nurix

Leader in Targeted Protein Modulation

First Targeted Protein Degradation for Hematological Malignancies

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Chief Scientific Officer

3rd Annual Targeted Protein Degradation Europe
London, UK
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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 Degradation (TPD)

Harness ligases to decrease specific protein levels

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

Targeted Protein Elevation (TPE)

Inhibit ligases to increase specific protein levels

Nurix Is Advancing a Broad Pipeline of Proprietary and Partnered Programs

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				

Addressing current and emergent clinical challenges in hematologic malignancies

BTK degradation can overcome treatment-emergent resistance: event-driven pharmacology shows resilience to mutation

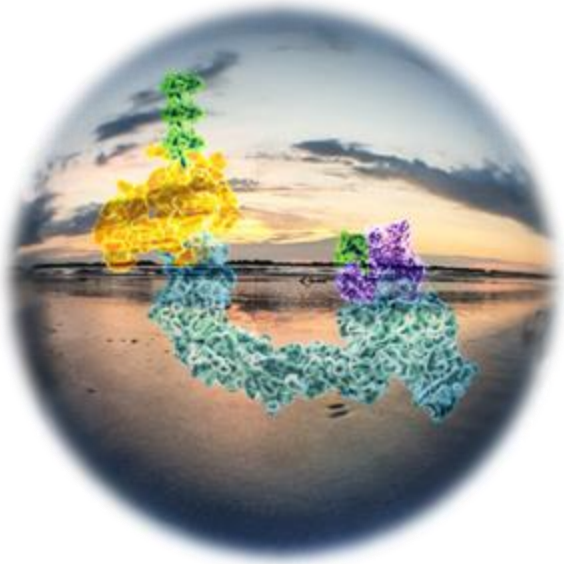
BTK degraders uniquely address BTK scaffolding function

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

NX-5948

BTK DEGRADATION

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



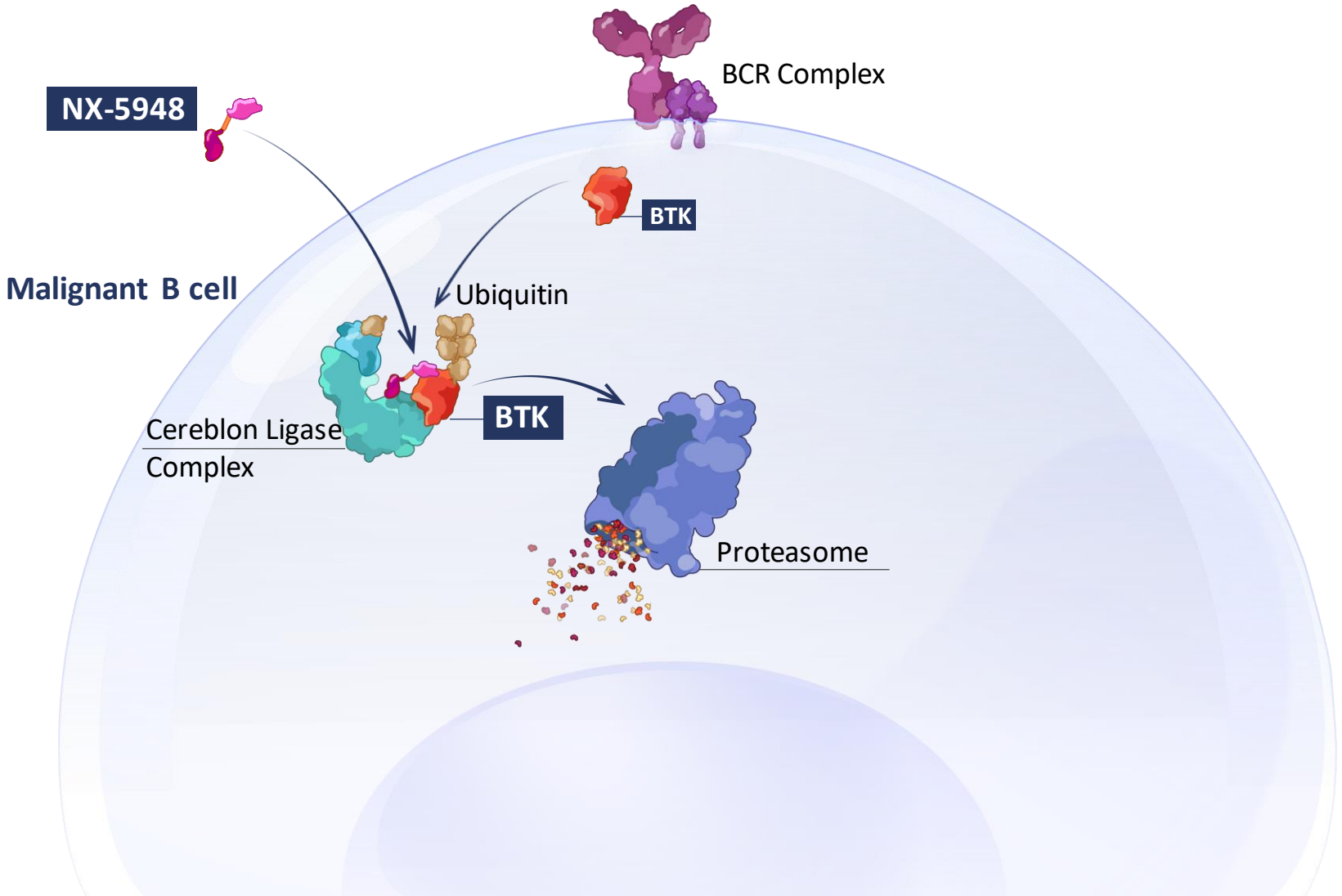
NX-2127

BTK DEGRADATION
& IMMUNOMODULATION

- Positive clinical activity in CLL patients, including responses in patients with BTK or BCL2 mutations
- Active in the clinic against 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

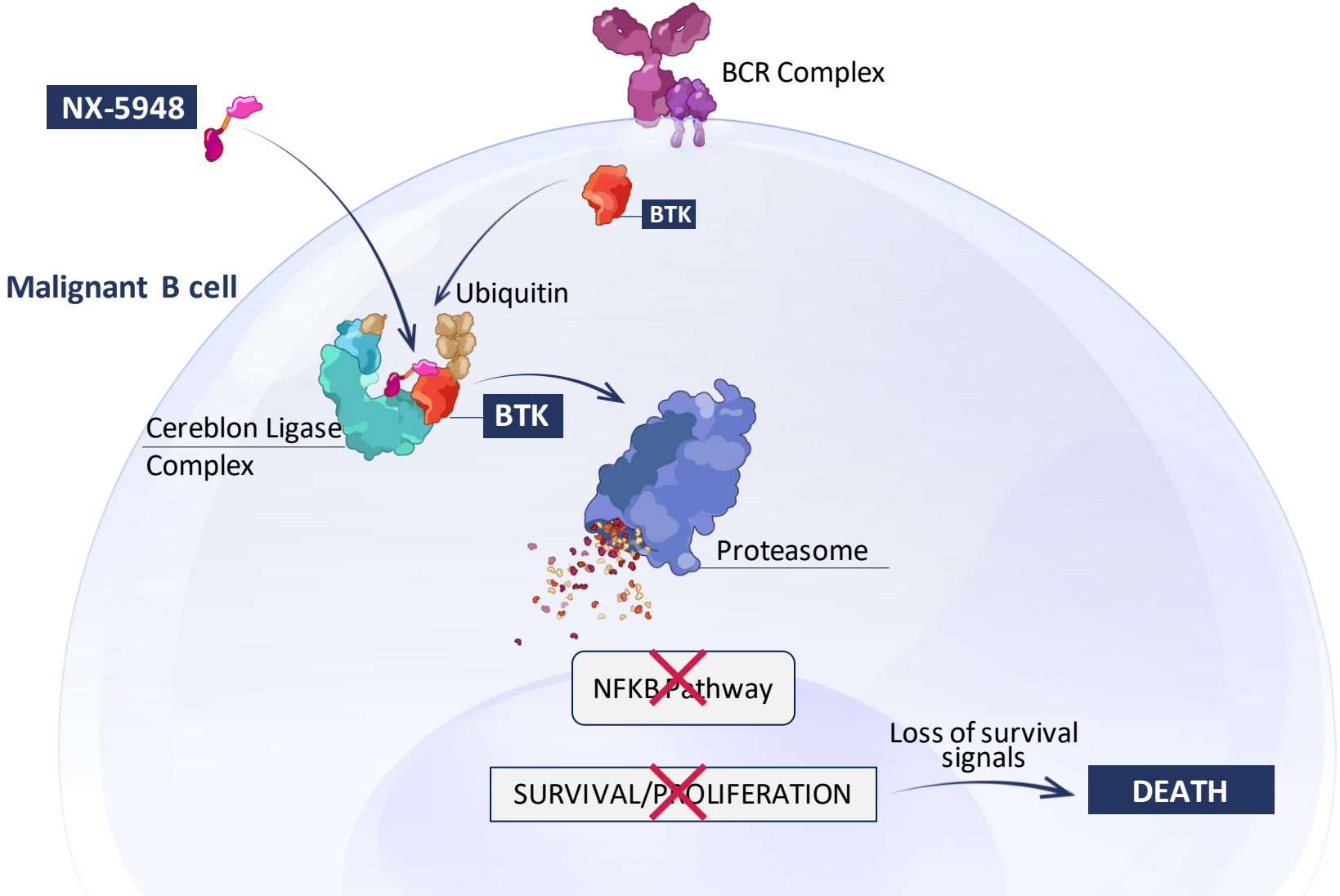
NX-5948 is a potent and selective degrader of BTK

Targeted degradation of Bruton's Tyrosine Kinase



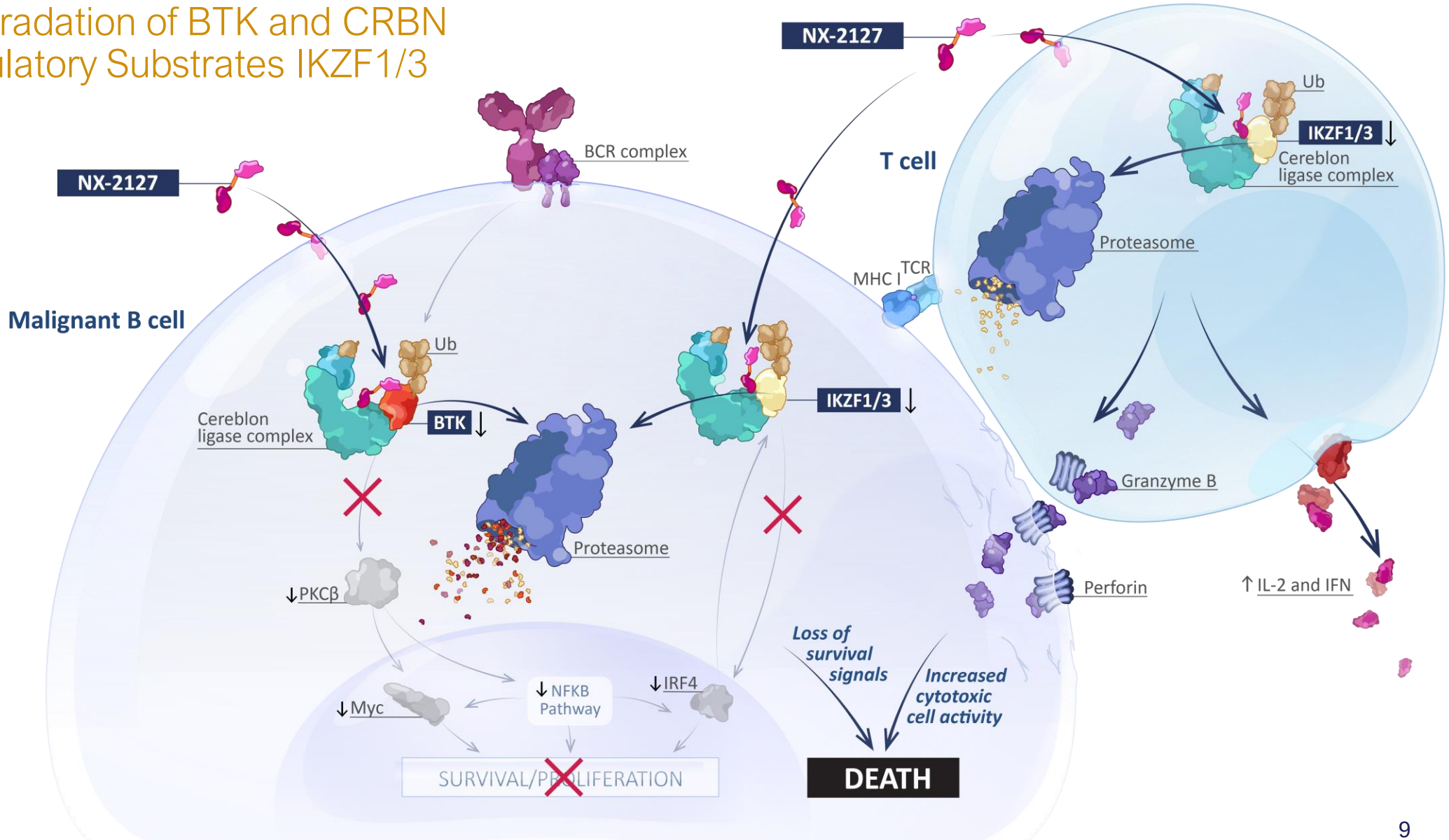
NX-5948 is a potent and selective degrader of BTK

Targeted degradation of Bruton's Tyrosine Kinase

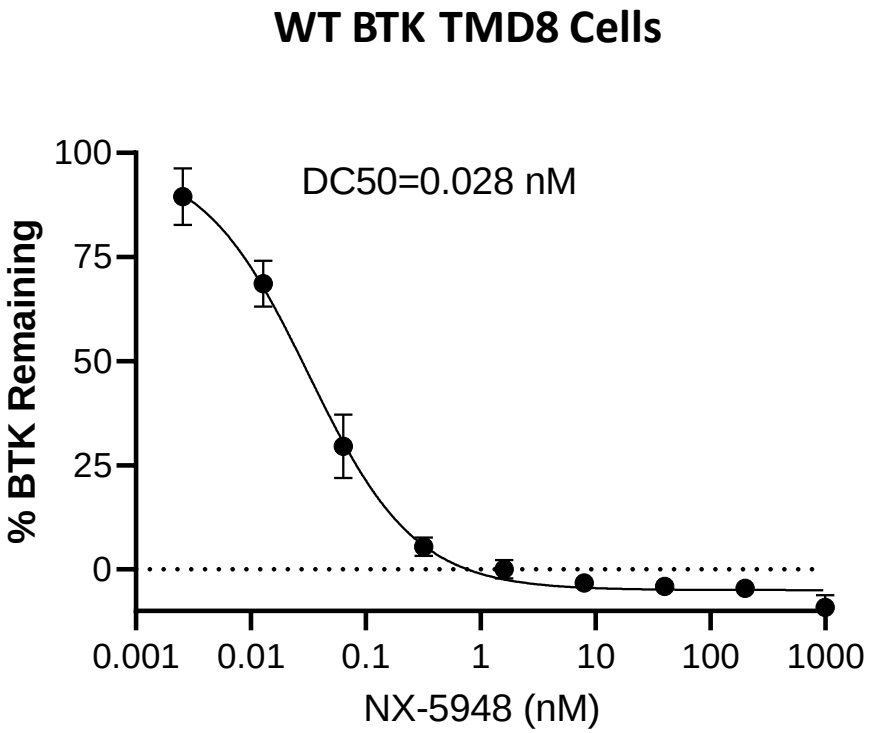


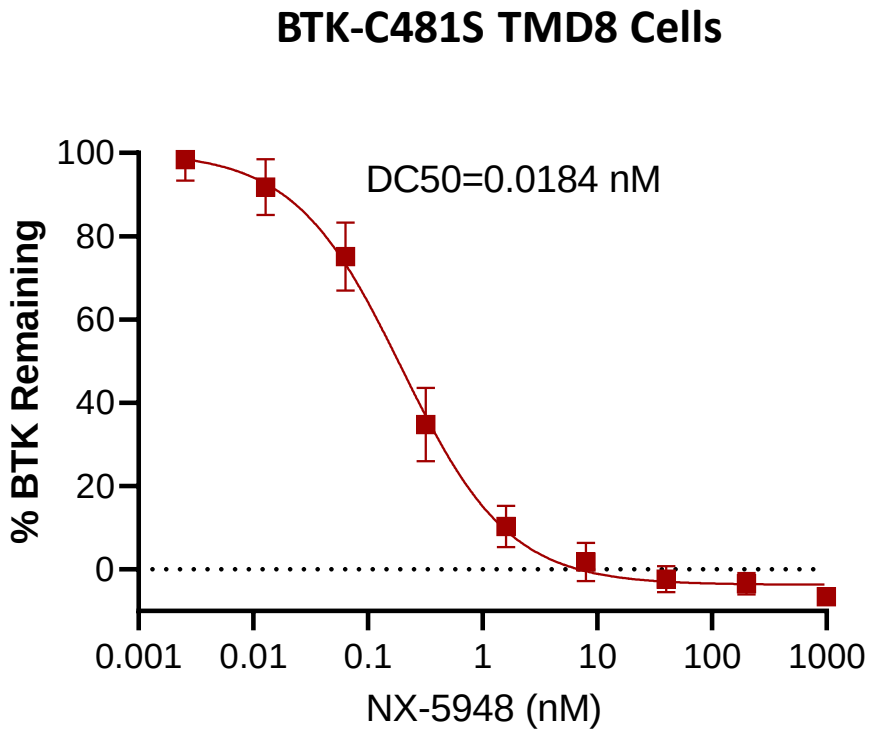
NX-2127 Dual Mechanism of Action

Targeted Degradation of BTK and CRBN Immunomodulatory Substrates IKZF1/3



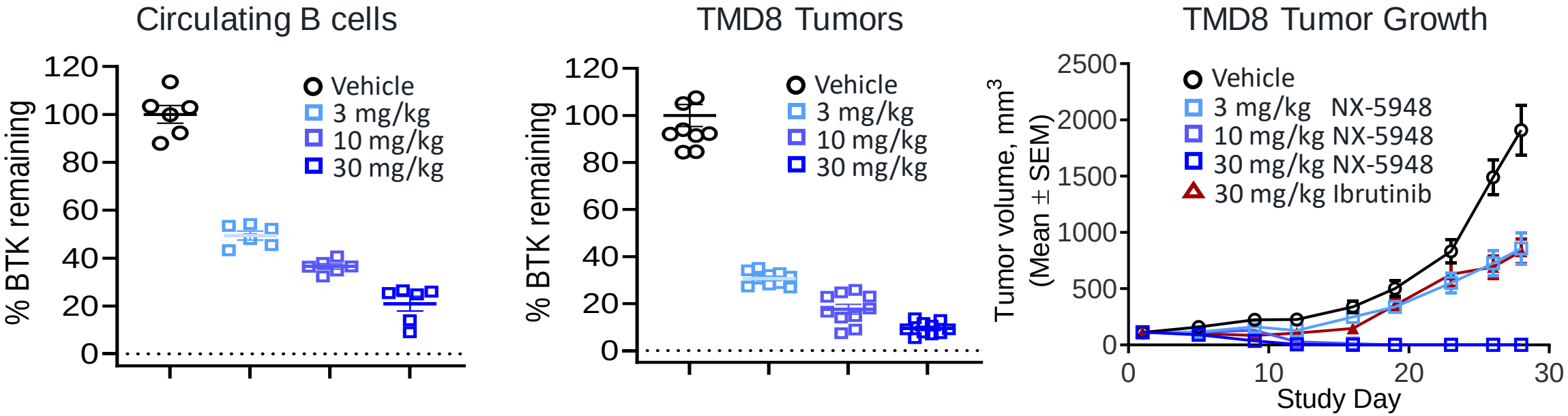
NX-5948 was Designed for Potent and Rapid Degradation of Wildtype and C481S-Mutated BTK





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.

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

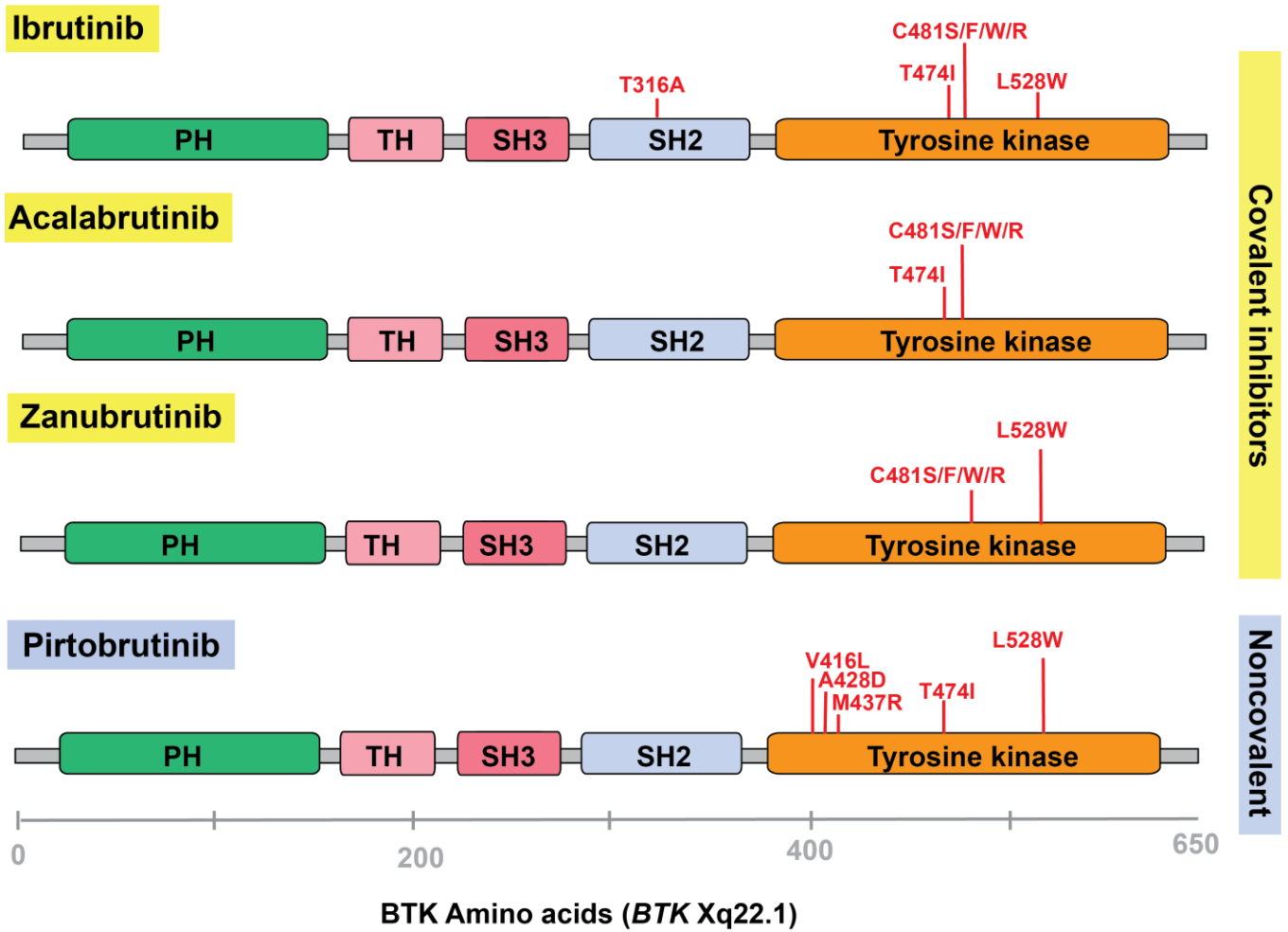


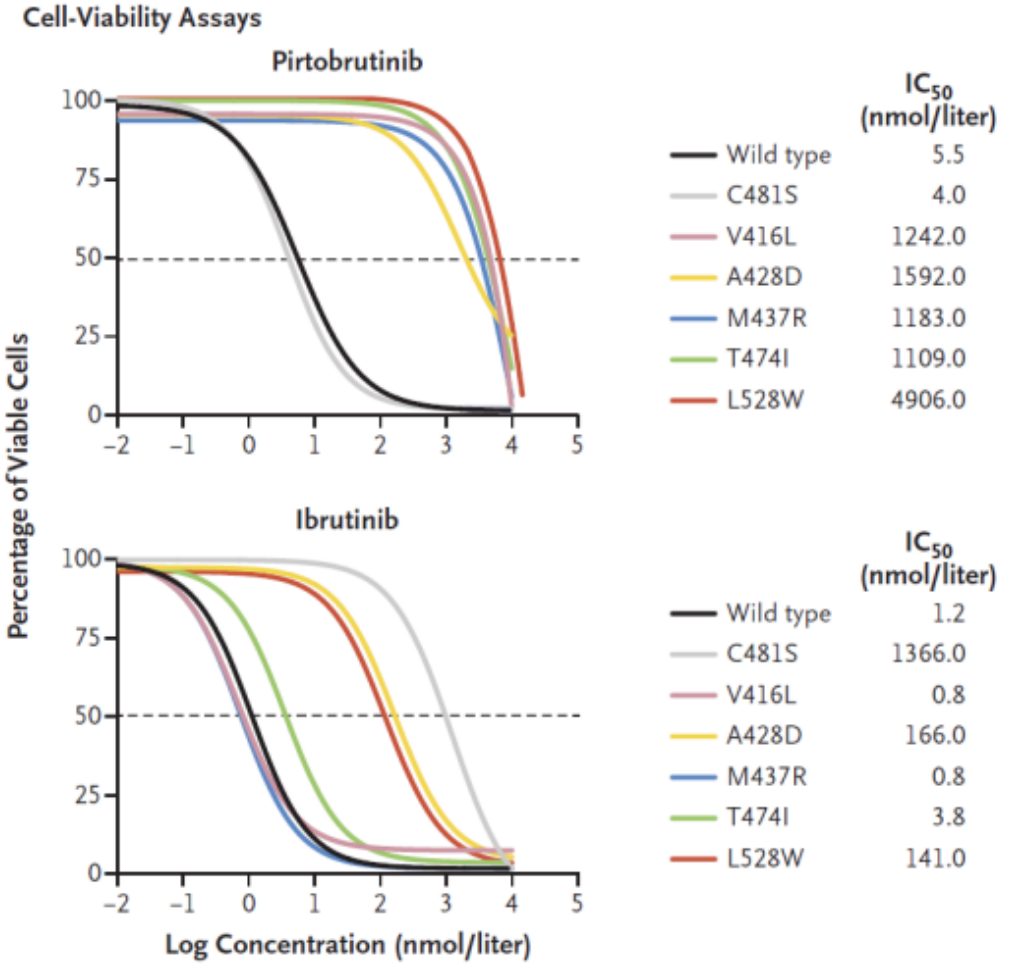
Treatment	Oral gavage dose (mg/kg)	% BTK degradation in circulating B cells	% BTK degradation in TMD8 tumor tissue	% TGI vs Vehicle (Day 26)	*P* value vs Vehicle
Vehicle	0	0.0±3.7	0.0±4.7	N/A	N/A
NX-5948	3	50.5±1.9	69.2±0.9	54%	0.0025
	10	63.5±1.1	82.4±2.1	100%	<0.0001
	30	79.0±3.1	90.5±0.5	100%	<0.0001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

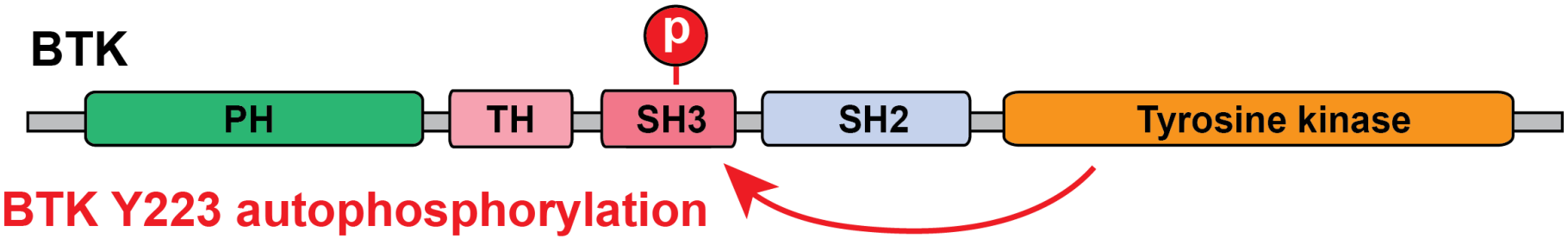
Increasing Use of BTK Inhibitors in the Clinic have Revealed a Growing Spectrum of Treatment-Emergent Resistance Mutations

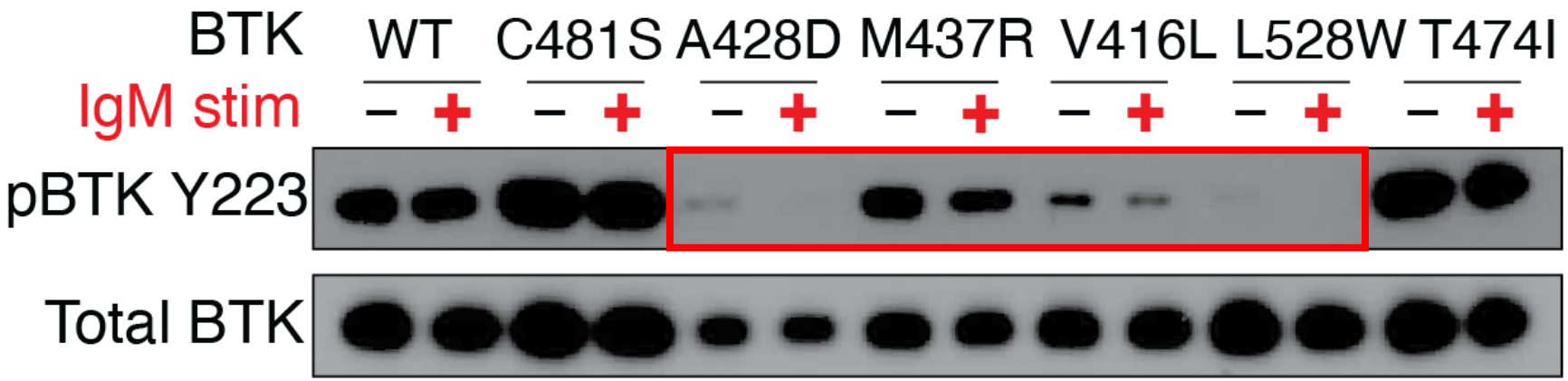




Wang, Mi, Thompson, et al. NEJM 2022

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

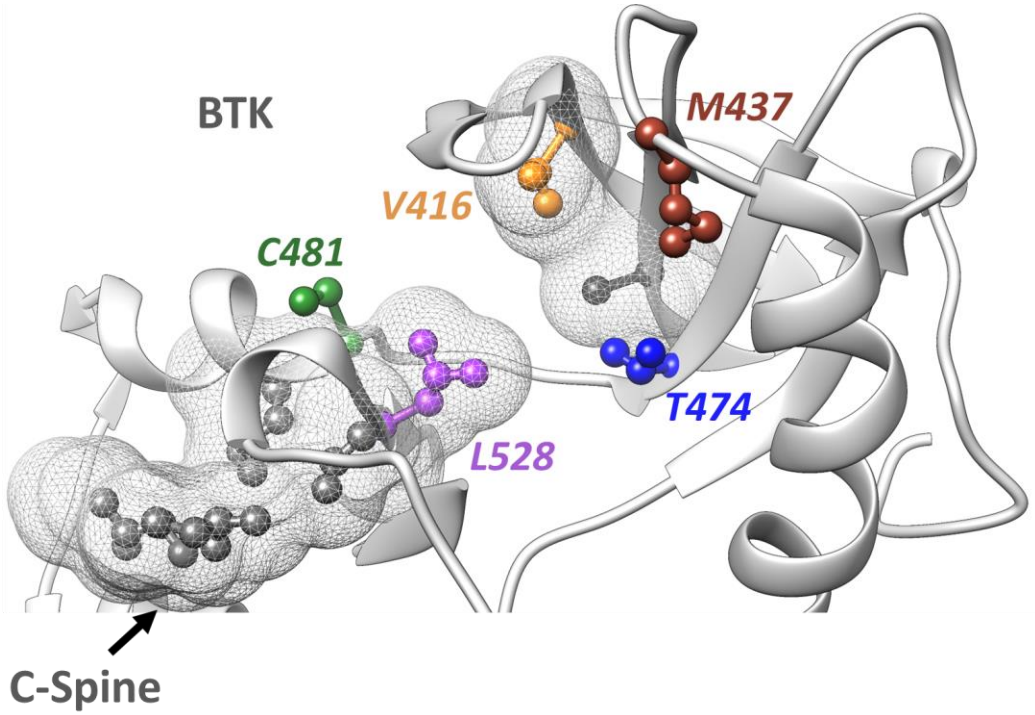




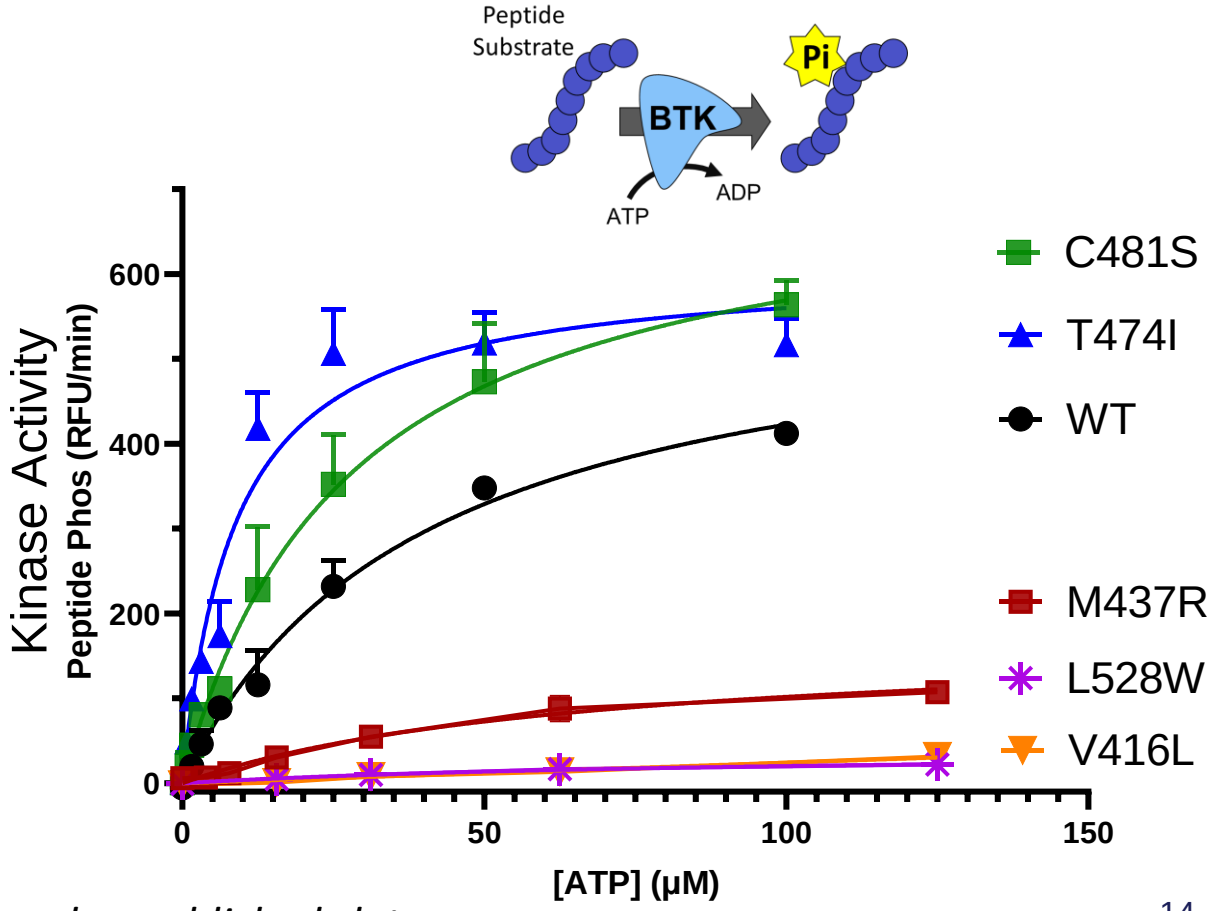
Wang, Mi, Thompson, et al. NEJM 2022

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

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

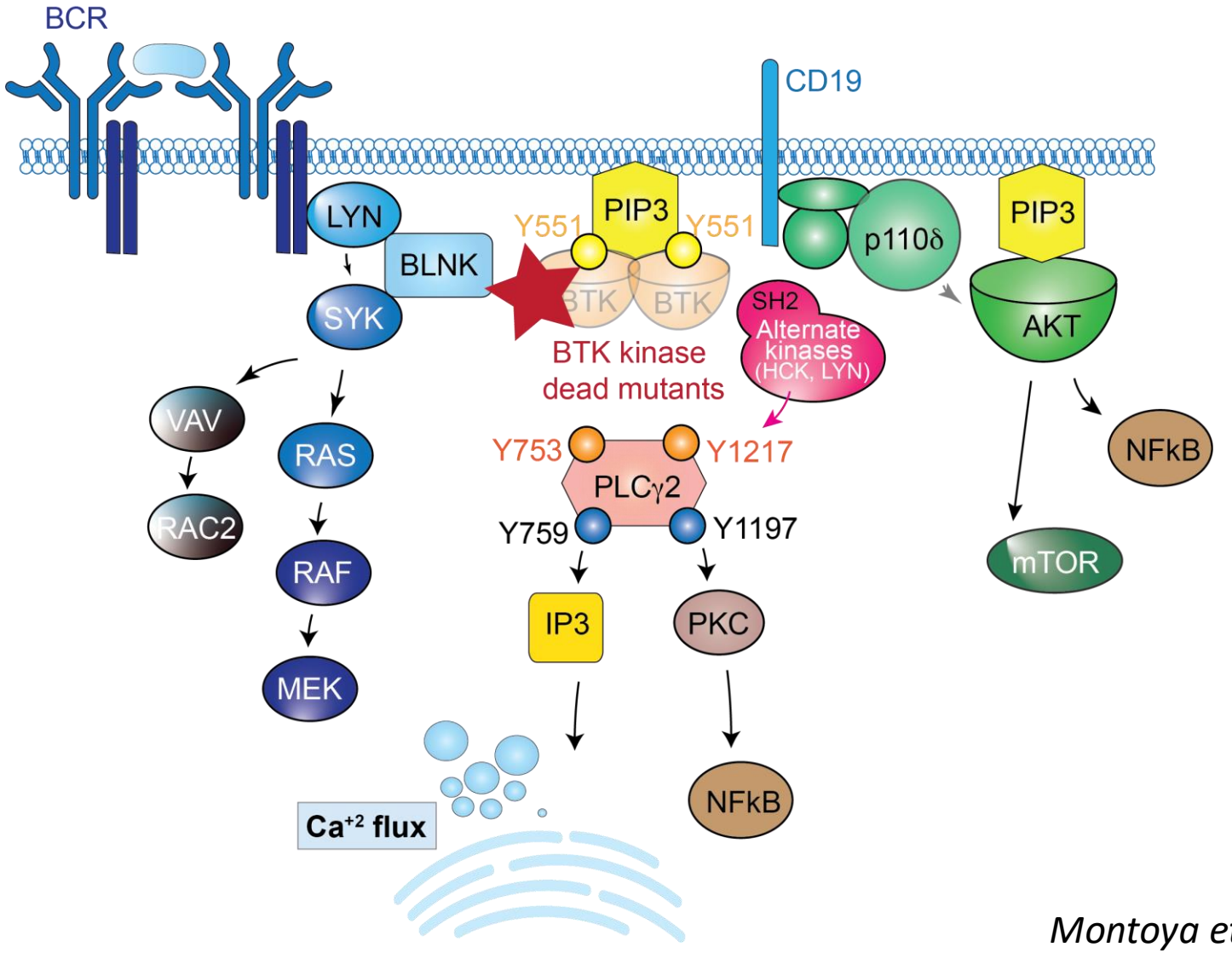


Some mutations that confer resistance to BTKis lack kinase activity yet still potentiate BCR signaling



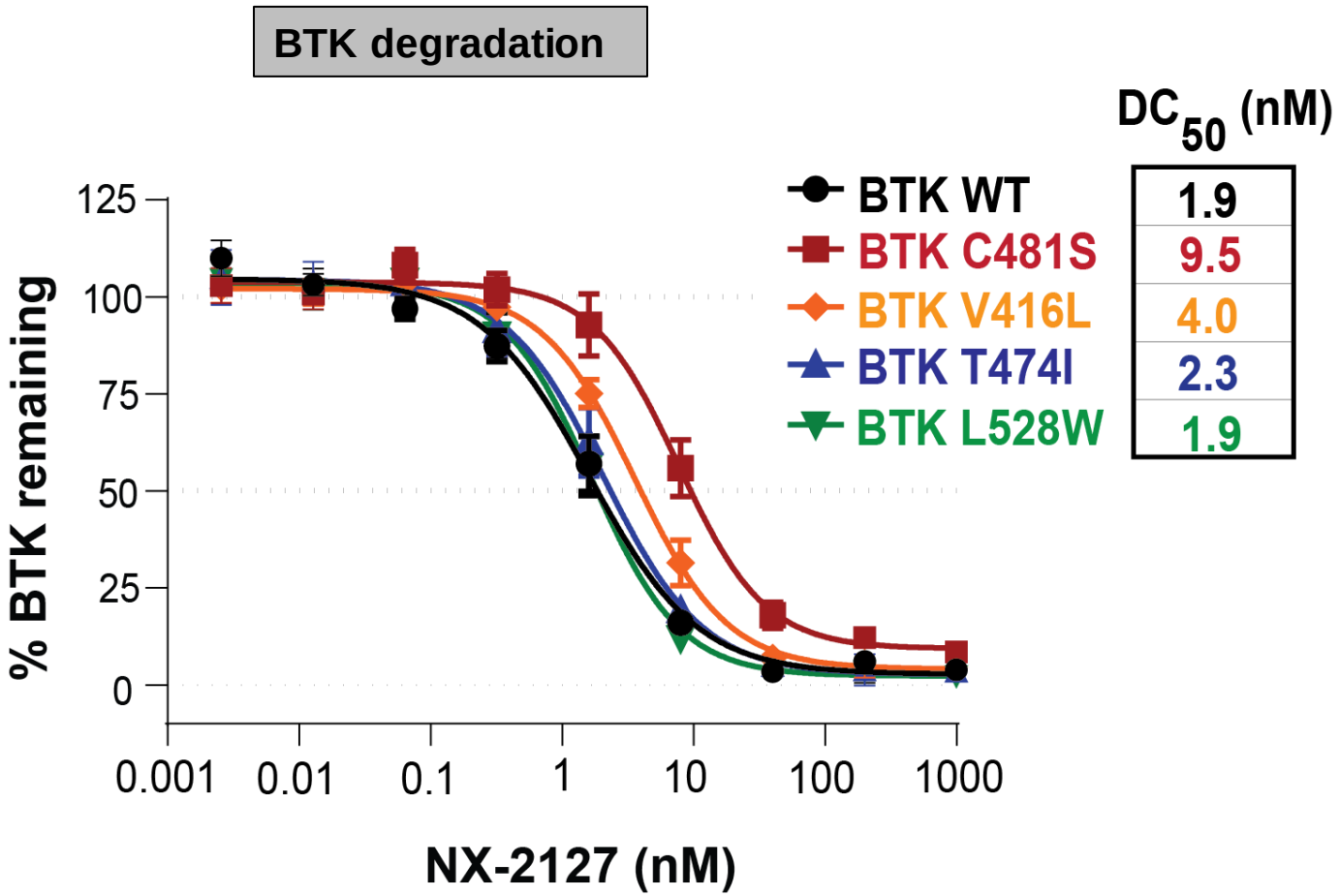
Montoya et al., ASH 2022 and unpublished data

Can Targeted Protein Degradation Address the Scaffolding Function of Mutant BTK?

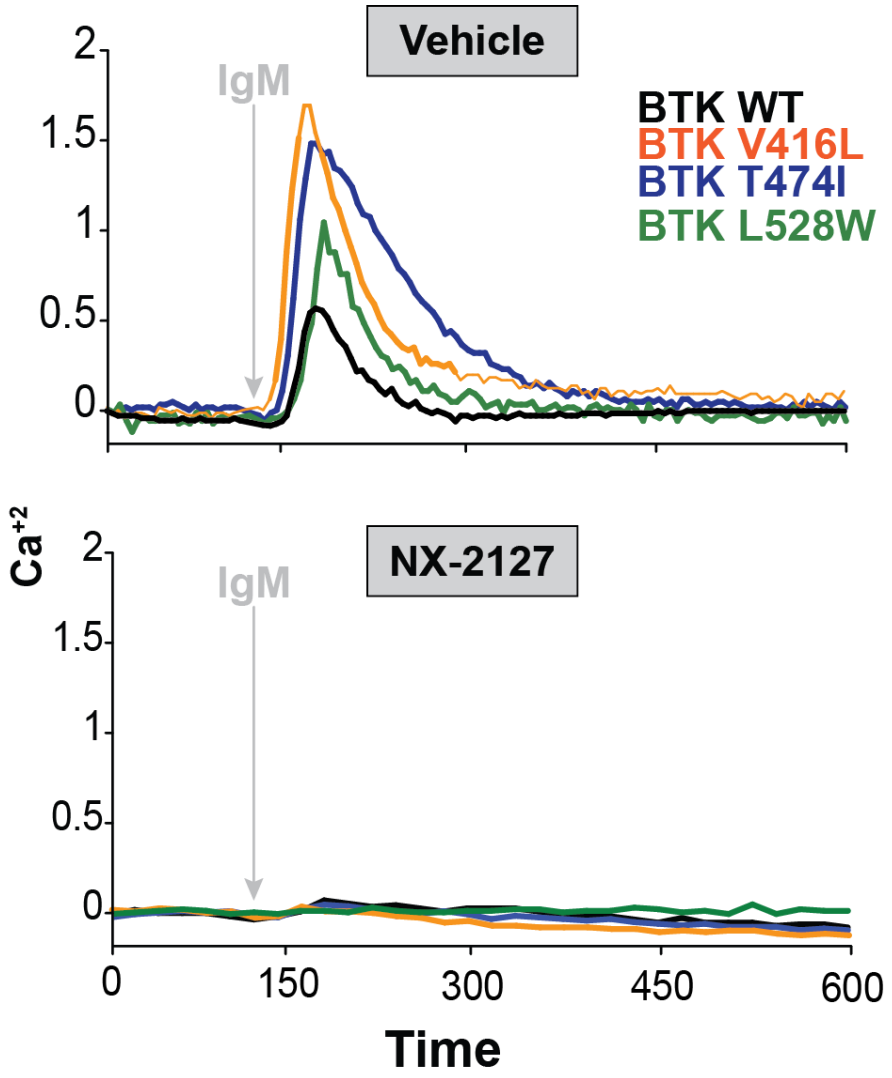


Montoya et al., ASH 2022

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

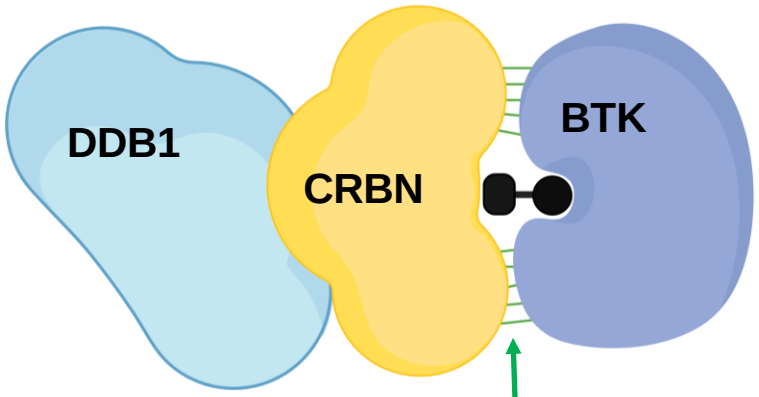


DC_{50} (nM)
1.9
9.5
4.0
2.3
1.9



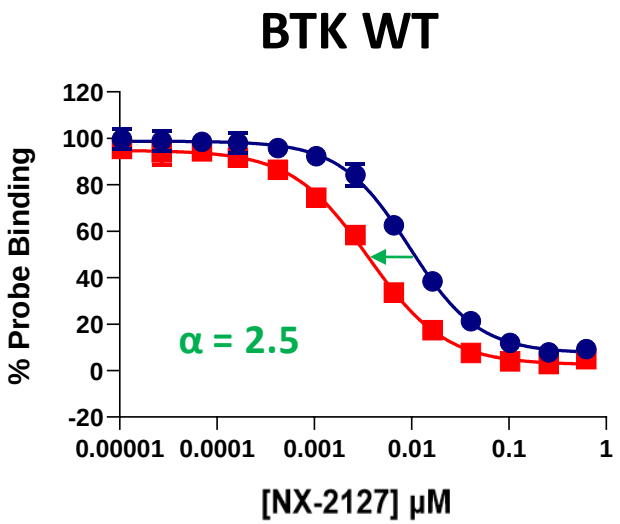
Montoya et al., ASH 2022

NX-2127 Induces Positive Cooperativity Between BTK and Cereblon



NX-2127

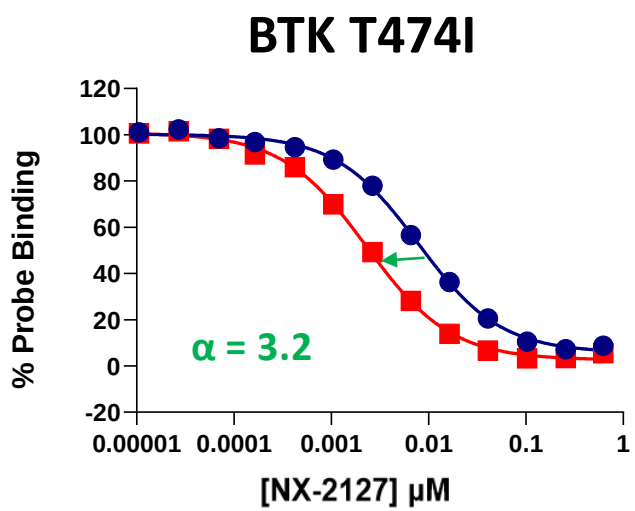
- Positive Cooperativity (α>1)
- Stable ternary complex
- Induced protein-protein interactions
- Greater tolerance for reduced binary affinity

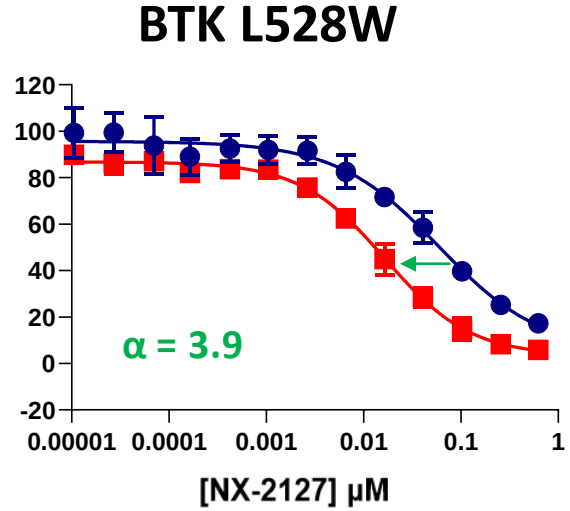


No CRBN

⊕ CRBN (1 µM)

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





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

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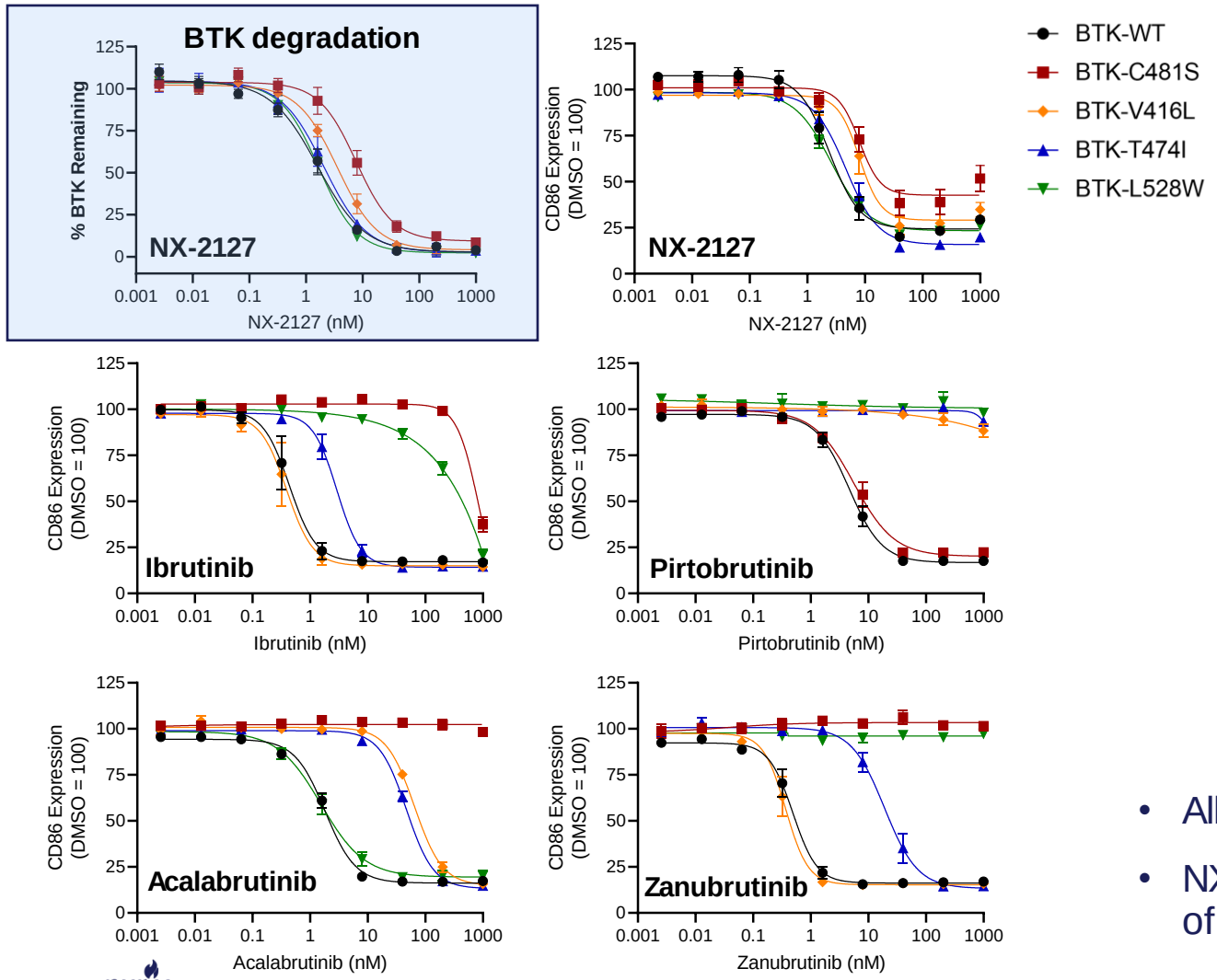
Montoya et al., ASH 2022

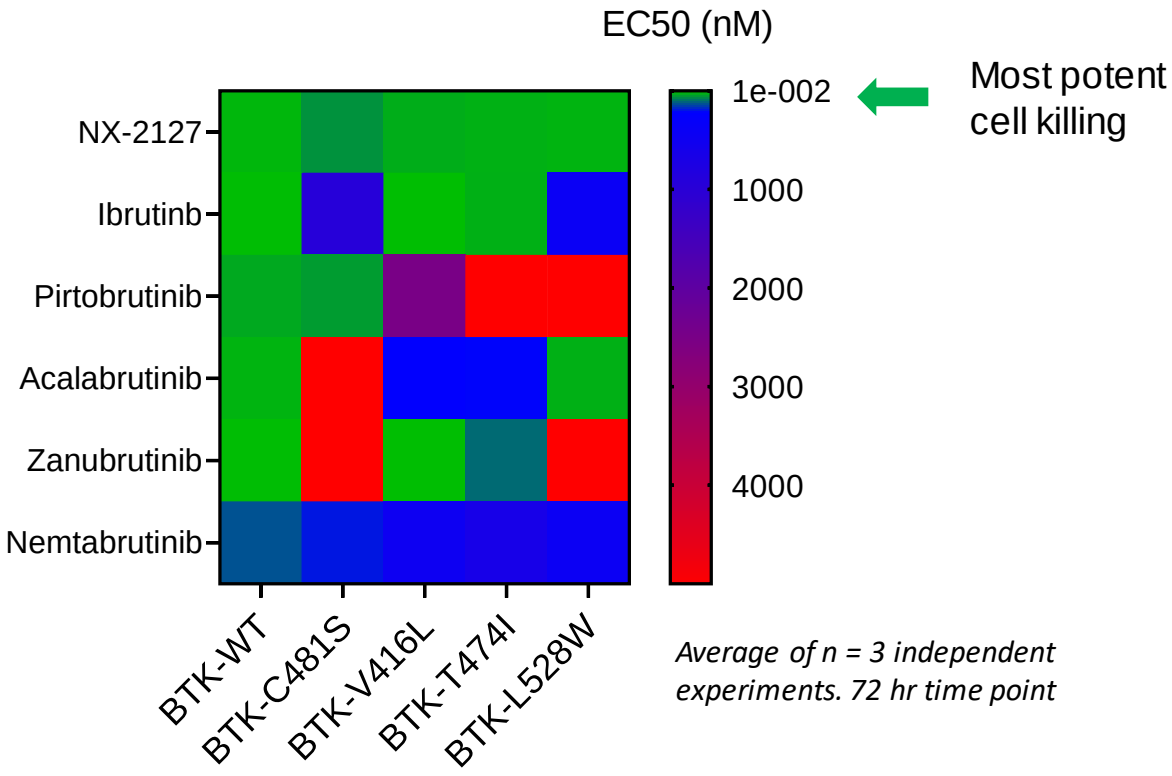
NX-2127 is Potent and More Broadly Active Than All BTK Inhibitors Tested

BTK degradation and activation marker suppression in TMD8 tumor cells



Average of n = 3 independent experiments +/- SEM

TMD8 tumor cell killing

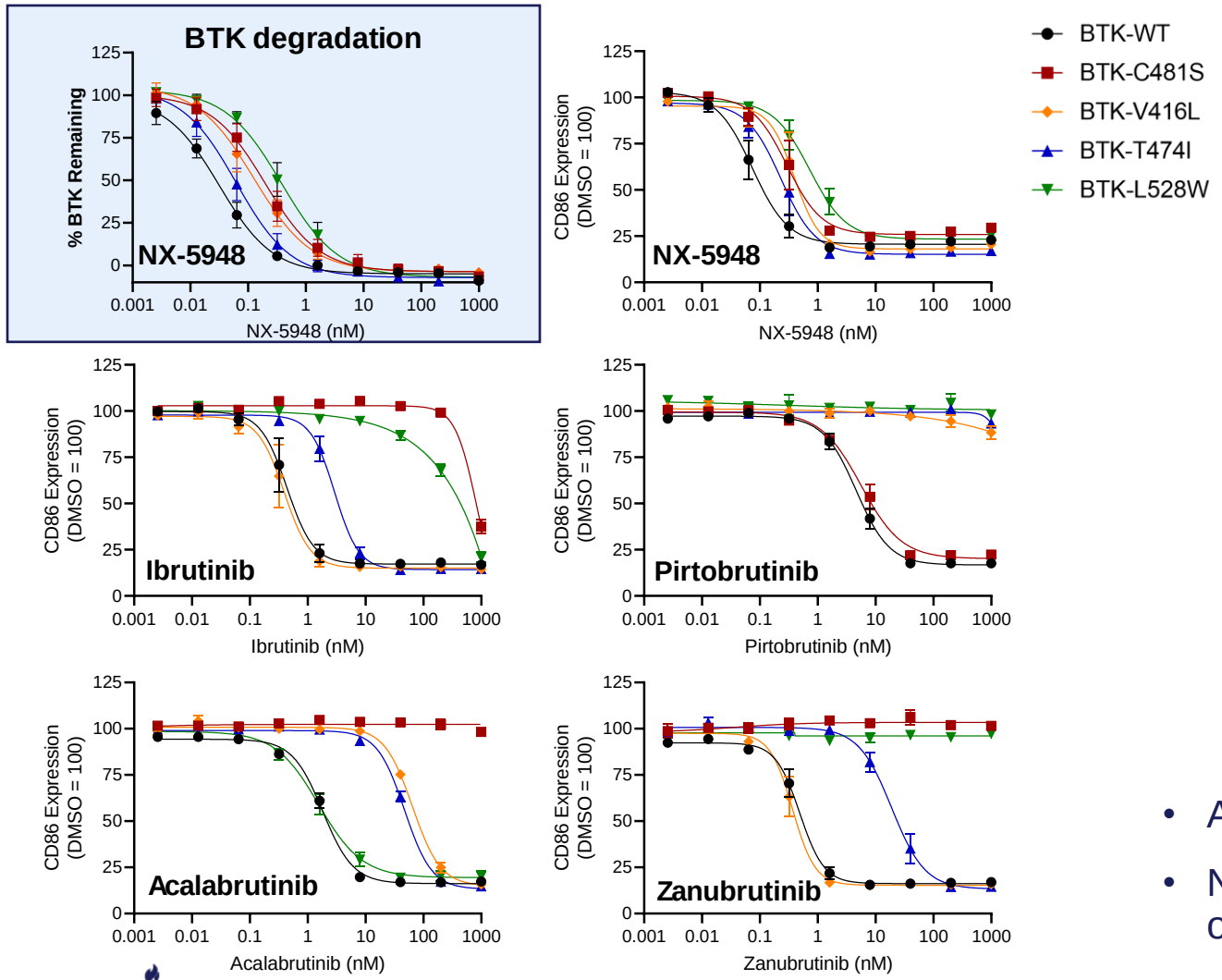


Average of n = 3 independent experiments. 72 hr time point

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

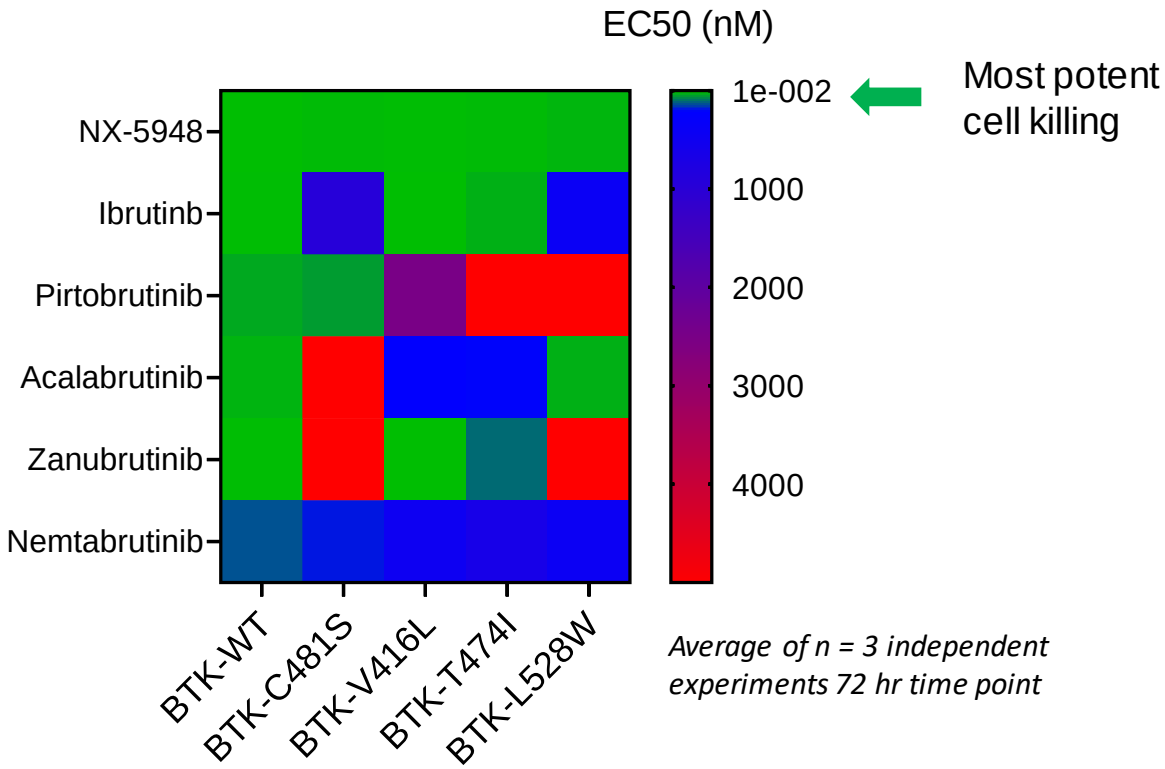
NX-5948 is More Potent and Broadly Active Than All BTK Inhibitors Tested

BTK degradation and activation marker suppression in TMD8 tumor cells



Average of n = 3 independent experiments +/- SEM

TMD8 tumor cell killing

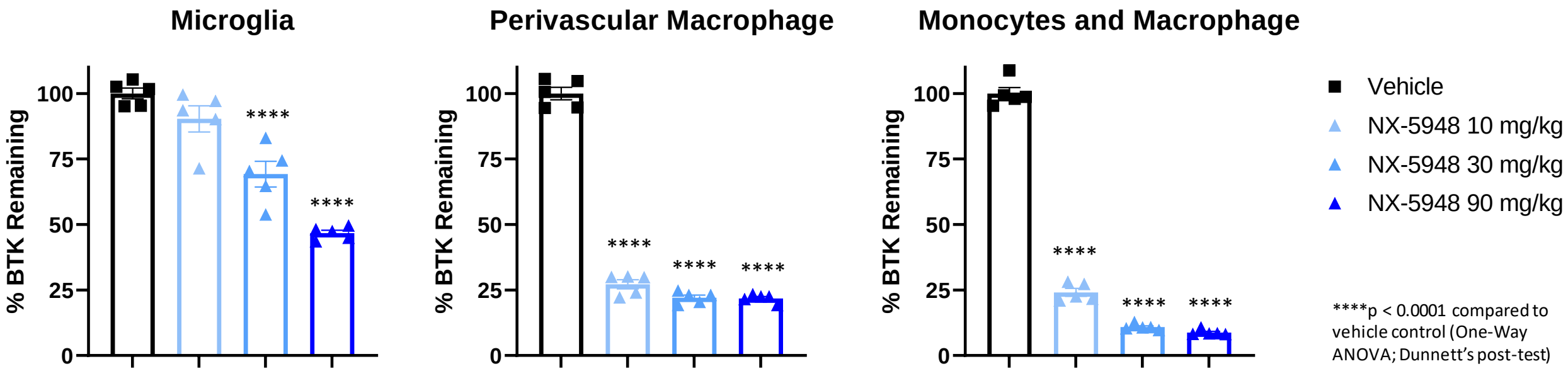


Average of n = 3 independent experiments 72 hr time point

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

NX-5948 Degrades BTK in Microglia and Macrophage in Brains of Naïve Mice

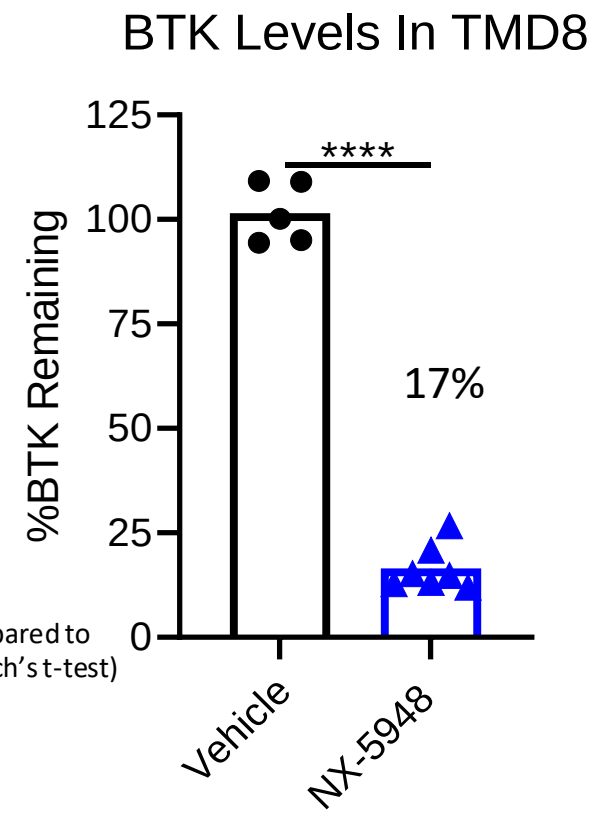
- NX-5948 drives dose-dependent BTK degradation in cells isolated from brains
- Magnitude of BTK degradation depends on dose and cell type



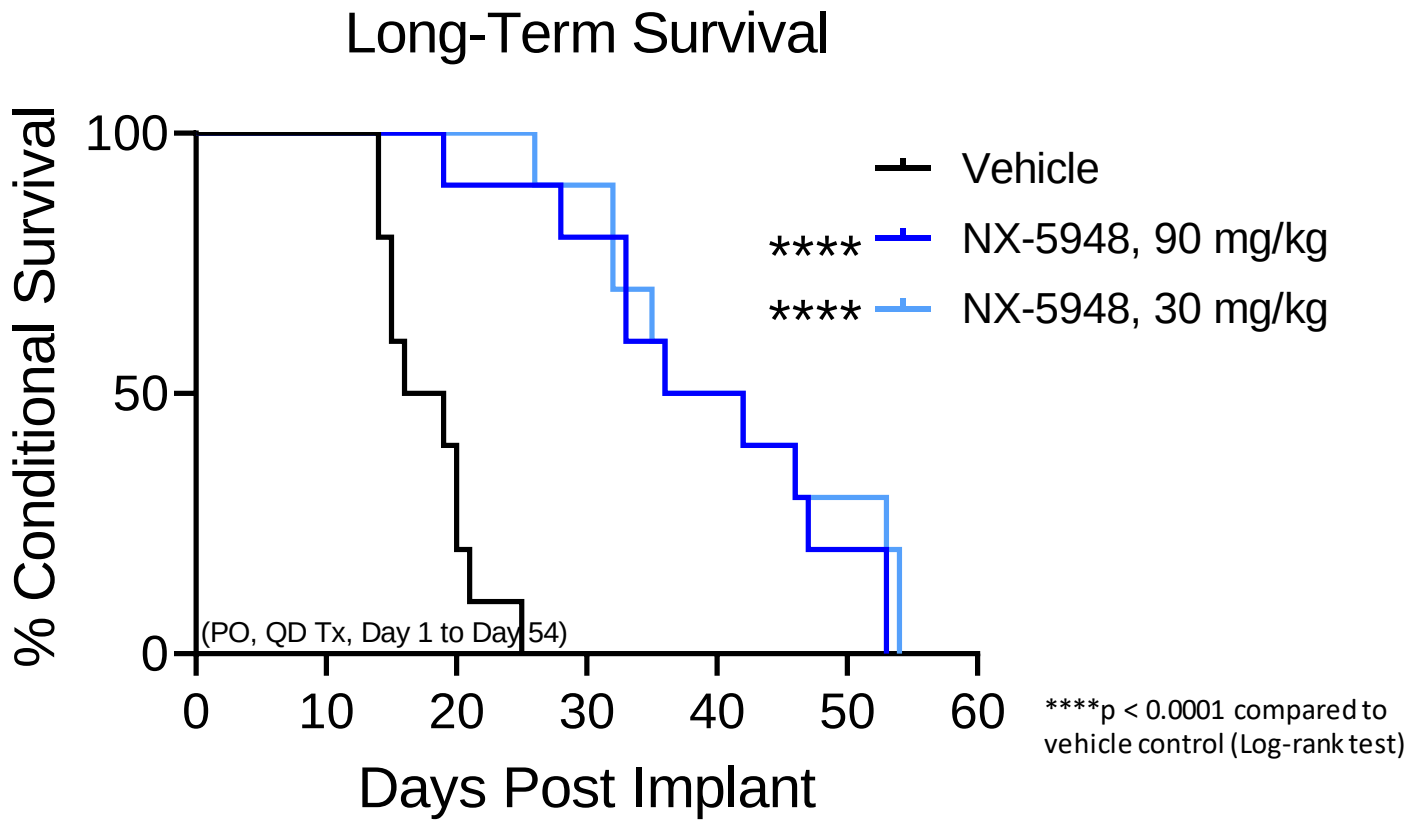
NX-5948 administered orally QD x 3 days to naïve C57BL/6J mice. BTK levels assessed 8 h after 3rd dose by flow cytometry.

Rountree et al., TPD 2022

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



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



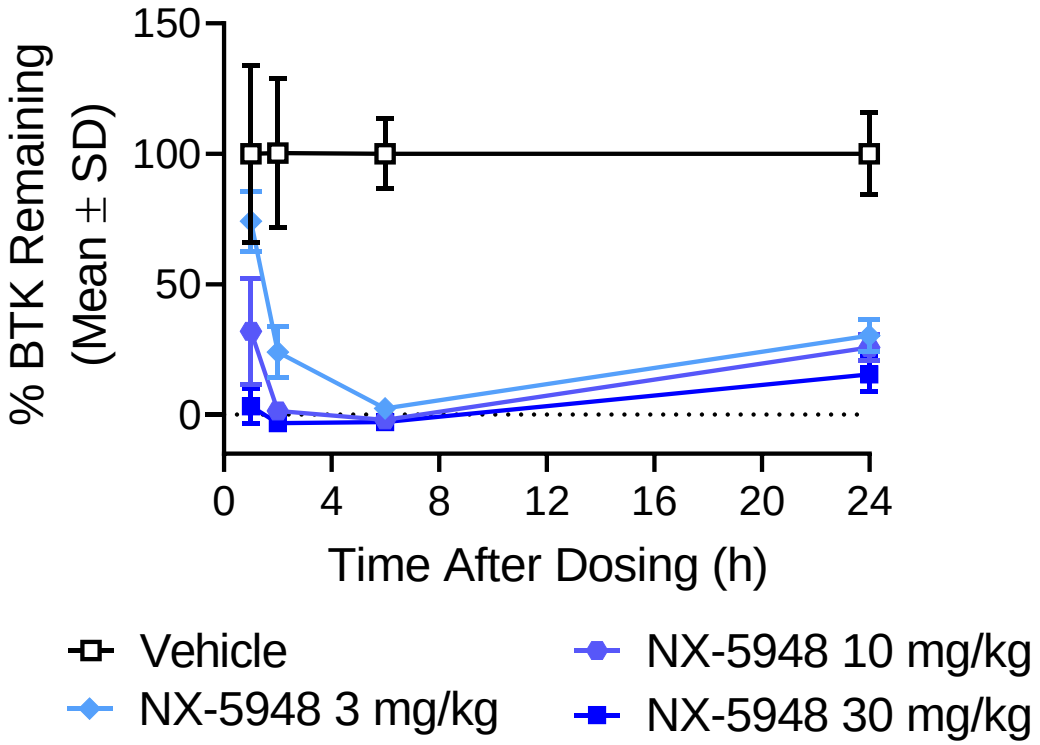
****p < 0.0001 compared to vehicle control (Log-rank test)

5 x 10e^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 11th dose by flow cytometry

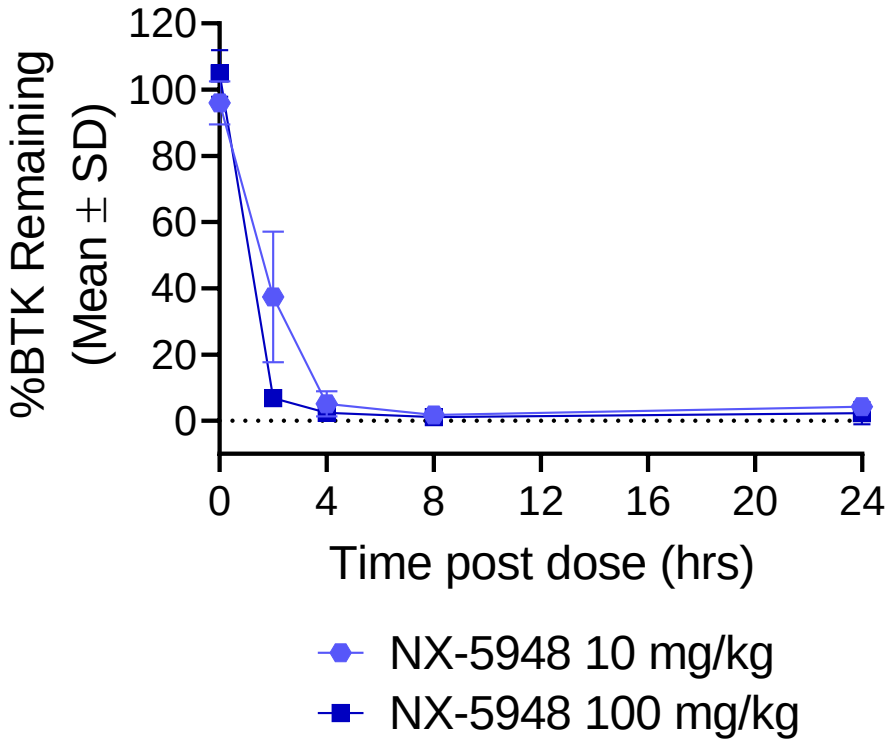
Rountree et al., TPD 2022

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

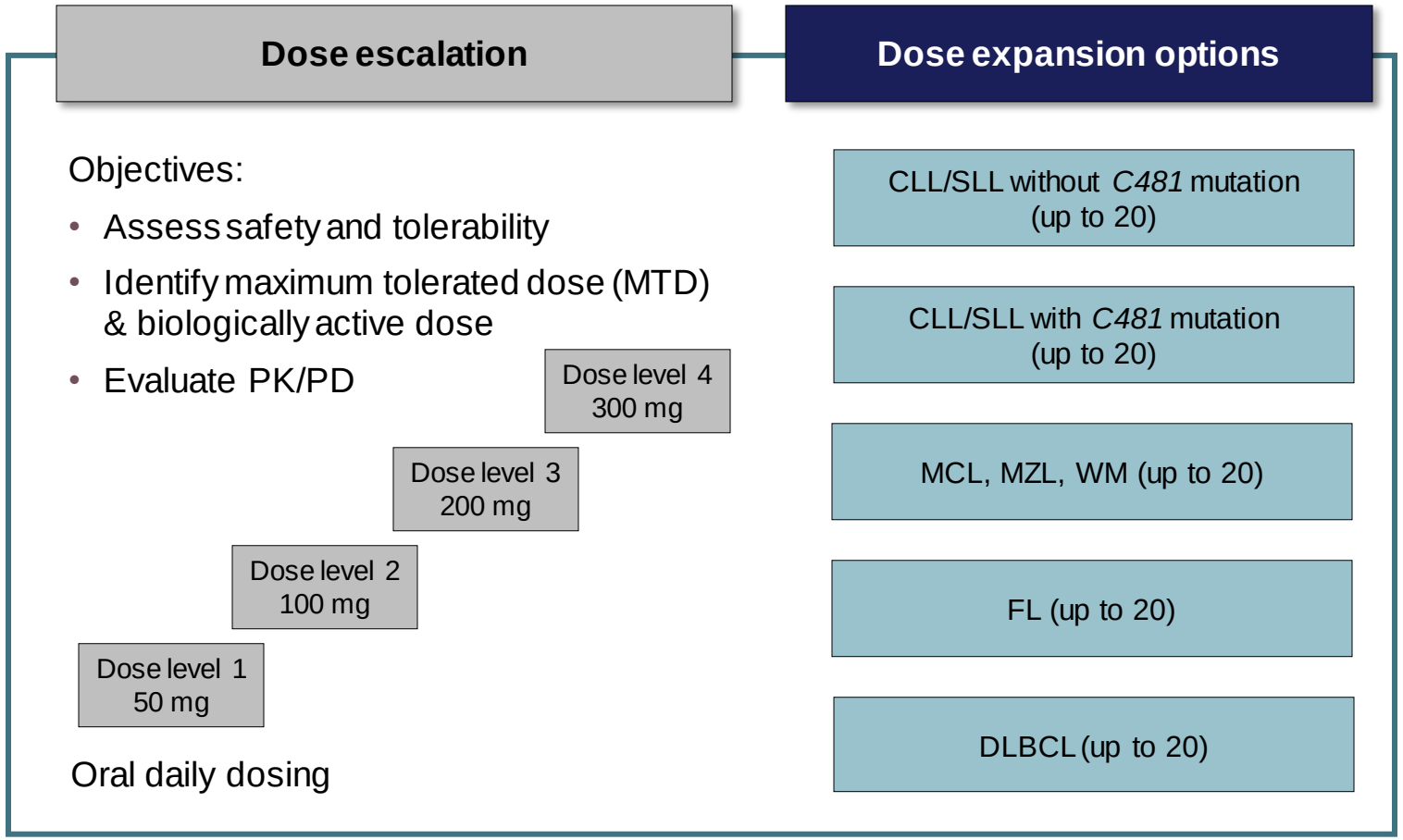


- In mice, BTK levels increased 24 hours after dosing from BTK resynthesis
- In cynomolgus monkeys, BTK levels remained suppressed at 24 hours

Rountree et al., TPD 2022

NX-5948-301: Trial design

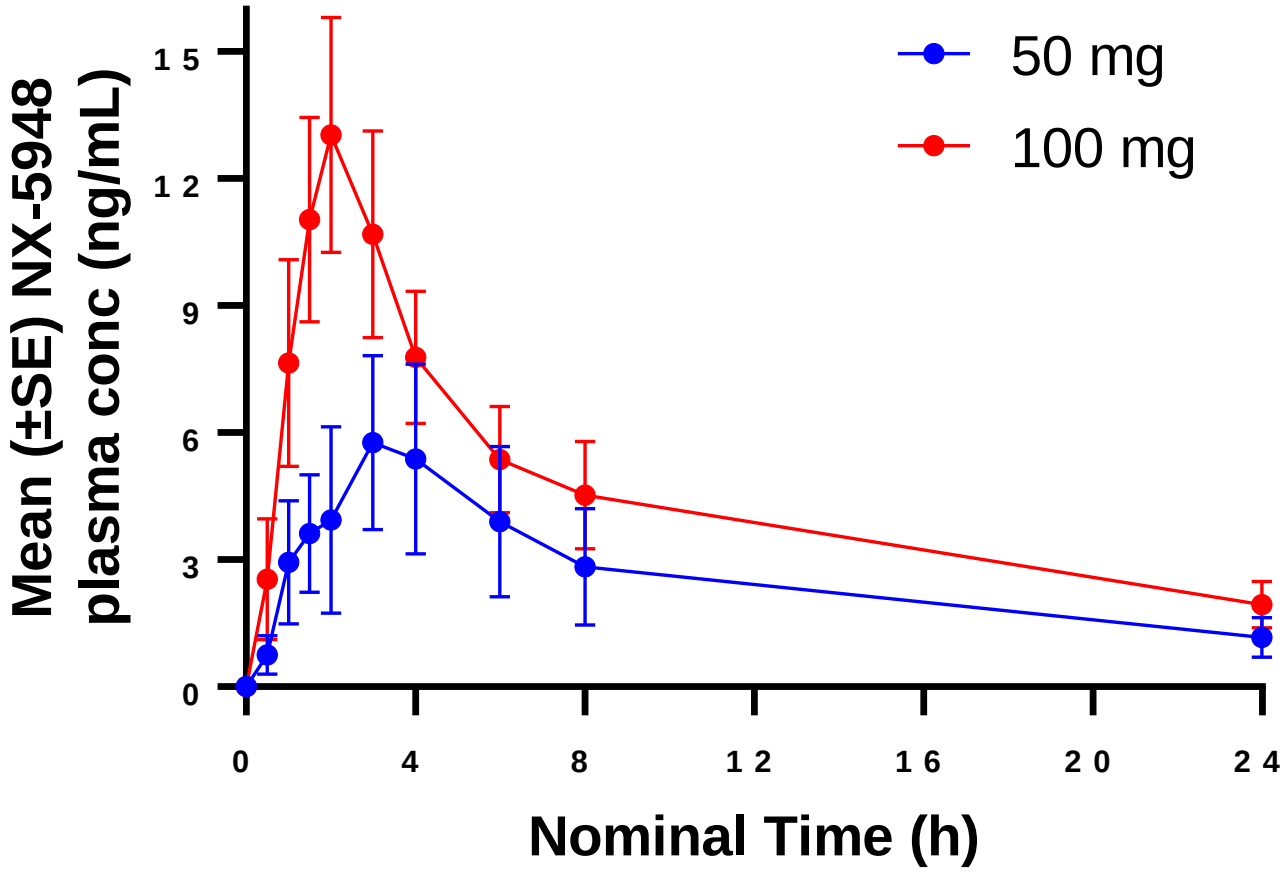
Phase 1 trial in adults with relapsed/refractory B-cell malignancies



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

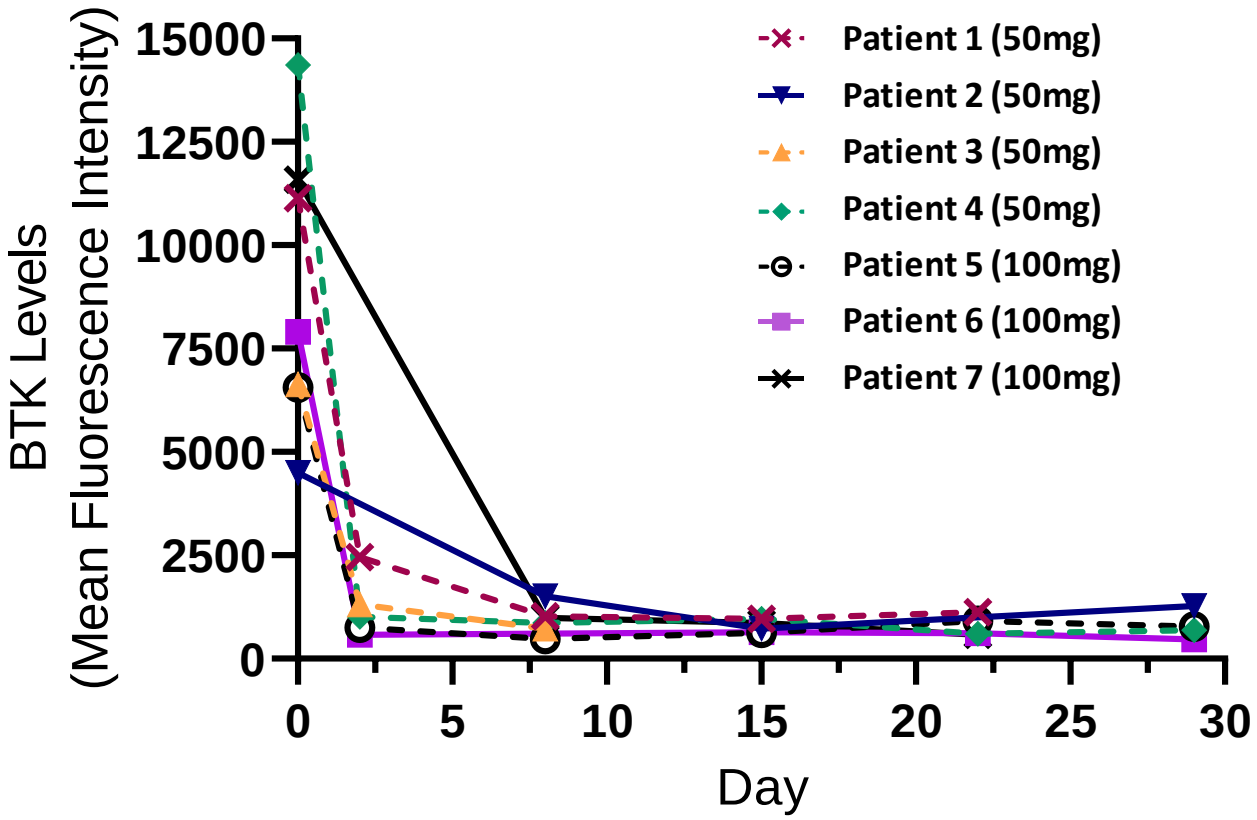
CLL, chronic lymphocytic leukemia; **DLBCL**, diffuse large B-cell lymphoma; **FL**, follicular lymphoma; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **PD,** pharmacodynamics; **PK,** pharmacokinetics; **WM**, Waldenstrom's macroglobulinemia

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

NX-5948: BTK Degrader Demonstrates Rapid and Sustained BTK Degradation With Early Signs of Differentiated Safety

Phase 1a Dose Escalation

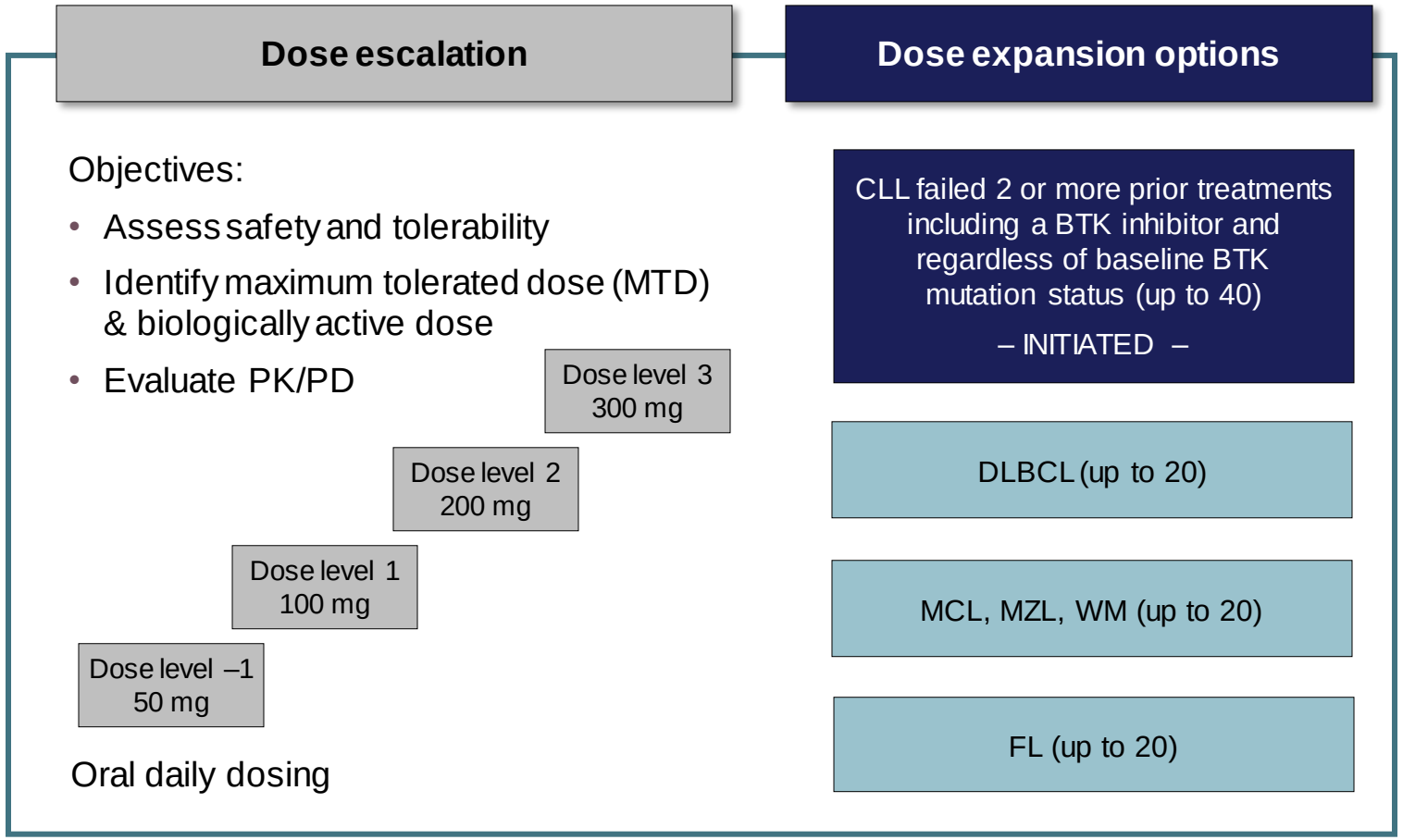
- Early evidence of target engagement
- Rapid and sustained BTK degradation in all patients
- No evidence of immunomodulatory associated adverse events

Next steps:

- Initiate clinical sites in the U.S.
- Identify Phase 1b expansion dose
- Select indications for cohort expansion with initial focus likely in CLL

NX-2127-001: Trial Design

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



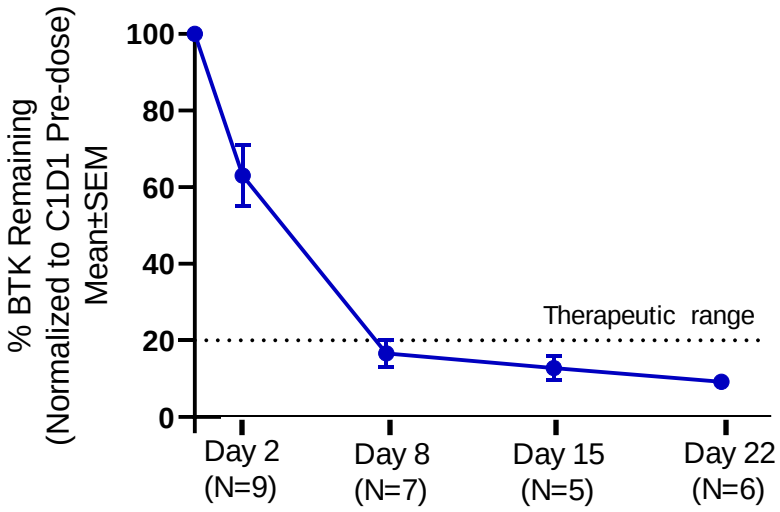
- CLL Phase 1b expansion cohort at 100 mg dose
  - MTD not established
  - 100 mg dose chosen as expansion dose based on PD, clinical activity and safety profile
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL (e.g. DLBCL, MCL, MZL, WM, FL)

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; **PD,** pharmacodynamics; **PK,** pharmacokinetics; **WM**, Waldenstrom's macroglobulinemia

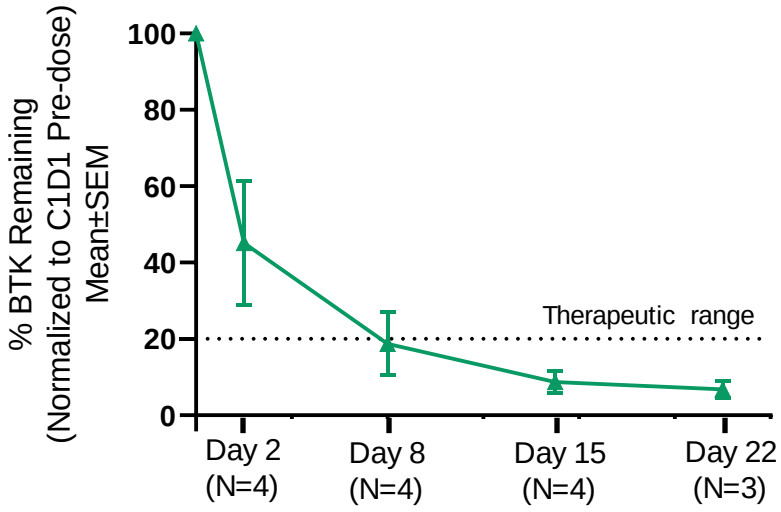
Robust BTK Degradation Observed with NX-2127 Across All Dose Levels and Malignancies

NX-2127-001

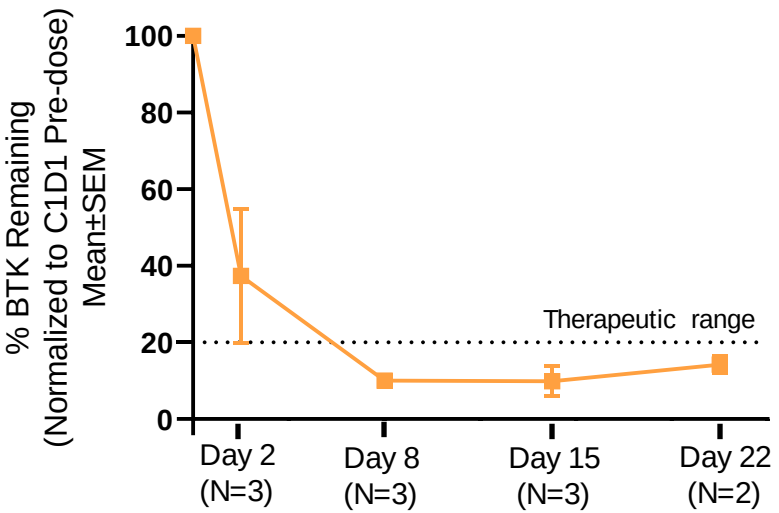
Cohort 1-100 mg
% BTK remaining in CD19+ B cells



Cohort 2-200 mg
% BTK remaining in CD19+ B cells



Cohort 3- 300 mg
% BTK remaining in CD19+ B cells

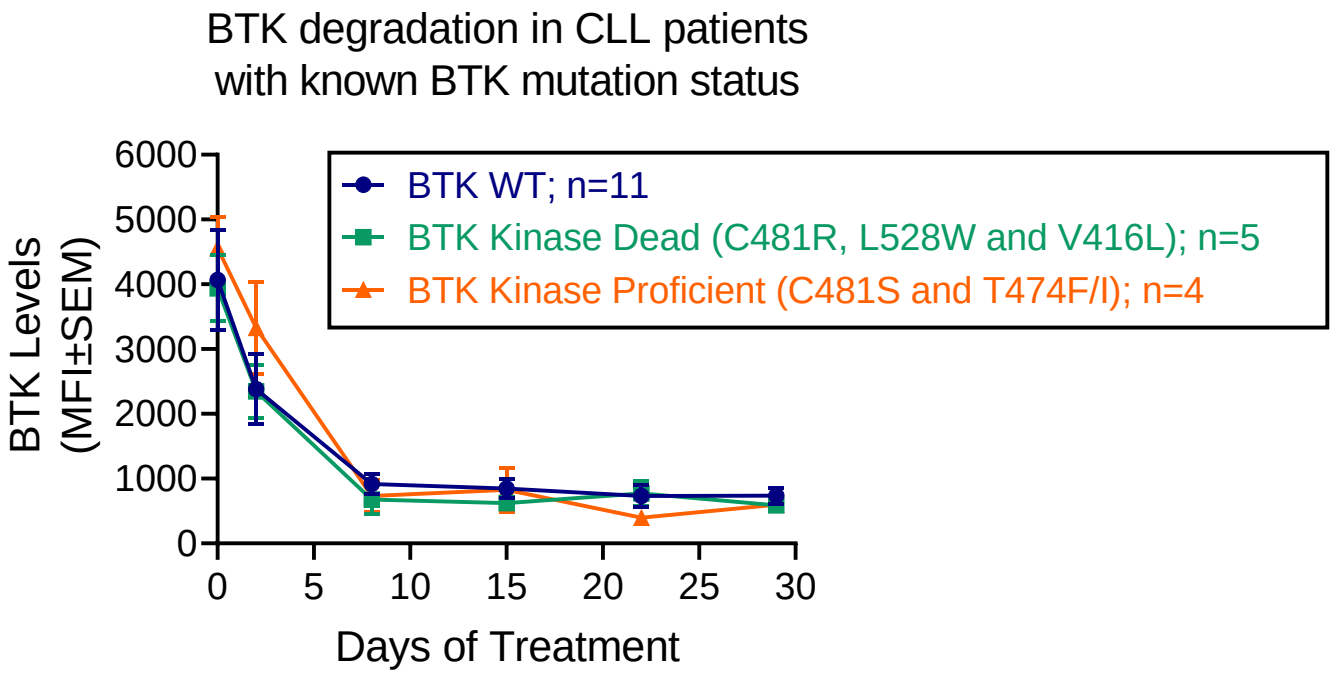


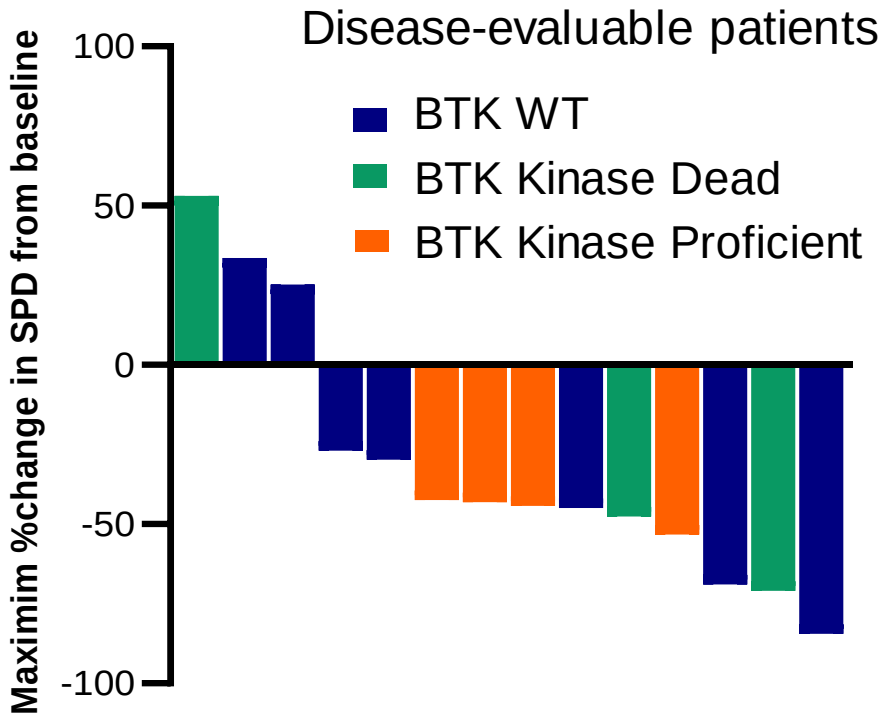
Dose	% BTK Degraded (Average trough)				
	Baseline	Day 2	Day 8	Day 15	Day 22
100 mg	0	37	83	87	90
200 mg	0	55	81	91	93
300 mg	0	63	90	90	86¥

¥ Includes 1 patient who was dose-reduced from 300mg to 100mg mid-cycle.

Treatment with Nurix's NX-2127 Degrader Leads to BTK Degradation and Clinical Response Irrespective of Mutation Status

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





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

Mechanistic Rationale for Dual Degrader in DLBCL

CLINICAL TRIALS AND OBSERVATIONS

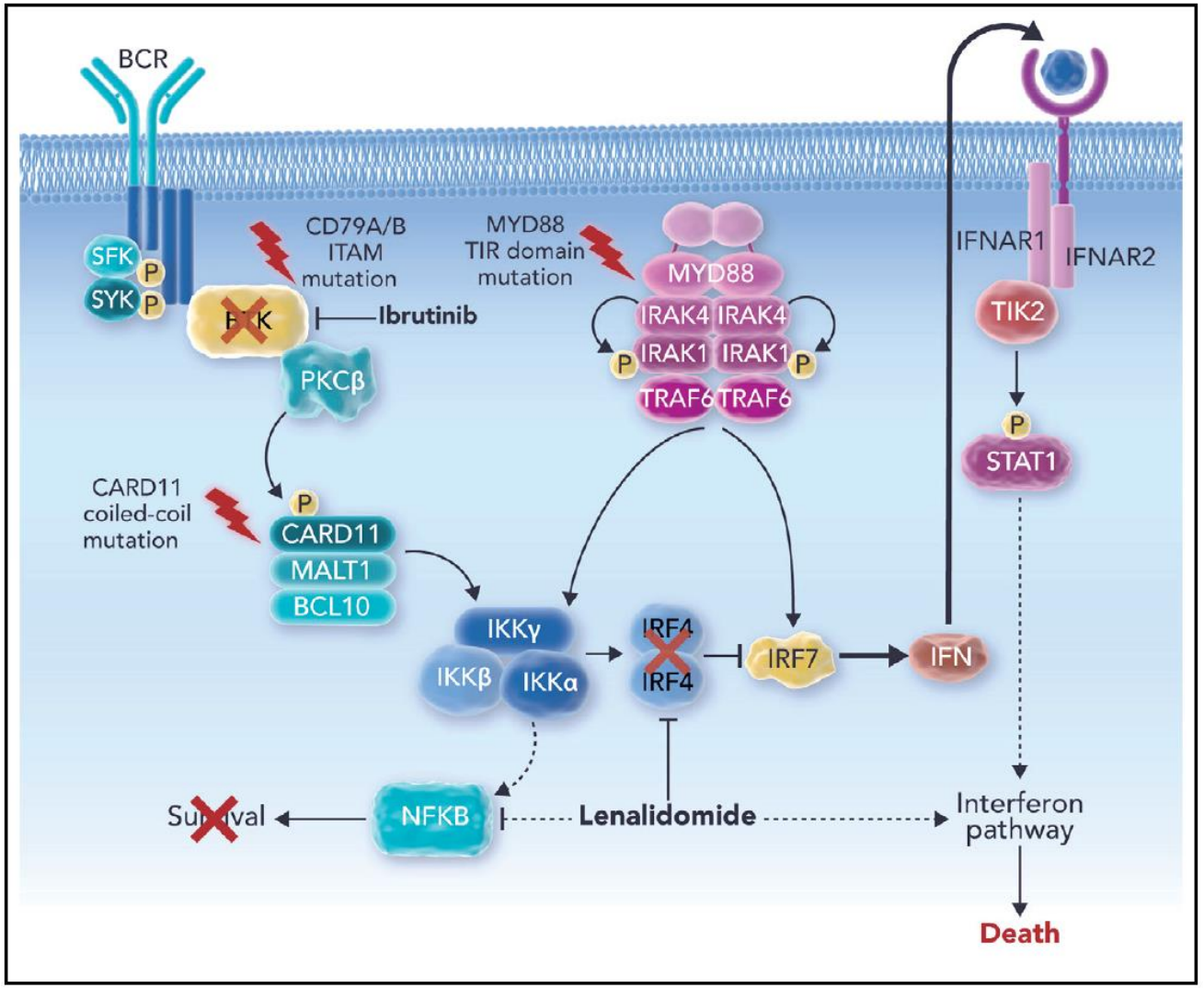
Comment on Goy et al, page 1024

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

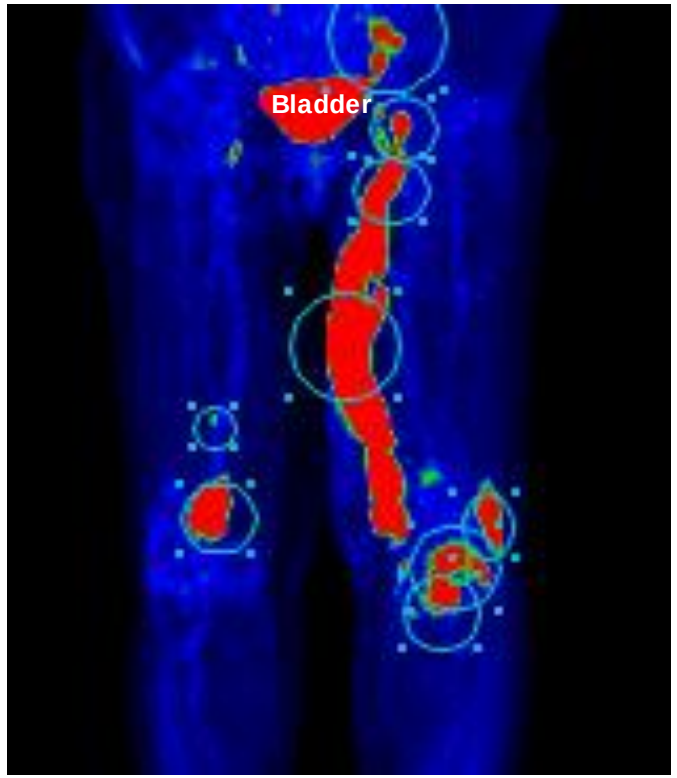


[1] Westin J. Blood 2019;134:996–8

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

FDG-PET CT Scan Disease Assessment

Baseline



Max SUV: 17.6
Deauville score: 5

SUV: Standard Uptake Value

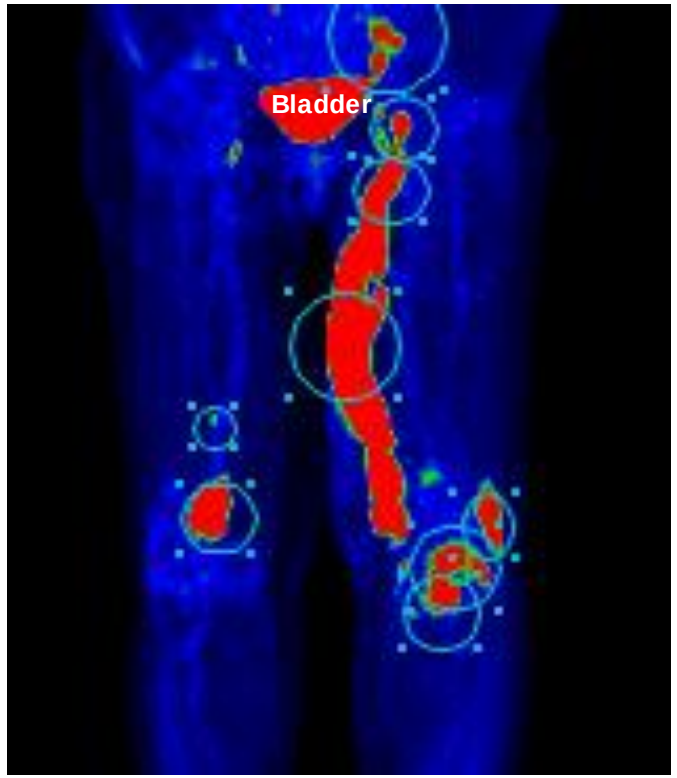
- 84-year-old woman with multiply relapsed ABC-DLBCL following 4 lines of aggressive therapy (including combination of Rituximab, Ibrutinib, and Lenalidomide).

Data as reported TPD October 26, 2022

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

FDG-PET CT Scan Disease Assessment

Baseline



Max SUV: 17.6
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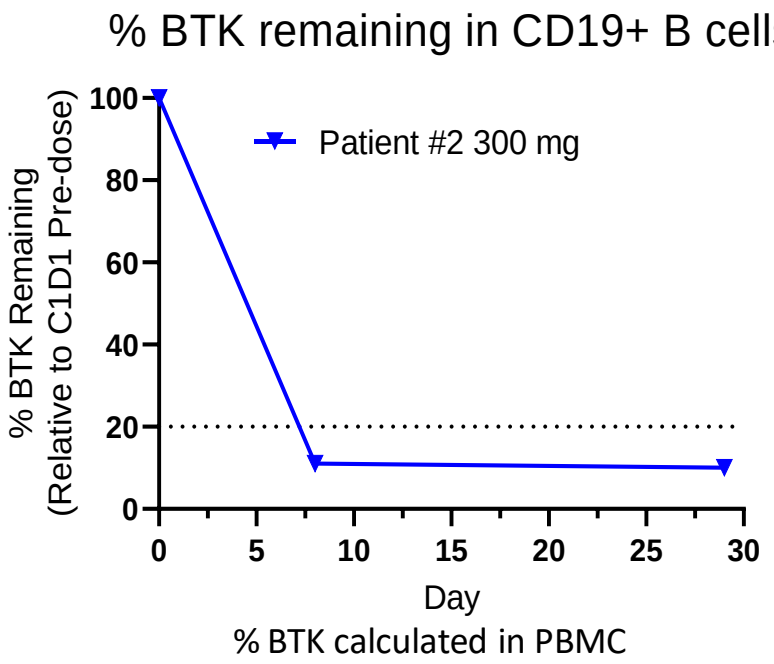
SUV: Standard Uptake Value



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

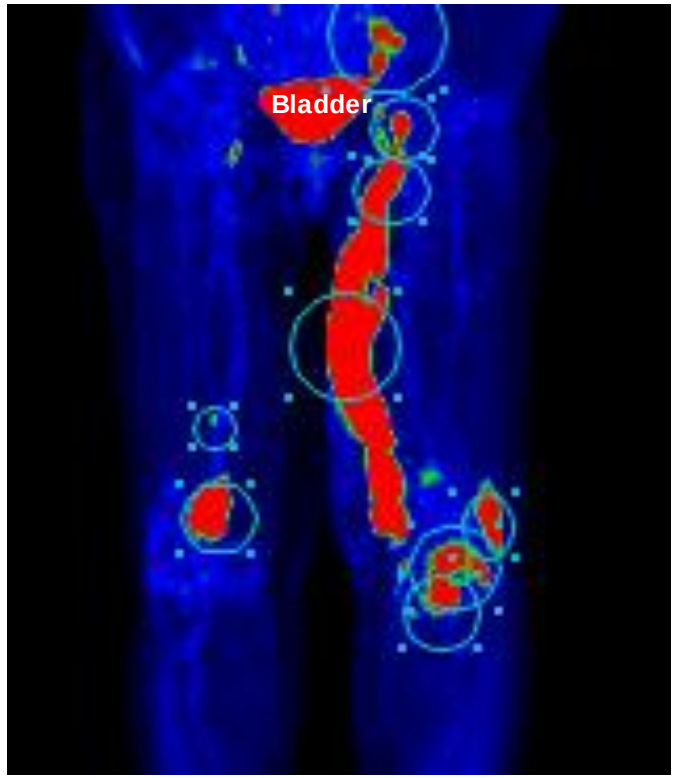
Significant Ikaros and Aiolos degradation also confirmed by day 8

Data as reported TPD October 26, 2022

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

FDG-PET CT Scan Disease Assessment

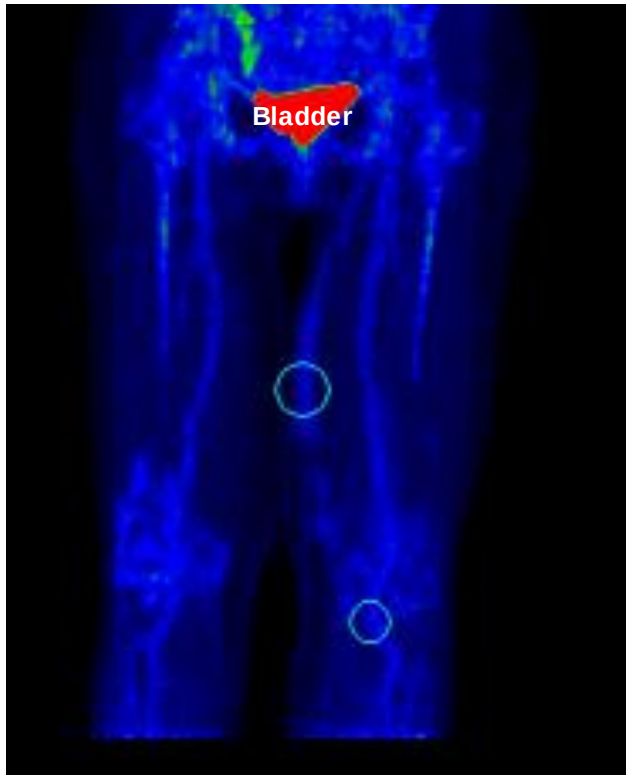
Baseline



Max SUV: 17.6
Deauville score: 5

SUV: Standard Uptake Value

Week 16



Max SUV: 2.5
Deauville score: 2

Normal SUV

- 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.

nurix

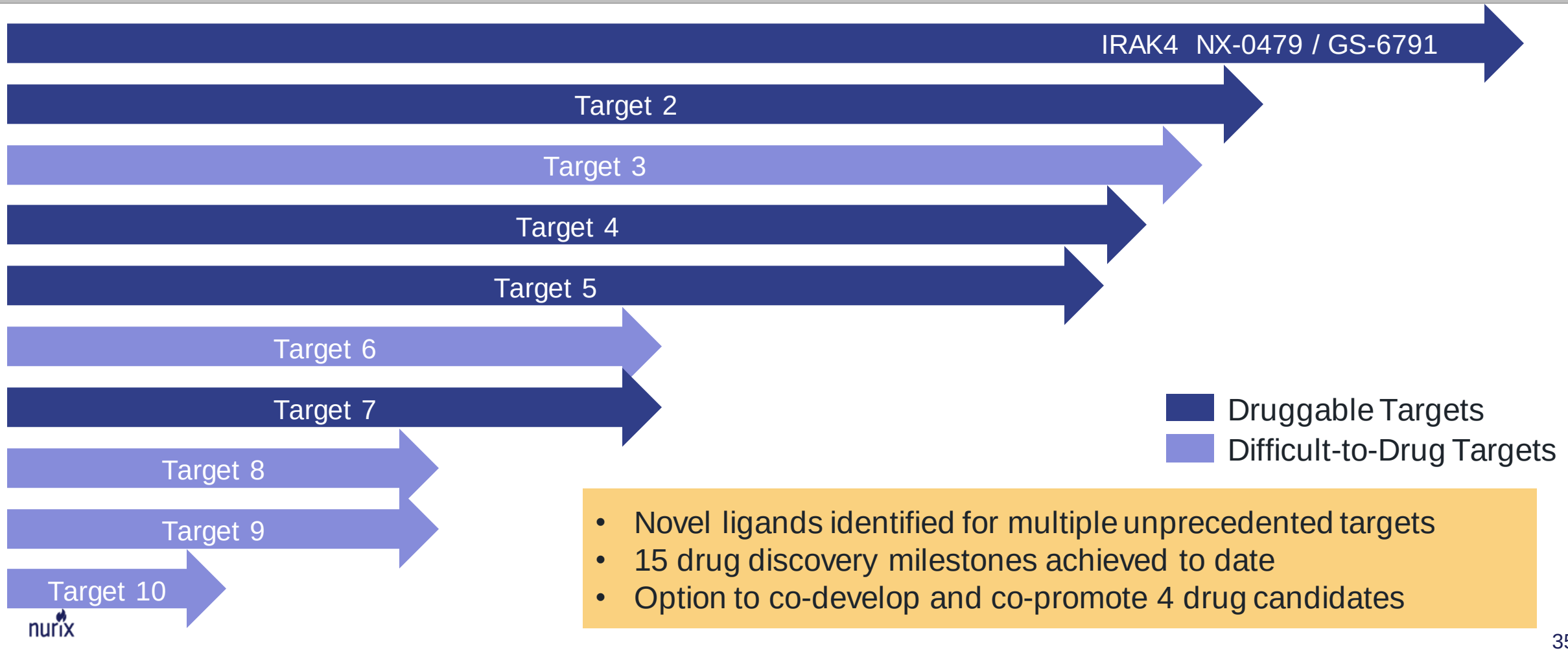
Data as reported TPD October 26, 2022

Nurix's Clinical Experience with Targeted Protein Degradation Illustrates the Benefits of Novel Therapeutic Modalities

Catalytic modality of TPD can provide:

1. Increased target coverage
   - One degrader can degrade many protein molecules
2. Prolonged activity against a target
   - Protein synthesis rather than drug clearance is required to restore target
   - Ideally suited for non-daily delivery methodologies
3. Ability to address mutational resistance
   - Nurix's BTK degraders are potent against unanticipated BTK active site mutations
4. Ability to address novel and non-enzymatic targets
   - Degraders are agnostic to protein catalytic function; noncatalytic proteins can be targeted
   - Structured (e.g. transcription factors) and 'plastic' proteins can be addressed

Leveraging Early Success with BTK Degraders to Build a Broad Collaboration Pipeline that Includes Many Unprecedented and First-In-Class Targets



- Novel ligands identified for multiple unprecedented targets
- 15 drug discovery milestones achieved to date
- Option to co-develop and co-promote 4 drug candidates

nurix

Thank you!