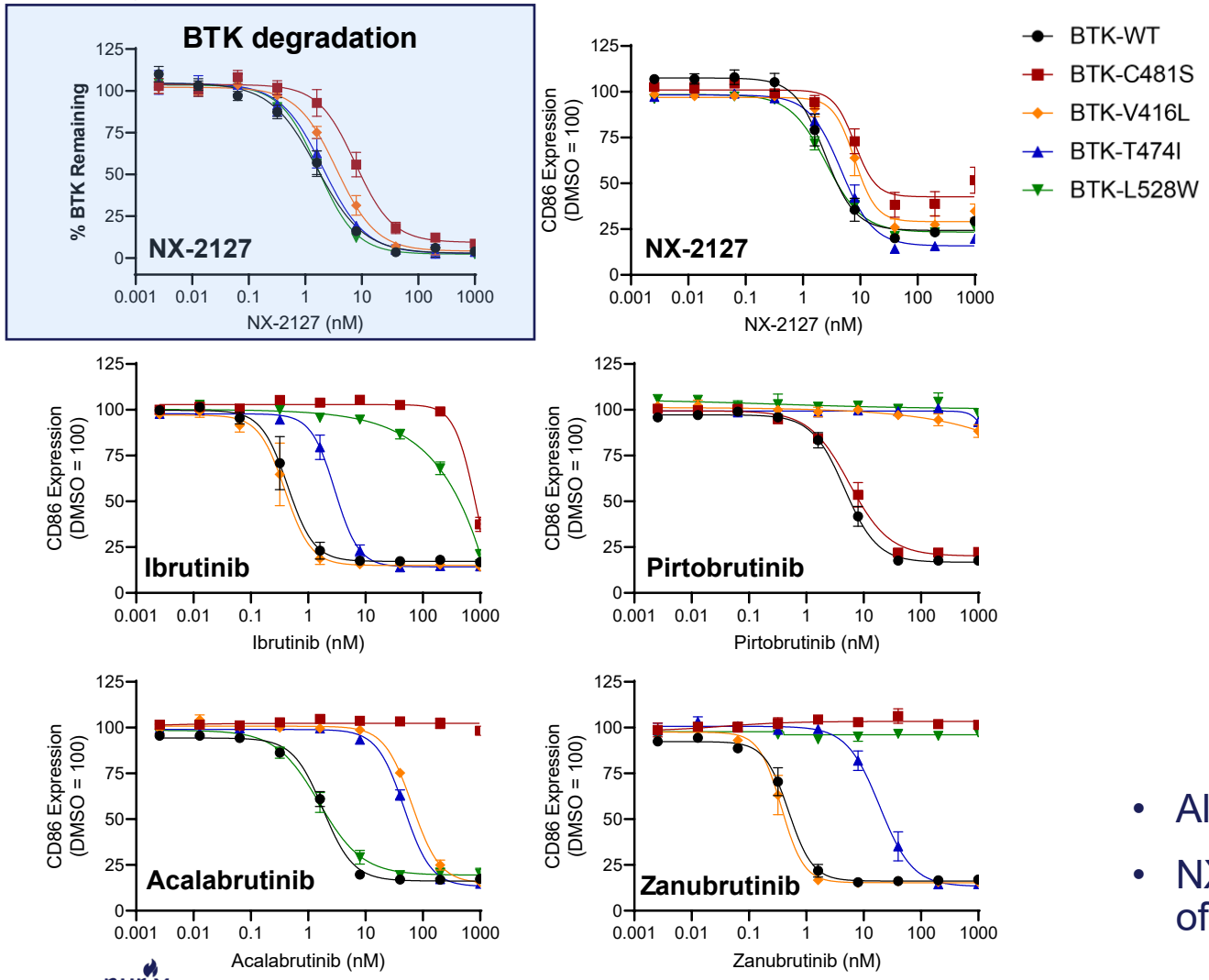
- Positive Cooperativity (α>1)
- Stable ternary complex
- Induced protein-protein interactions
- Greater tolerance for reduced binary affinity

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

Montoya et al., ASH 2022

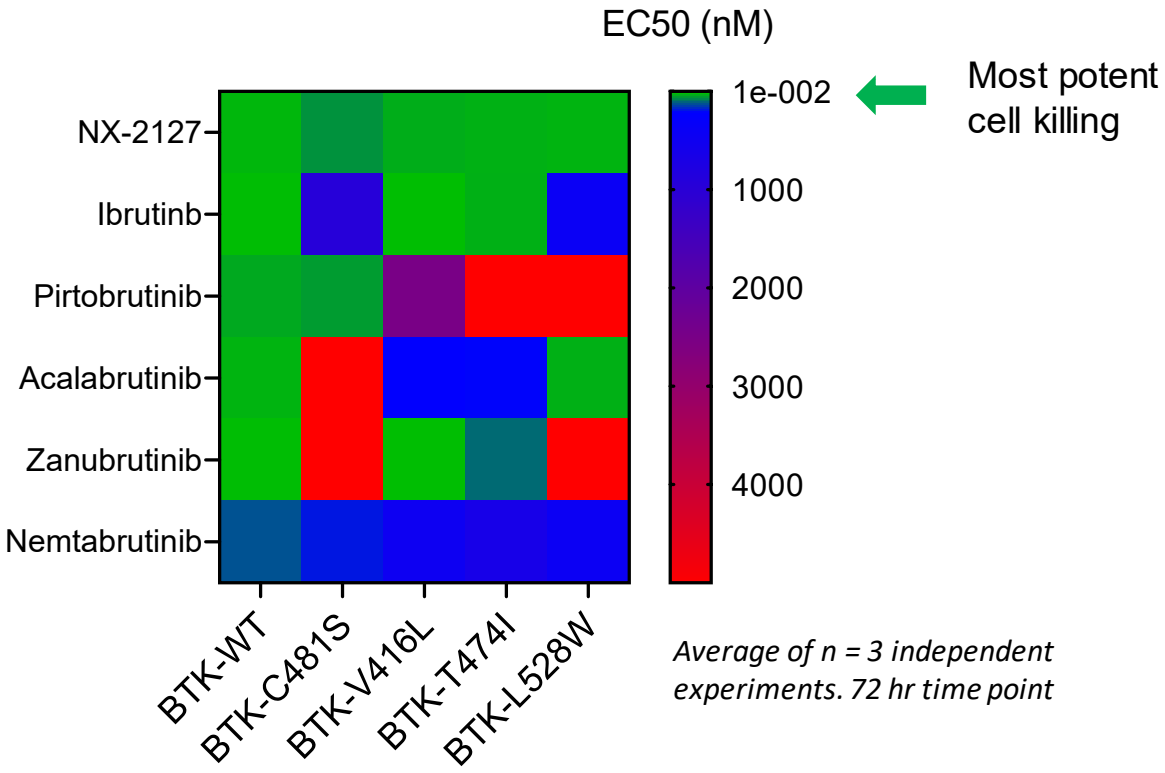
NX-2127 Is Potent and More Broadly Active Than All BTK Inhibitors Tested

BTK degradation and activation marker suppression in TMD8 tumor cells



Average of n = 3 independent experiments +/- SEM

TMD8 tumor cell killing

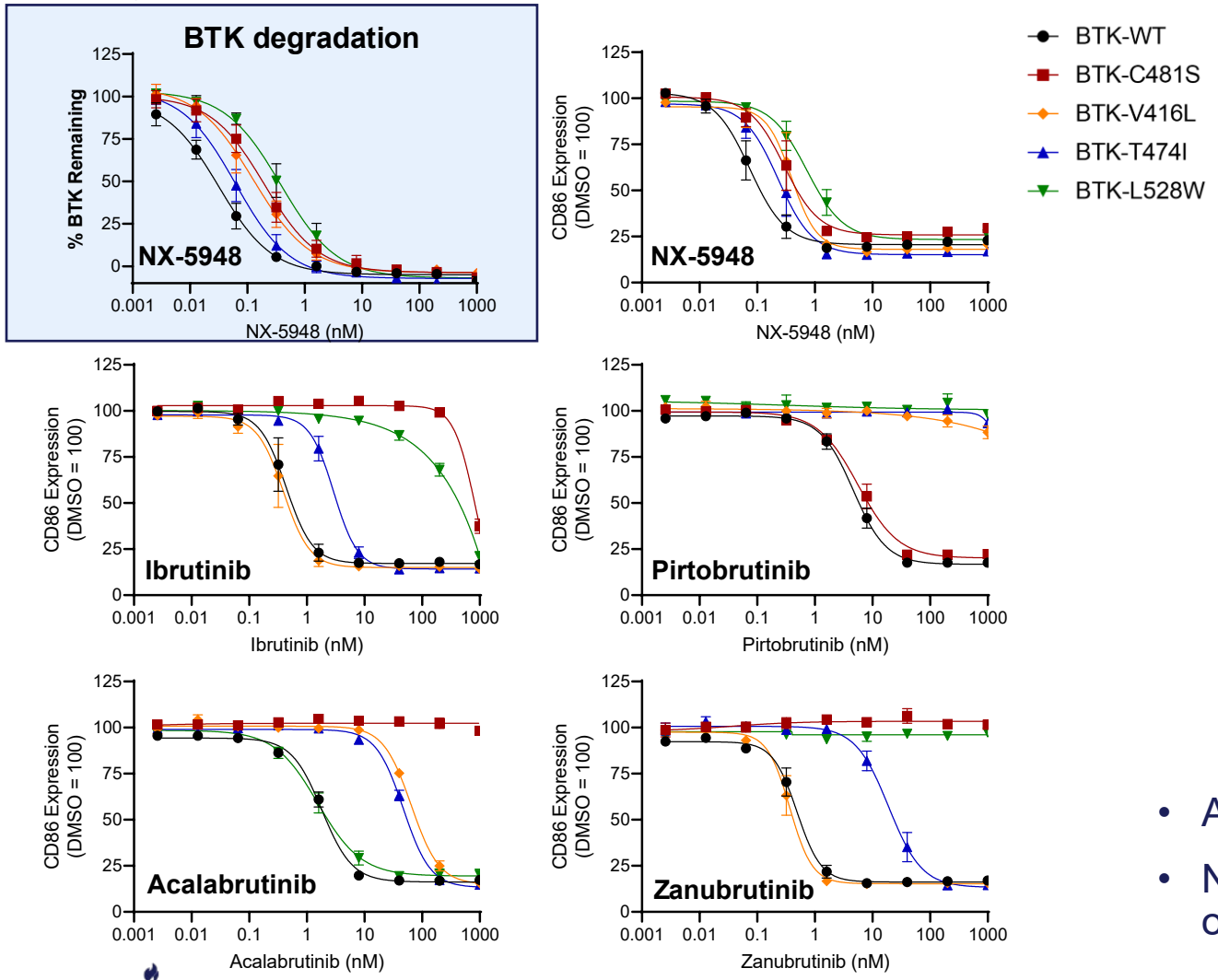


Average of n = 3 independent experiments. 72 hr time point

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

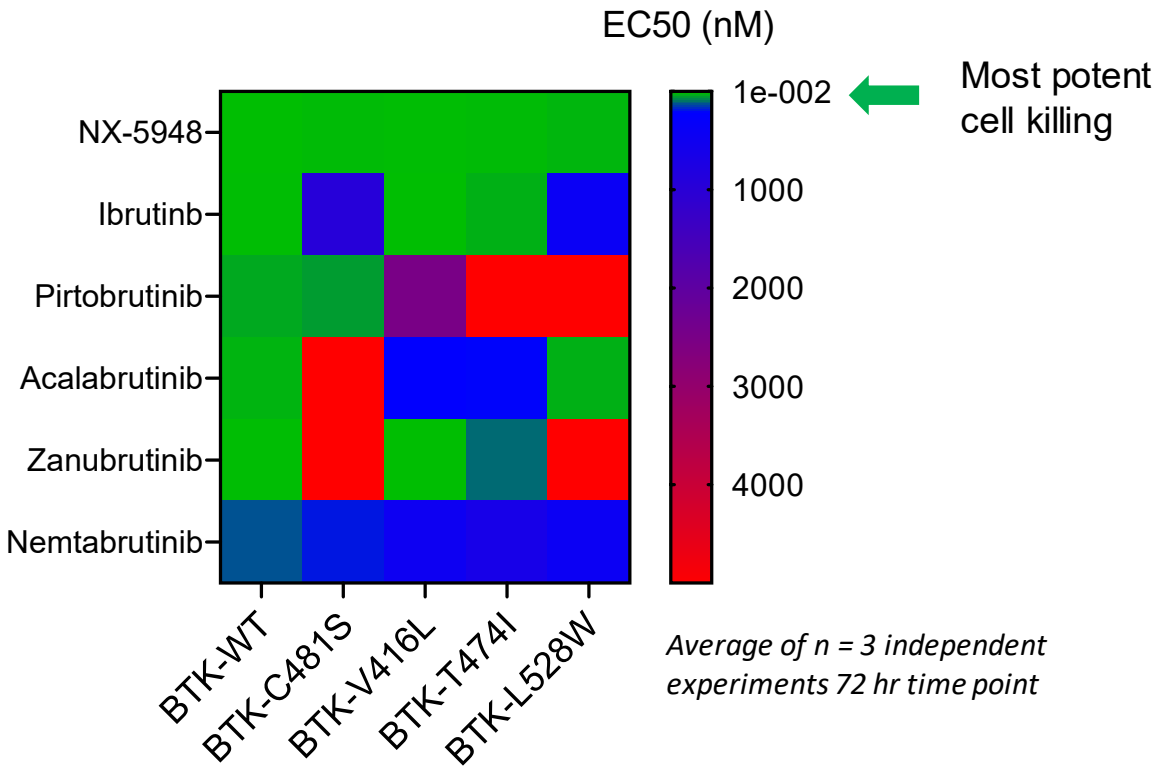
NX-5948 Is More Potent and Broadly Active Than All BTK Inhibitors Tested

BTK degradation and activation marker suppression in TMD8 tumor cells



Average of n = 3 independent experiments +/- SEM

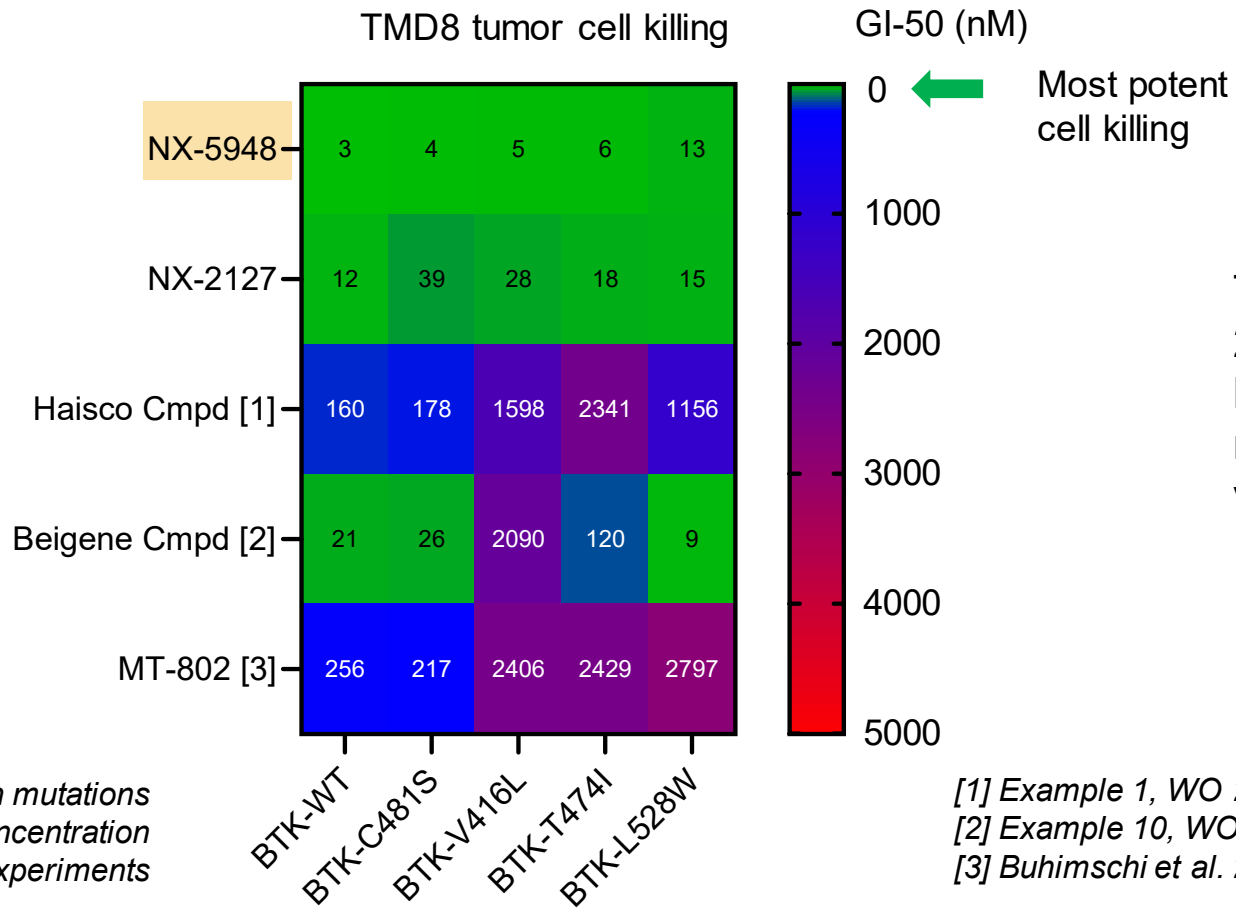
TMD8 tumor cell killing



Average of n = 3 independent experiments 72 hr time point

- 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



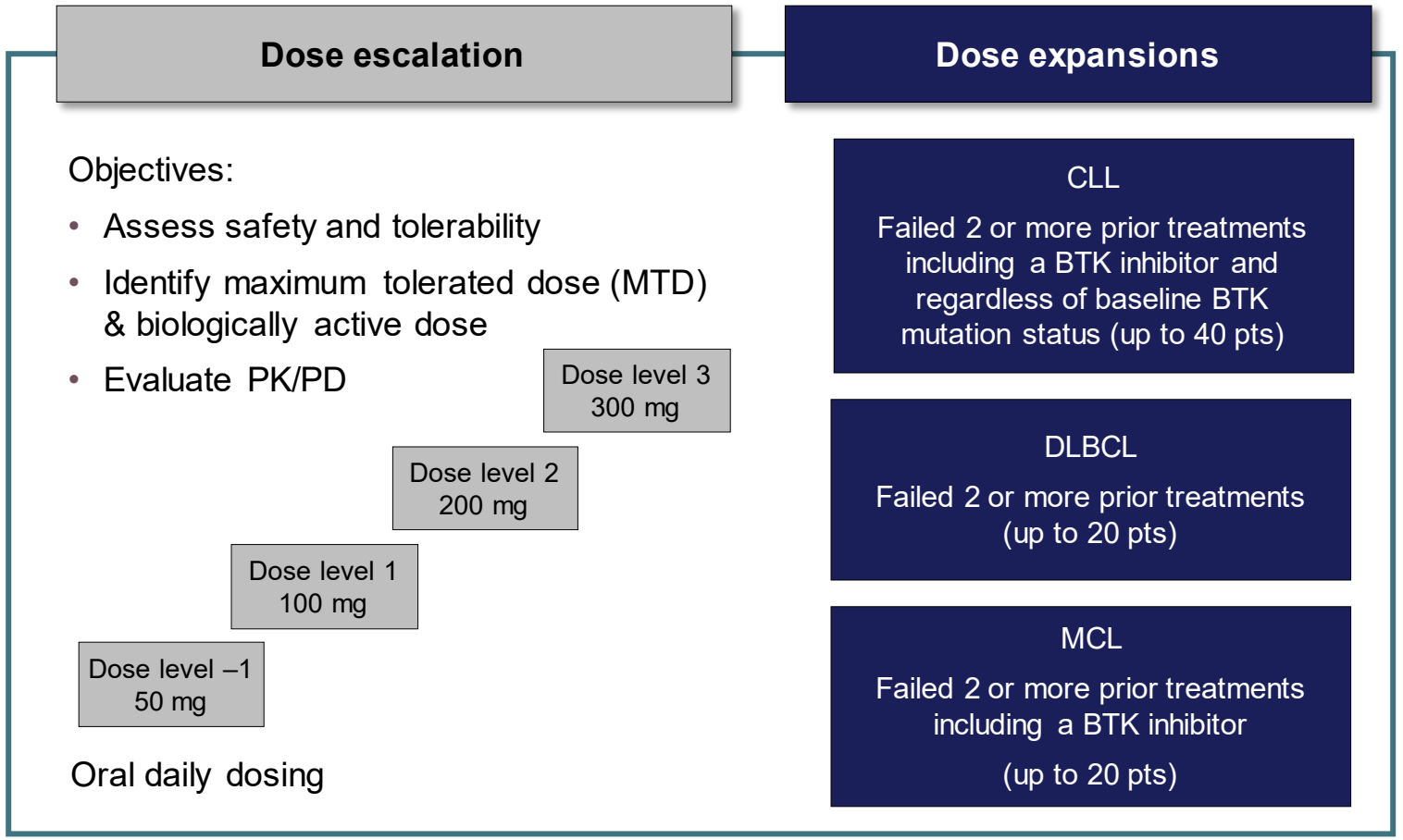
The ability of NX-5948 and NX-2127 to induce TMD8 tumor-cell killing was compared to other reported degraders in a 72-hour viability assay

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.

NX-2127-001: Trial Design

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



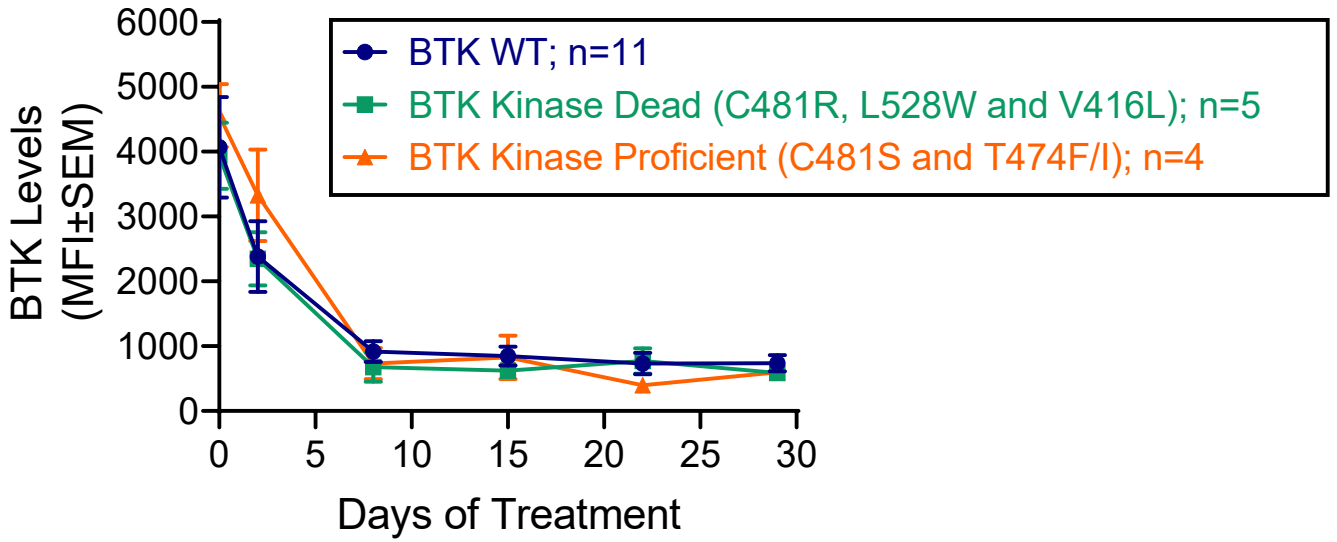
- CLL Phase 1b expansion cohort ongoing at 100 mg dose
- DLBCL Phase 1b expansion cohort ongoing at 300 mg
- MCL Phase 1b expansion cohort ongoing at 300 mg
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL

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

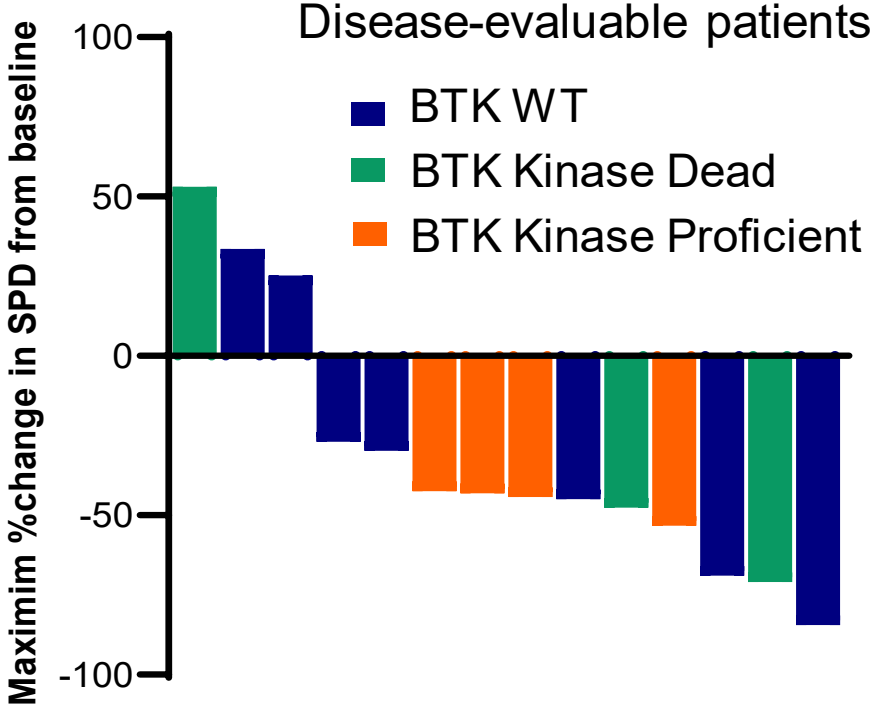
NX-2127 Preliminary Efficacy in Patients with CLL

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

Montoya, Dec. 2022 ASH

Mechanistic Rationale for Dual Degrader in DLBCL

CLINICAL TRIALS AND OBSERVATIONS

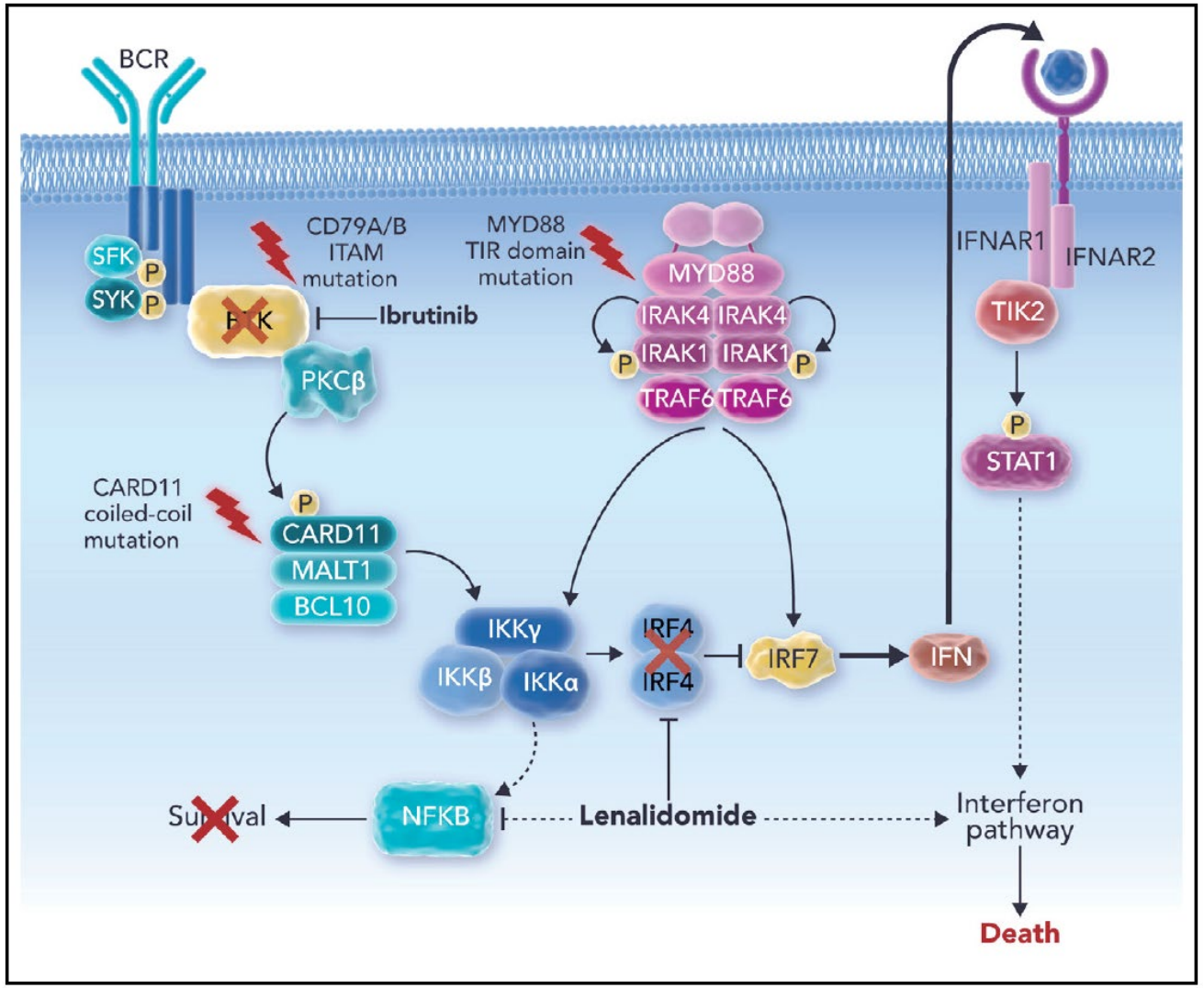
Comment on Goy et al, page 1024

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

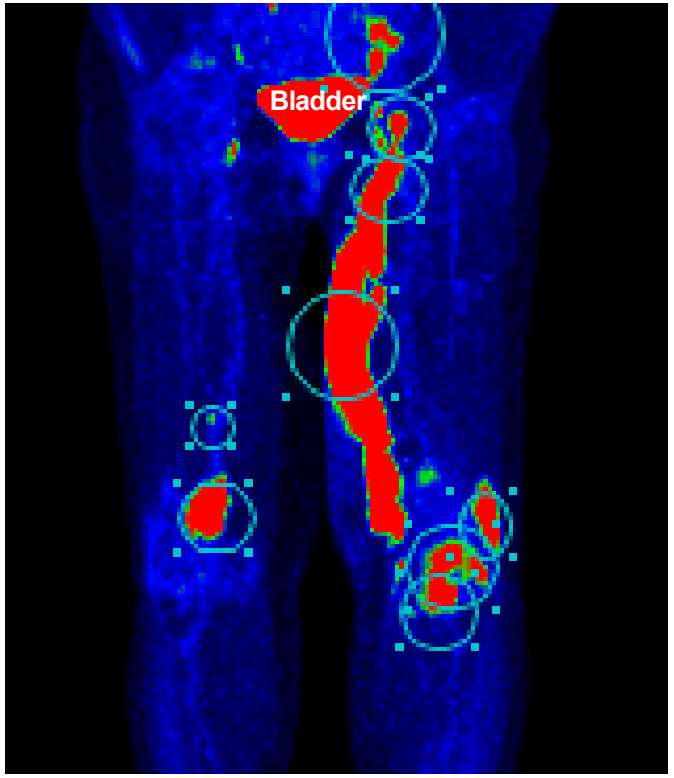


[1] Westin J. Blood 2019;134:996–8

Rapid BTK Degradation and Confirmed Complete Response Following NX-2127 Therapy in Patient with Aggressive Lymphoma

FDG-PET CT Scan Disease Assessment

Baseline

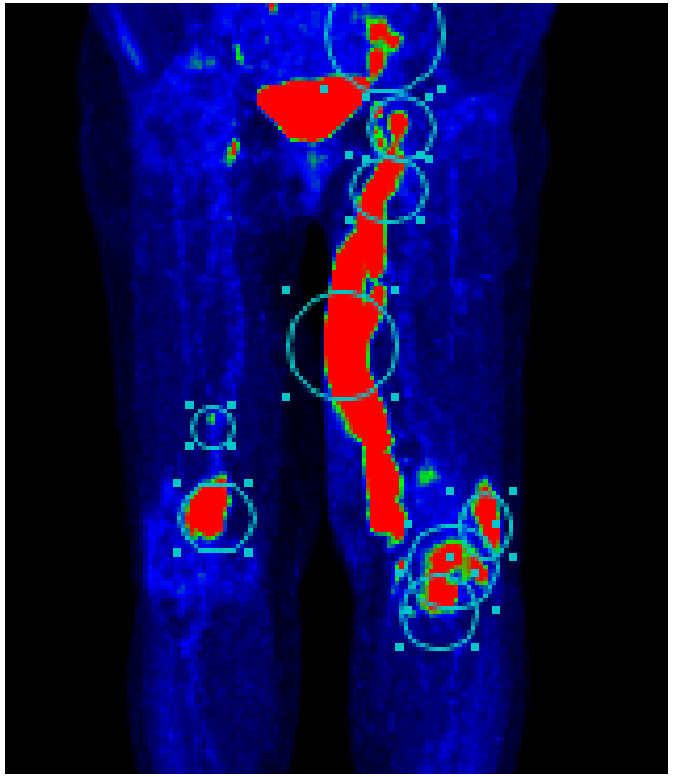


Deauville score: 5

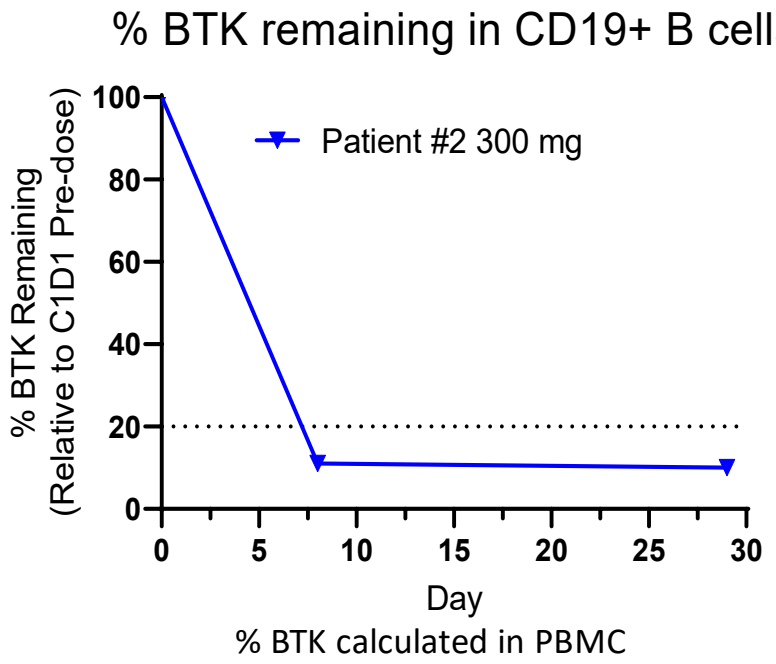
- 84-year-old woman with multiply relapsed ABC-DLBCL following 4 lines of aggressive therapy (including combination of Rituximab, Ibrutinib, and Lenalidomide).

Data as reported TPD October 26, 2022

Rapid BTK Degradation and Confirmed Complete Response Following NX-2127 Therapy in Patient with Aggressive Lymphoma



Deauville score: 5



- 84-year-old woman with multiply relapsed ABC-DLBCL following 4 lines of aggressive therapy (including combination of Rituximab, Ibrutinib, and Lenalidomide).

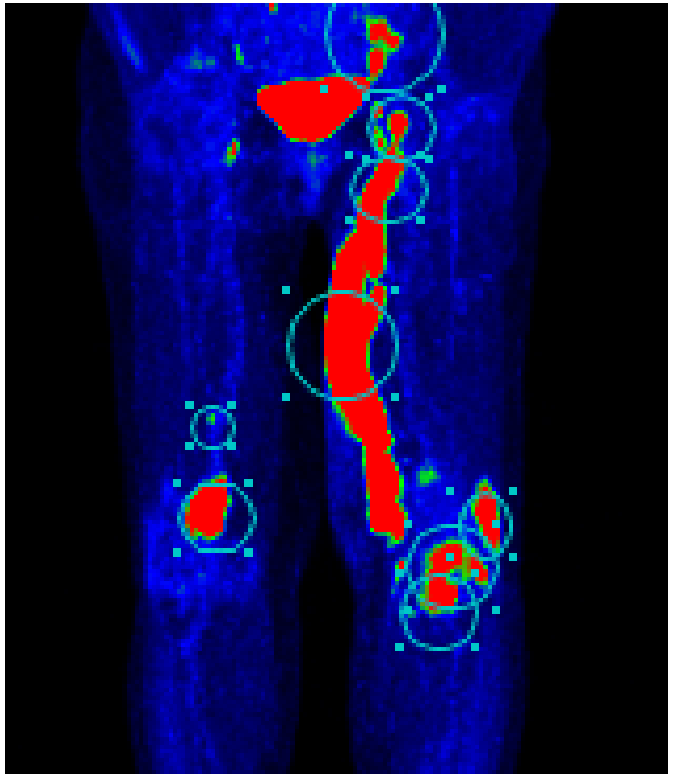
Significant Ikaros and Aiolos degradation also confirmed by day 8

Data as reported TPD October 26, 2022

Rapid BTK Degradation and Confirmed Complete Response Following NX-2127 Therapy in Patient with Aggressive Lymphoma

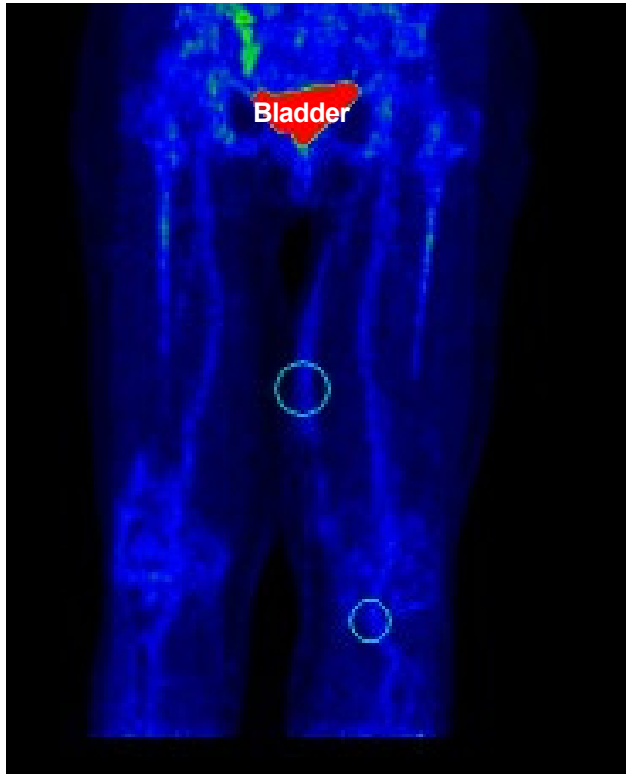
FDG-PET CT Scan Disease Assessment

Baseline



Deauville score: 5

Week 16



Deauville score: 2

- 84-year-old woman with multiply relapsed ABC-DLBCL following 4 lines of aggressive therapy (including combination of Rituximab, Ibrutinib, and Lenalidomide).
- Complete response at first assessment (Week 8) and confirmed at subsequent assessment (Week 16).
- Safety: No DLT or SAE. Manageable Grade 3 neutropenia without infection. No Rx interruptions.

Data as reported TPD October 26, 2022

Targeted Protein Degradation Holds Promise for Treating Cancer

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!