nurix

Leader in Targeted Protein Modulation

First Disclosure of NX-2127, an oral targeted degrader of Bruton's tyrosine kinase (BTK) with concurrent immunomodulatory activity for the treatment of B-cell malignancies

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AACR

Orlando, FL

April 17, 2023

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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)

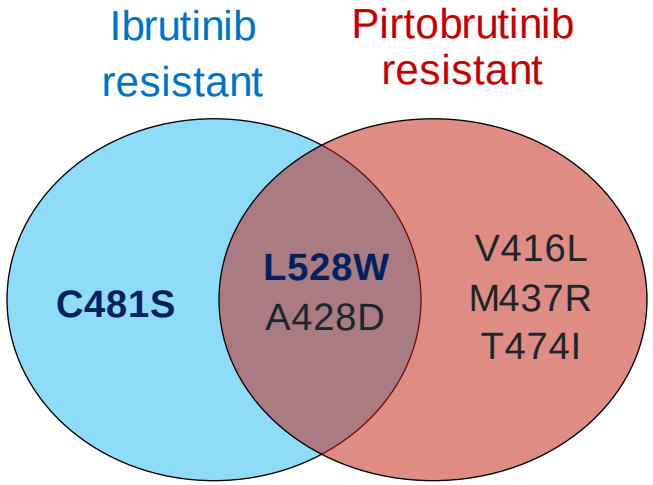
Targeted Protein Elevation (TPE)

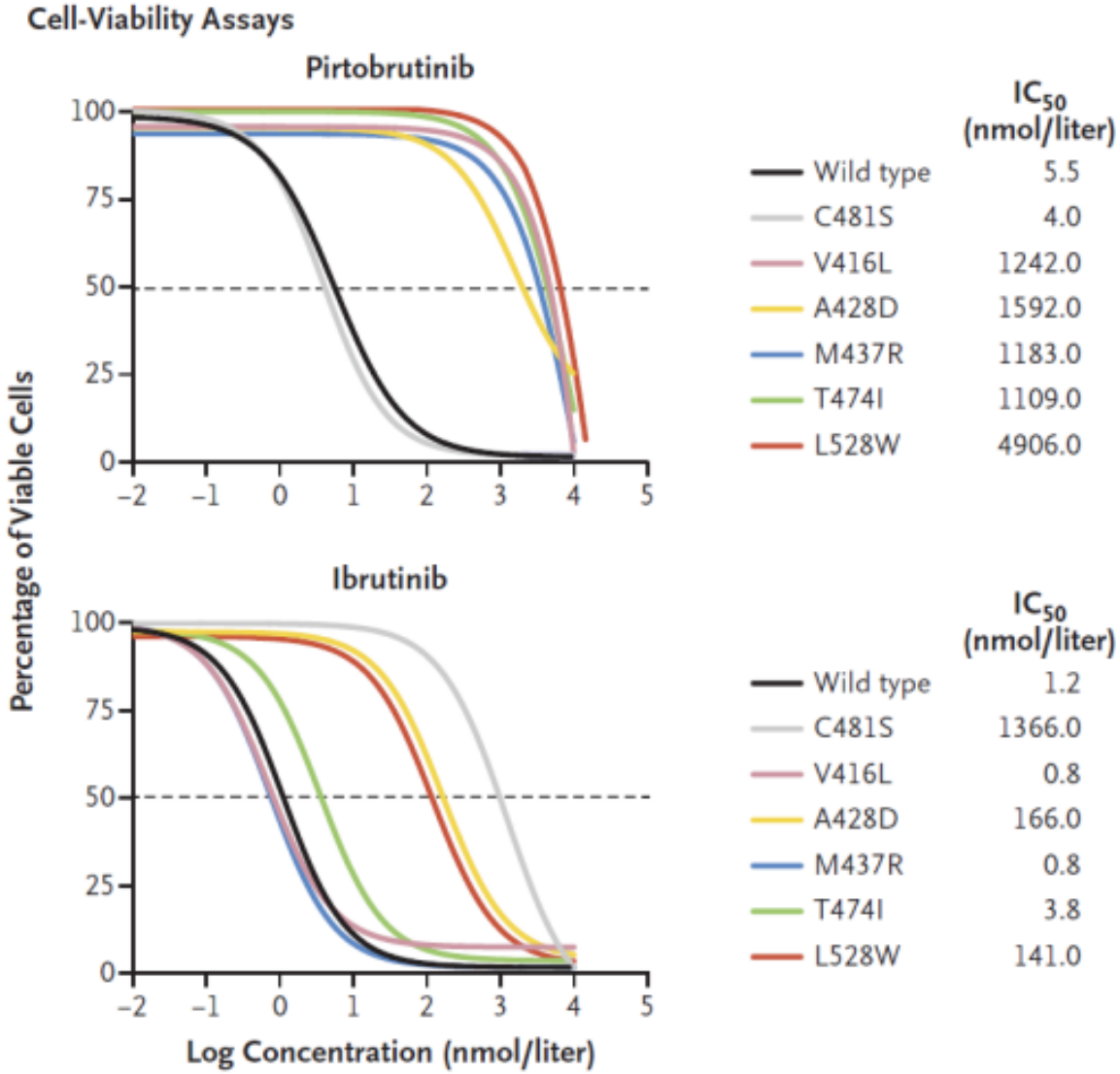
Inhibit ligases to increase specific protein levels

Emerging BTK mutations confer resistance to covalent and non-covalent BTK inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

"Our data suggest potential new therapeutic approaches to overcome the newly described BTK inhibitor resistance mechanisms. For example, these data provide a rationale for therapies aimed at addressing the potential scaffold function of BTK rather than inhibiting BTK kinase activity."

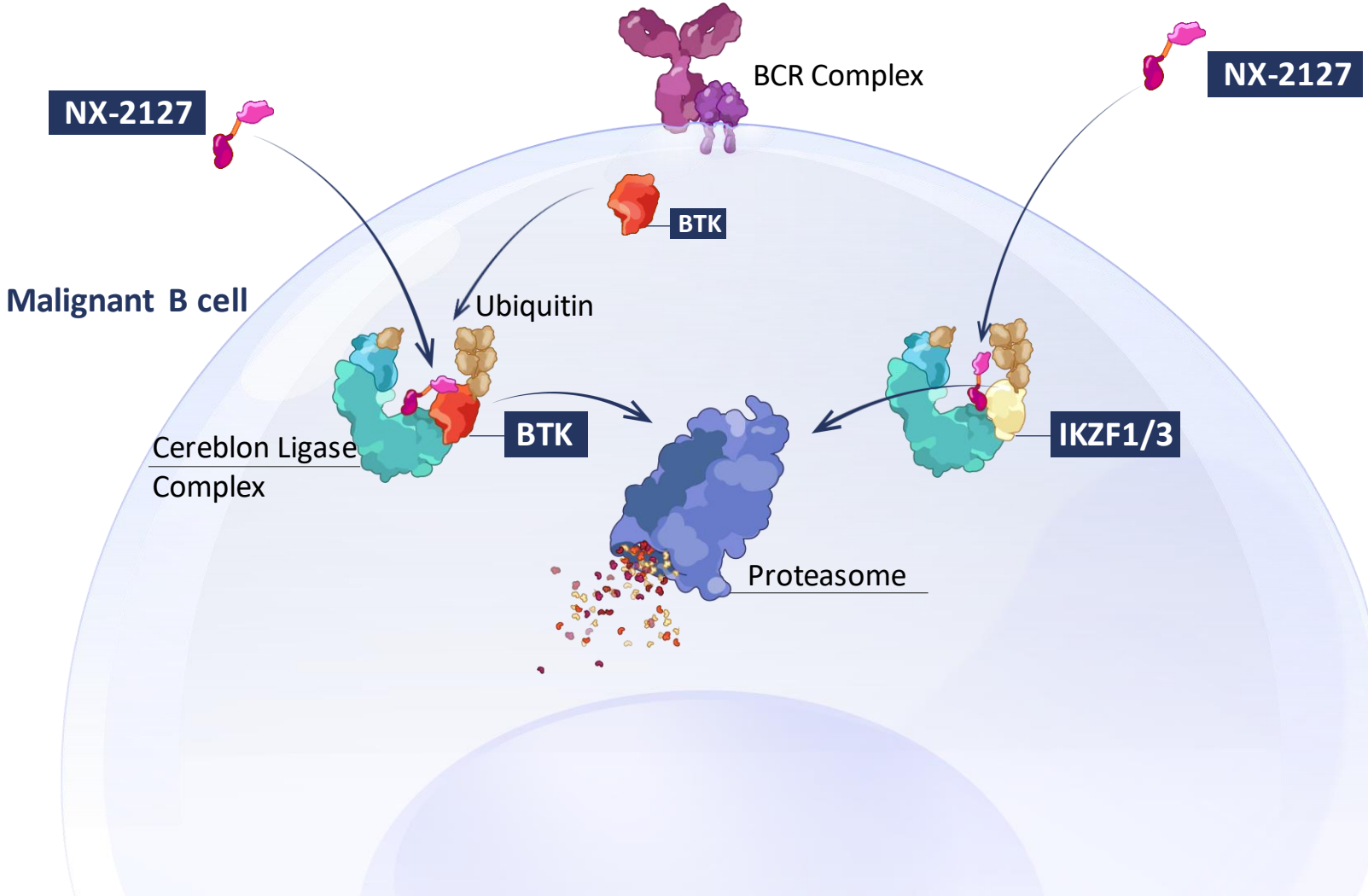




Wang et al., *N Eng. J. Med*, **2022**, 386:735-743

NX-2127 dual mechanism of action

Targeted degradation of BTK and CRBN immunomodulatory substrates IKZF1/3



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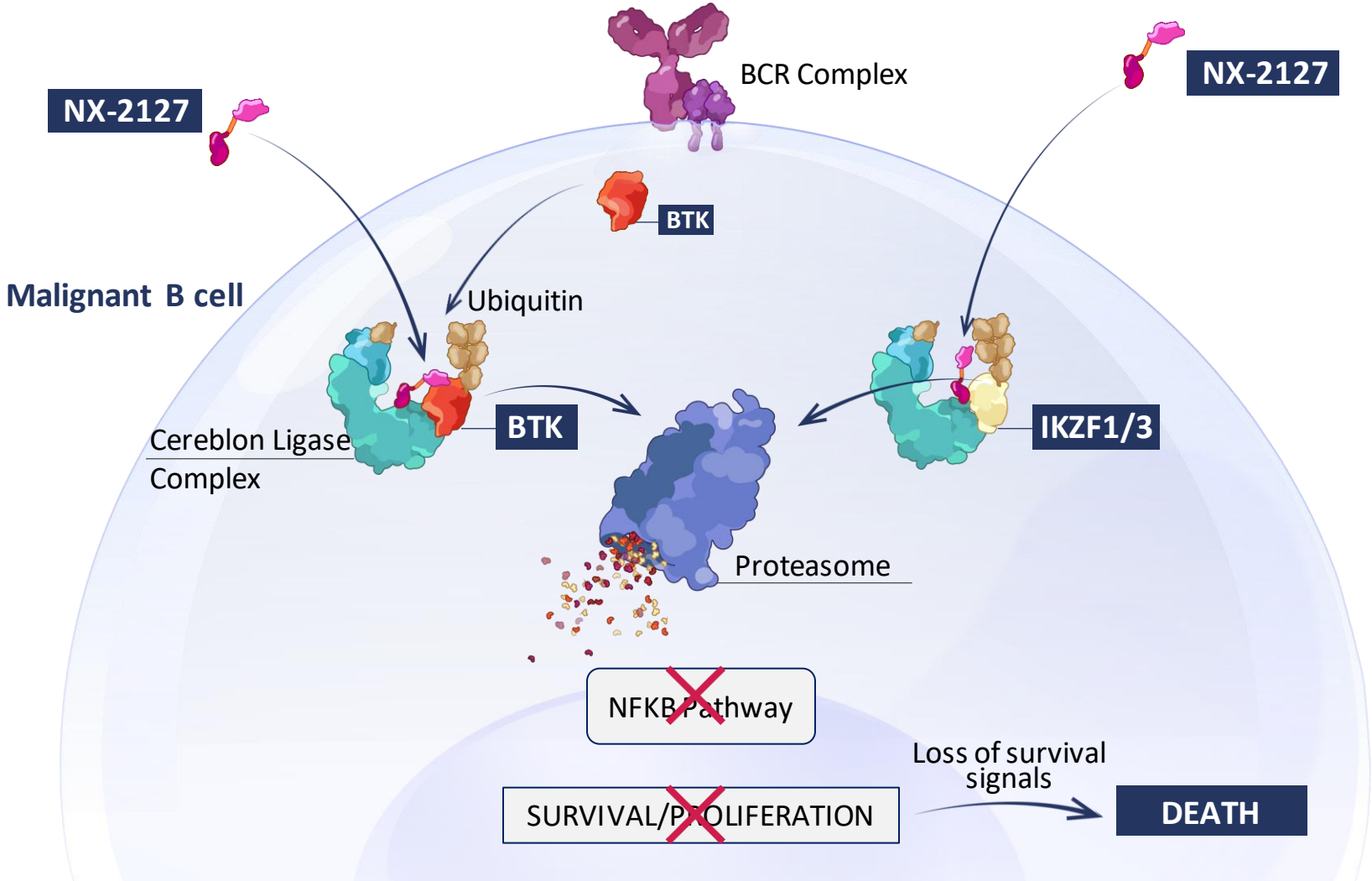
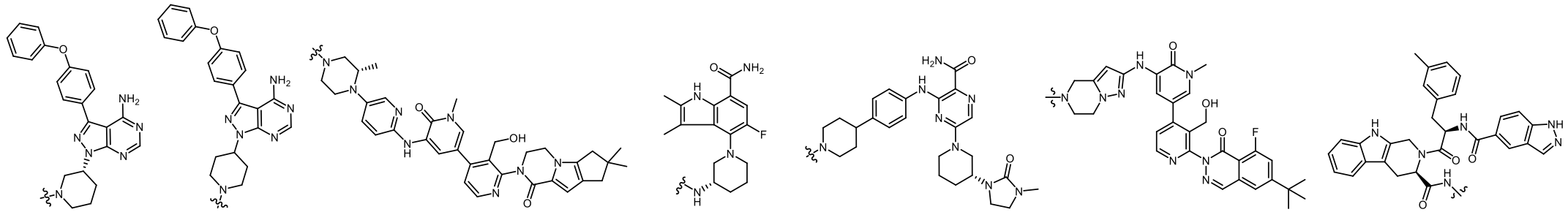
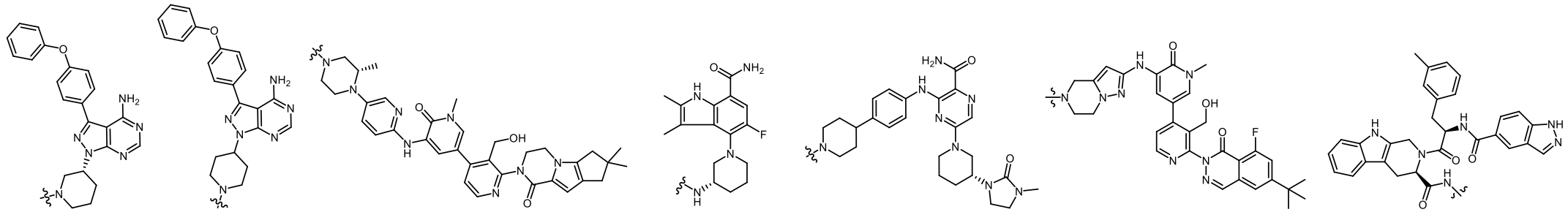


Evolution of BTK degraders



BTK binders combined with PEG and alkyl linkers to ligase binders for CRBN, VHL, IAP

Evolution of BTK degraders



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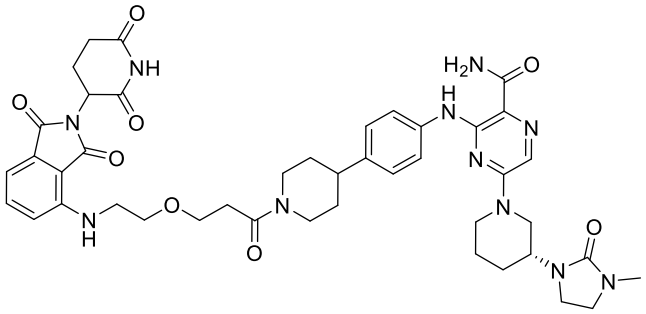
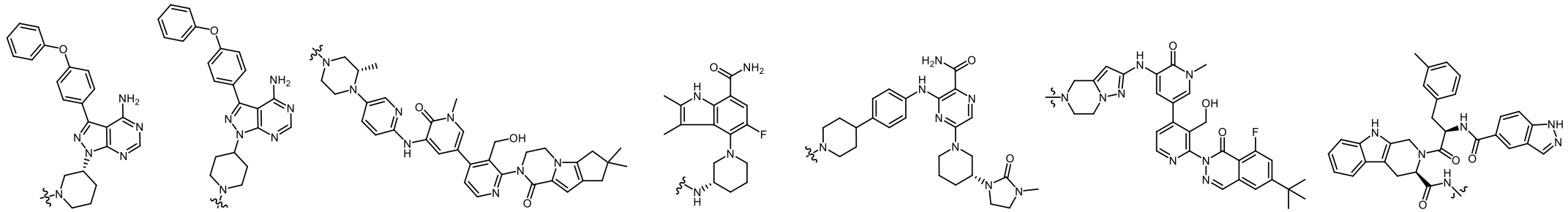


BTK DC_{50} = 7 nM (Dmax 86%)

No oral exposure (mouse)

Evolution of BTK degraders



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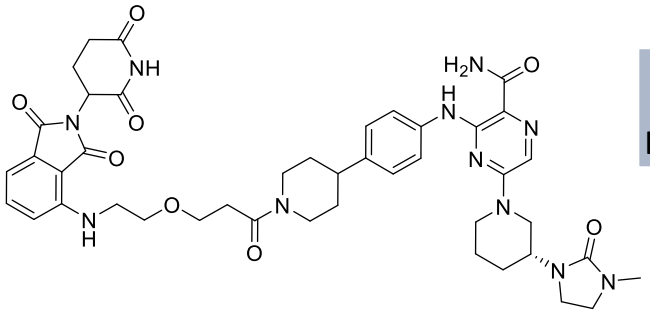
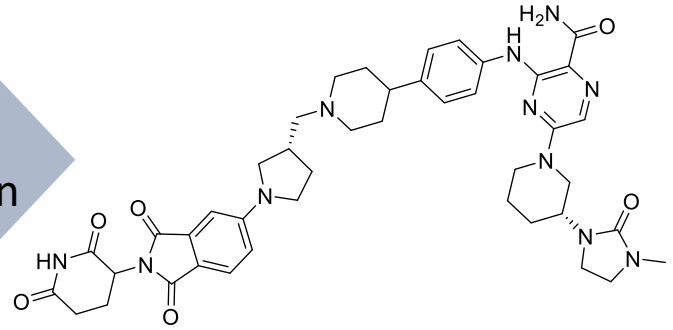


BTK DC_{50} = 7 nM (Dmax 86%)

No oral exposure (mouse)

Linker rigidification



NRX-0492

BTK DC_{50} = 0.5 nM (Dmax 96%)

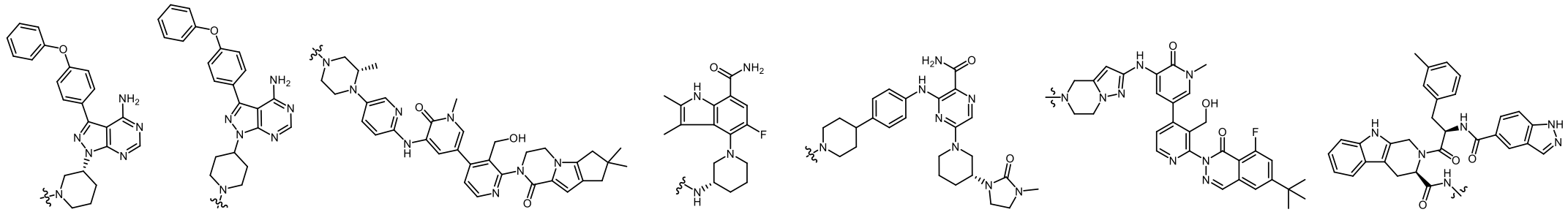
F = 8% (mouse)

High Blood:Plasma ratio

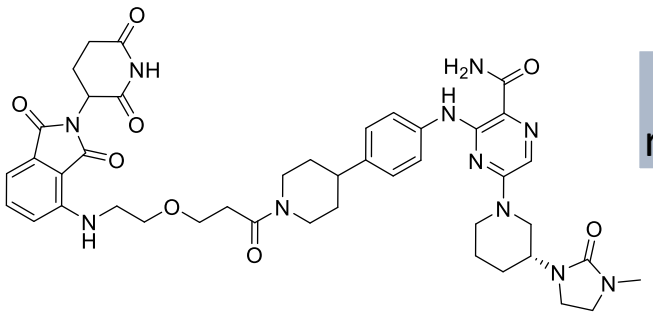
Dog = 6

Cyno = 11

Evolution of BTK degraders

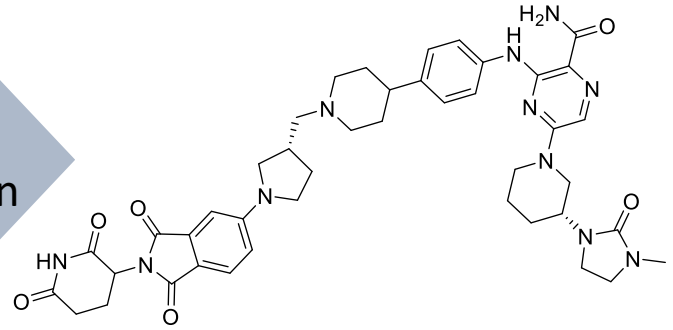


BTK binders combined with PEG and alkyl linkers to ligase binders for CRBN, VHL, IAP



BTK DC_{50} = 7 nM (Dmax 86%)
No oral exposure (mouse)

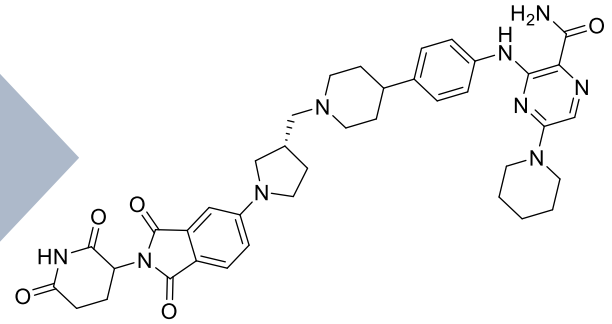
Linker rigidification



NRX-0492

BTK DC_{50} = 0.5 nM (Dmax 96%)
F = 8% (mouse)
High Blood:Plasma ratio
Dog = 6
Cyno = 11

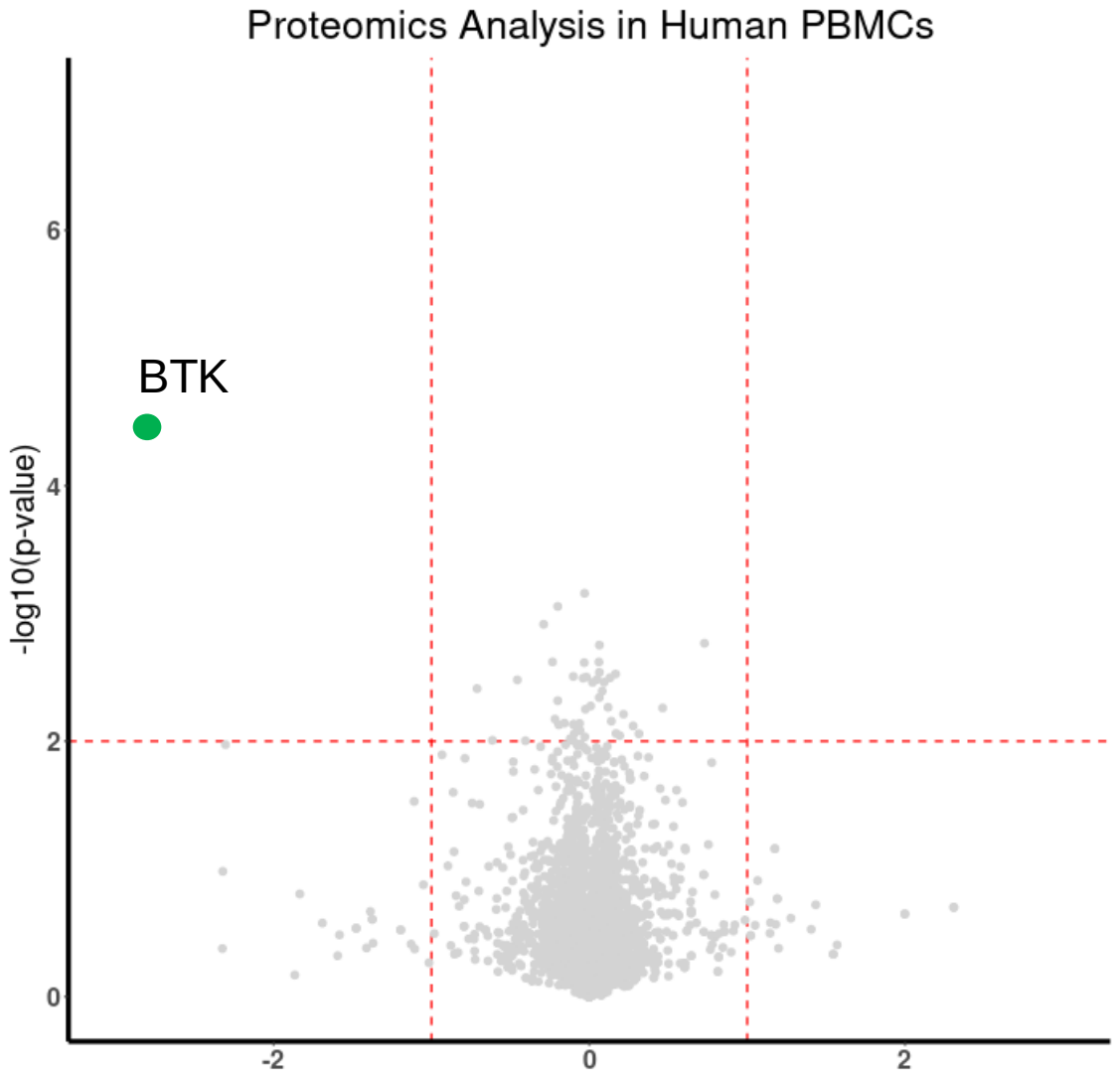
Reduction in MW



NX-2127

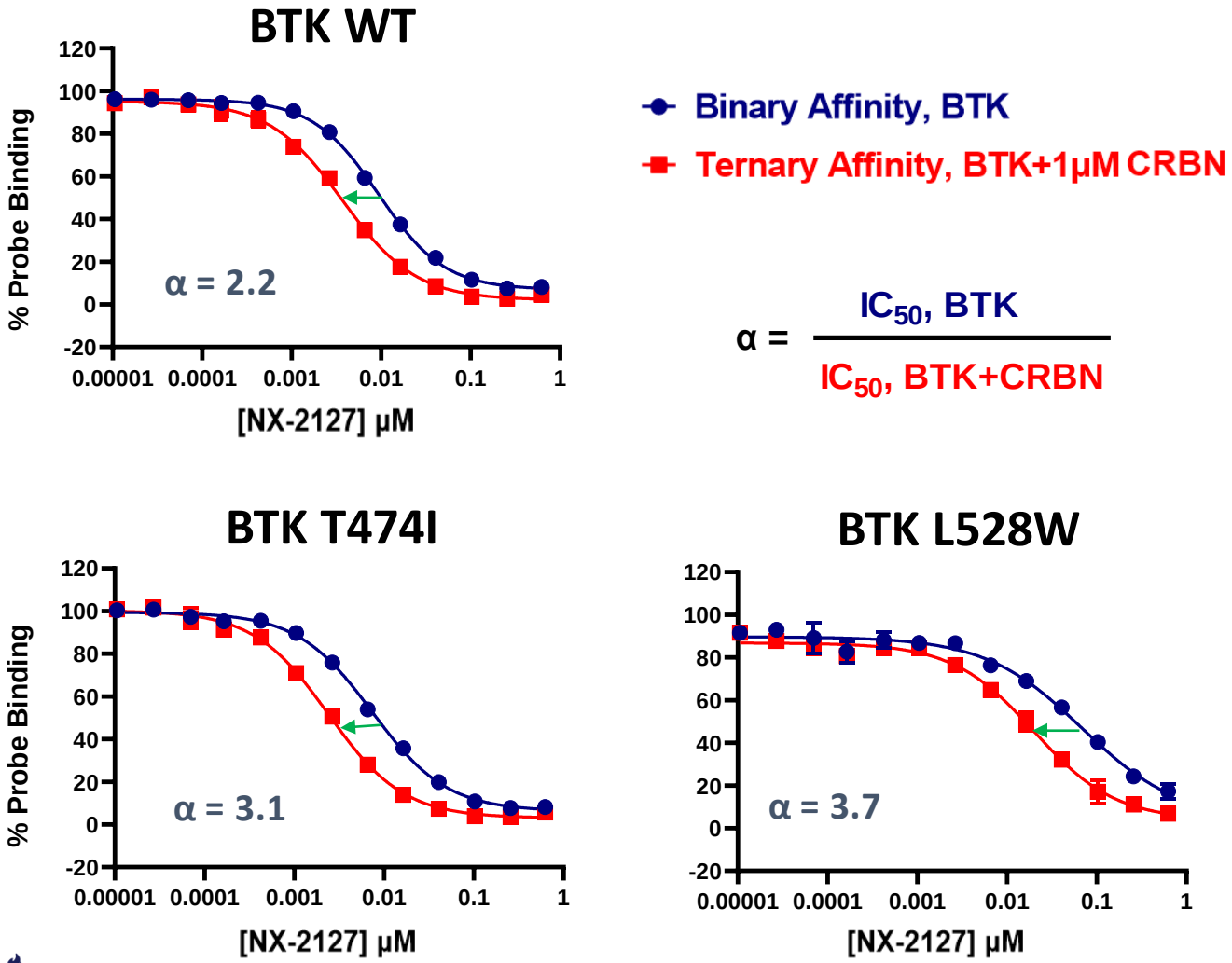
BTK DC_{50} = 4.5 nM (Dmax 86%)
F = 36% (mouse)
Blood:Plasma ratio
Dog = 0.65
Cyno = 0.78

Proteomics analysis indicates NX-2127 selectively degrades BTK



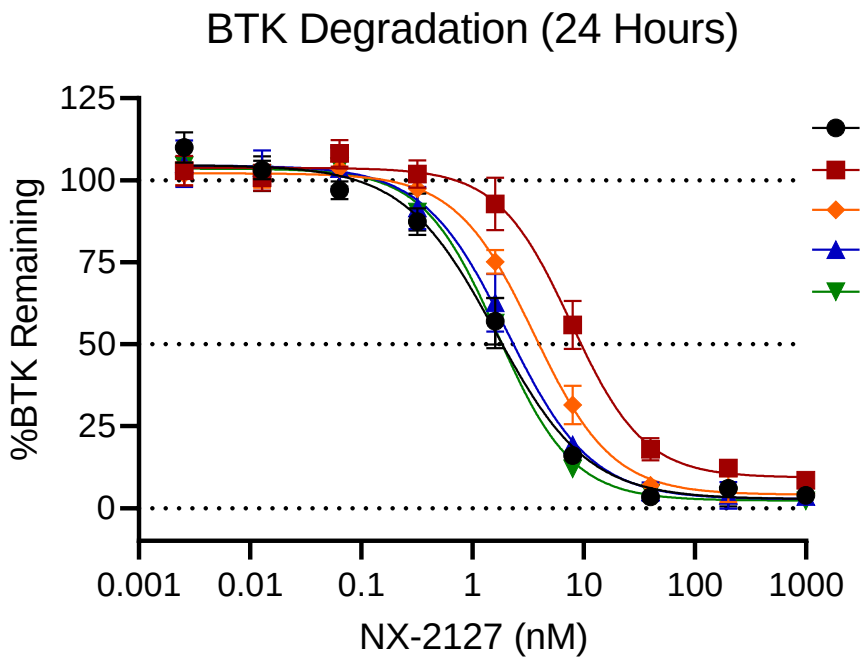
50 nM, 4h

NX-2127 induces positive cooperativity between BTK and CRBN



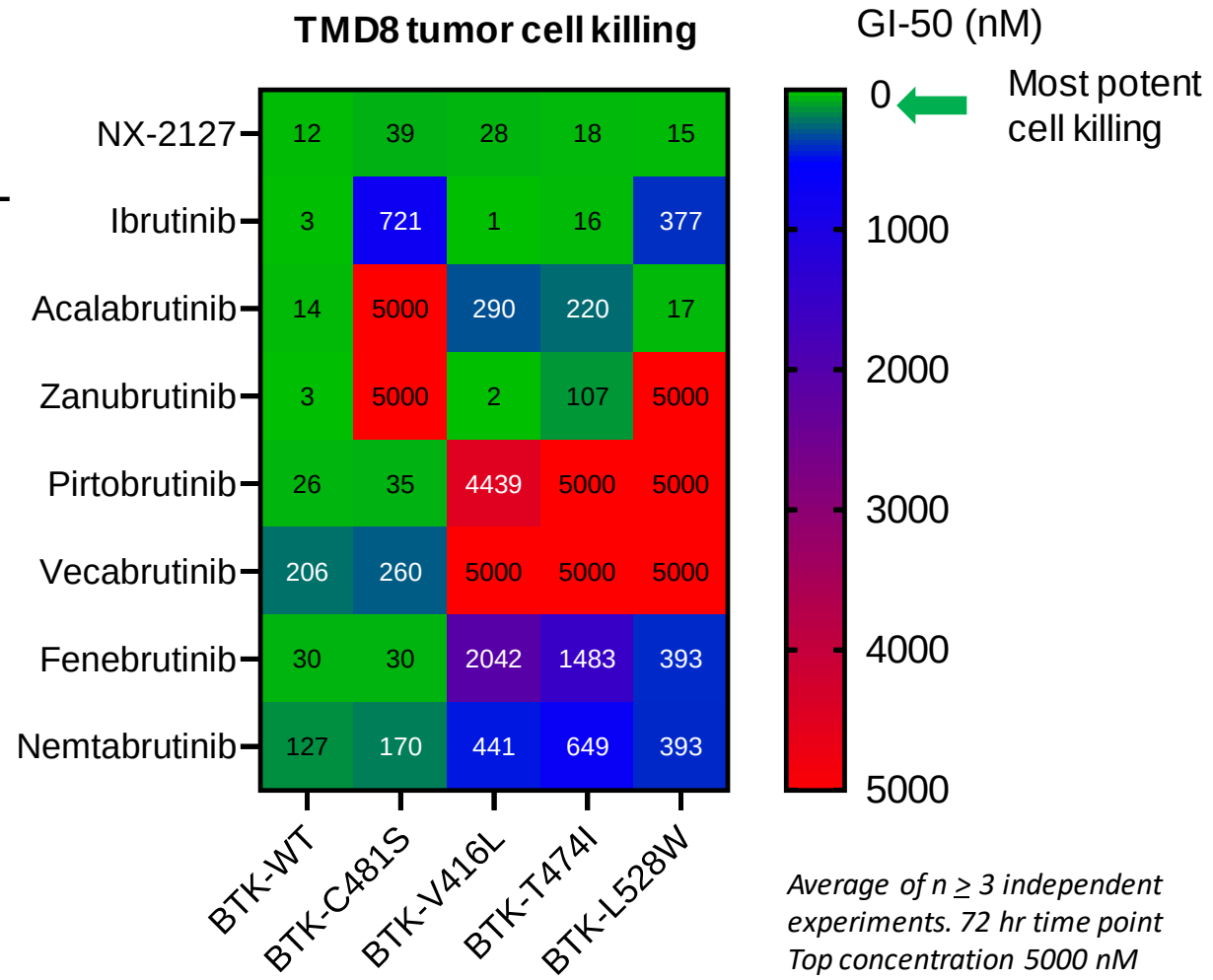
- Moderate positive cooperativity α>1 for multiple BTK mutations
- Favorable protein-protein interactions
- Greater tolerance for reduced BTK affinity

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



	DC50 ± SEM (nM)
WT	1.94 ± 0.41
C481S	9.68 ± 2.36
V416L	4.17 ± 0.75
T474I	2.41 ± 0.54
L528W	1.86 ± 0.39

TMD8 cells n = 3

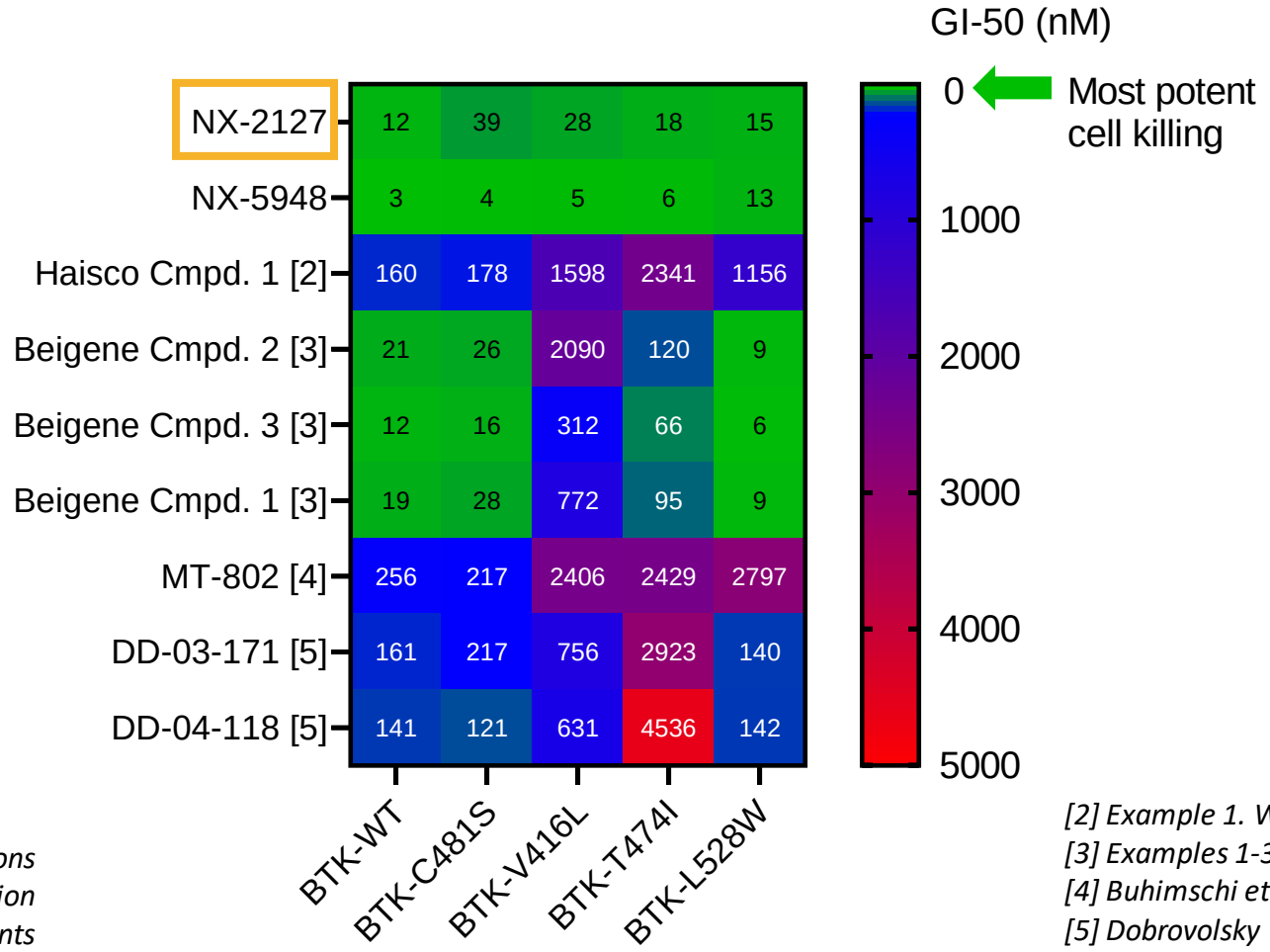


Average of n ≥ 3 independent experiments. 72 hr time point Top concentration 5000 nM

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

Not All BTK Degraders Are Created Equal

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



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

[2] Example 1. WO 2022/111449 (Haisco)
[3] Examples 1-3. WO 2021/219071 (BeiGene)
[4] Buhimschi et al. 2018. Biochemistry 57(26): 3564-3575.
[5] Dobrovolsky et al. 2019. Blood 133(9): 952-961.

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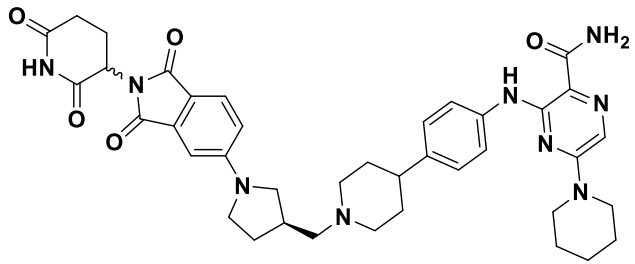
See also poster abstract number 2850 (section 20, board 8)

NX-2127 Cellular Potency and Cross-species PK



	Degradation Results
BTK DC_{50} (WT/C481S TMD8 cells, nM) @ 24h	1.9 / 9.7
IKZF3/IKZF1 DC_{50} (Primary Human T cells, nM) @ 24h	36 / 57

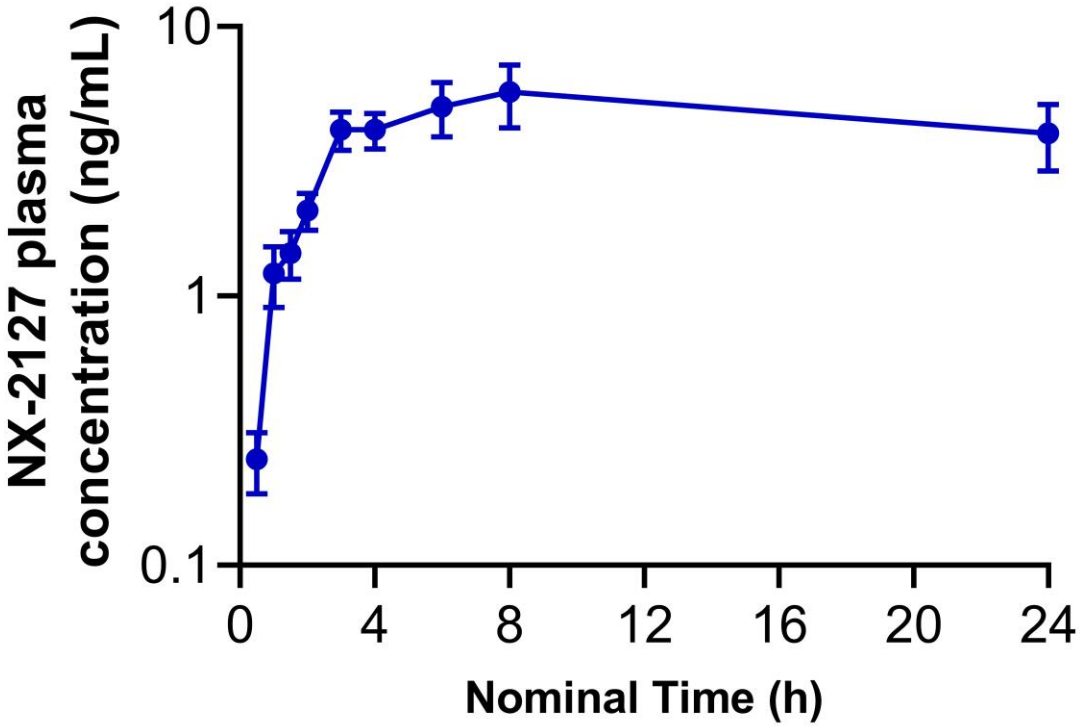
	Mouse	Rat	Dog	Cynomolgus Monkey
Cl_{obs} (mL/min/kg), 1 mg/kg IV dose	5.2	19.0	18.4	22.2
AUC (hr*µM), 10 mpk PO	16	1.2	0.13	0.09
Cmax (µM)	1.3	0.98	0.38	0.011
$V_{ss,obs}$ (L/kg)	1.0	2.8	7.0	7.5
%F	36	7.1	0.9	1.0
% BTK degraded 24 h following one 10 mg/kg PO dose)	79	ND	83	88

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

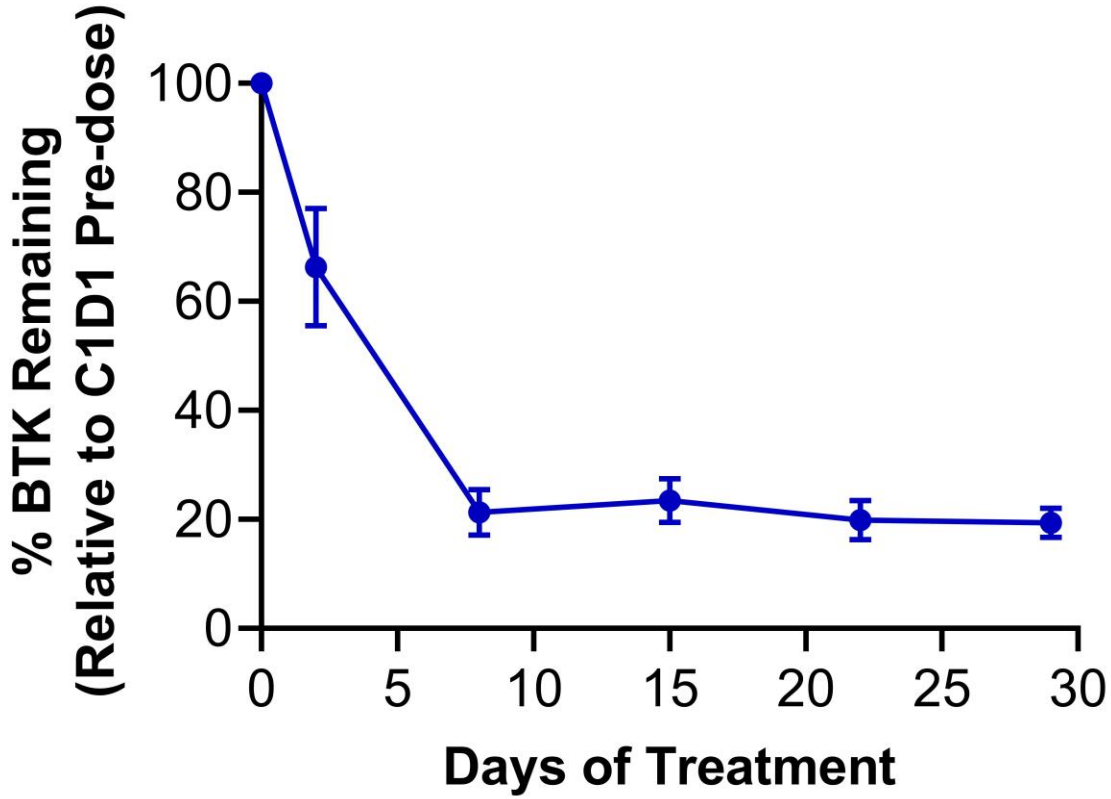
Degradation of BTK observed in Phase 1 patients

Cohort 1 - 100 mg N = 14

Cycle 1, Day 1

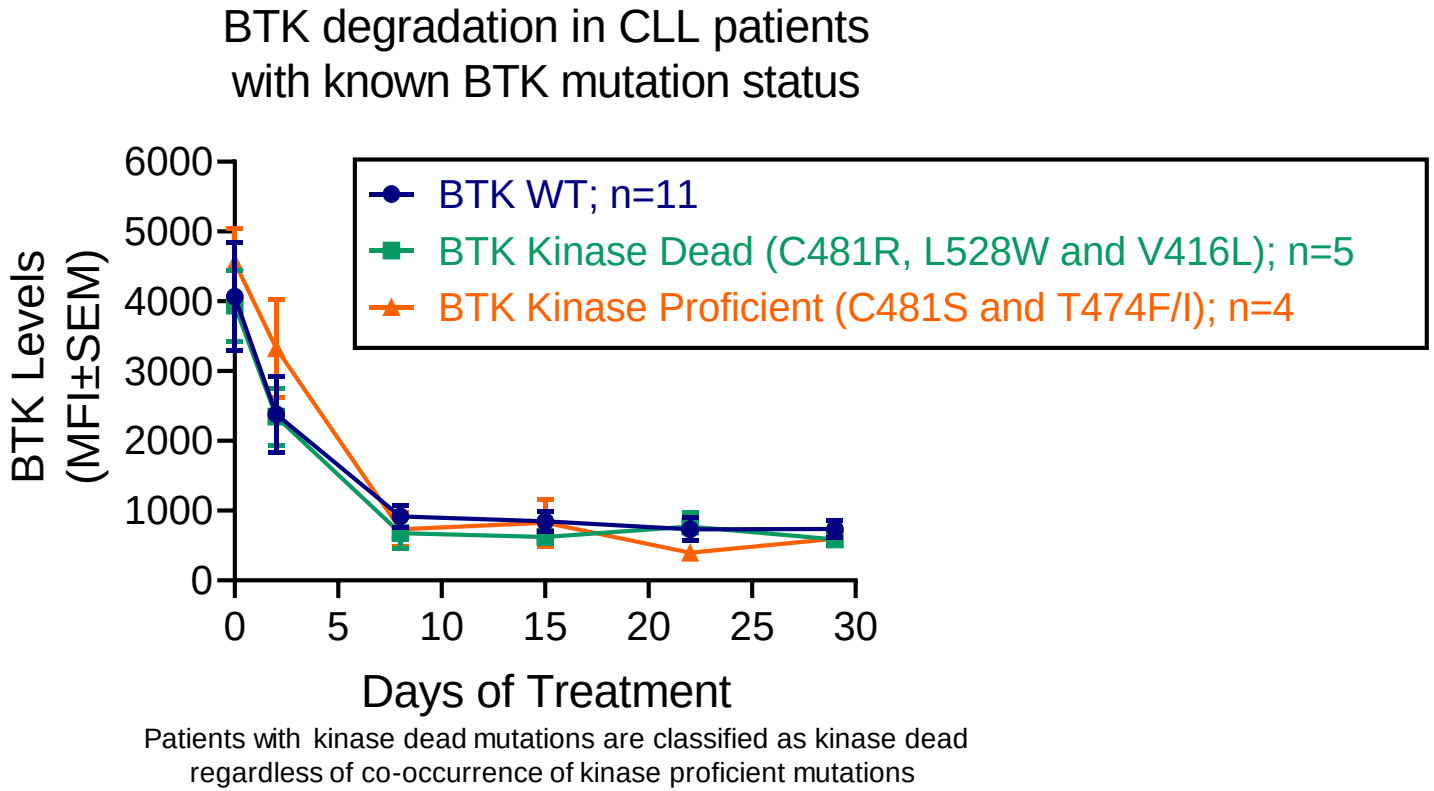


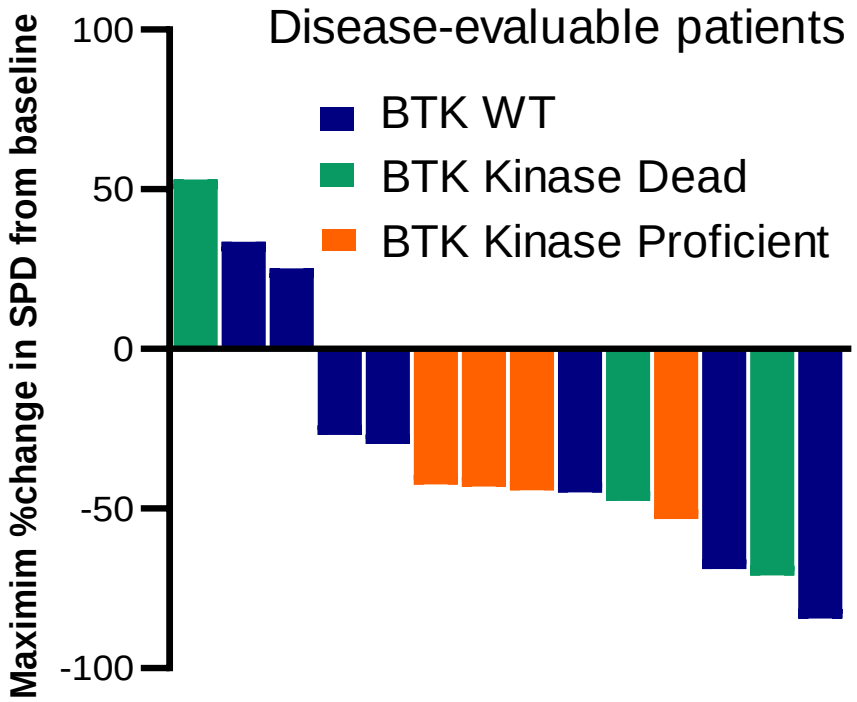
% BTK remaining in CD19+ B cells



Clinical trial NCT04830137

NX-2127 demonstrates clinical activity against a range of BTK mutations



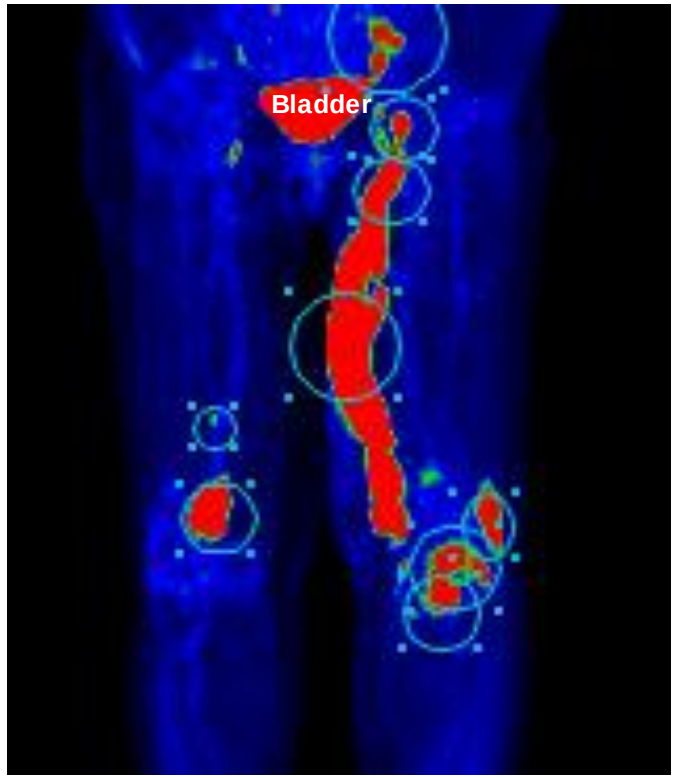


- BTK degradation of 80% achieved in CLL patients including those harboring BTK C481, T474, L528, and V416 resistance mutations
- IKZF1 and IKZF3 degradation also observed in patient samples

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

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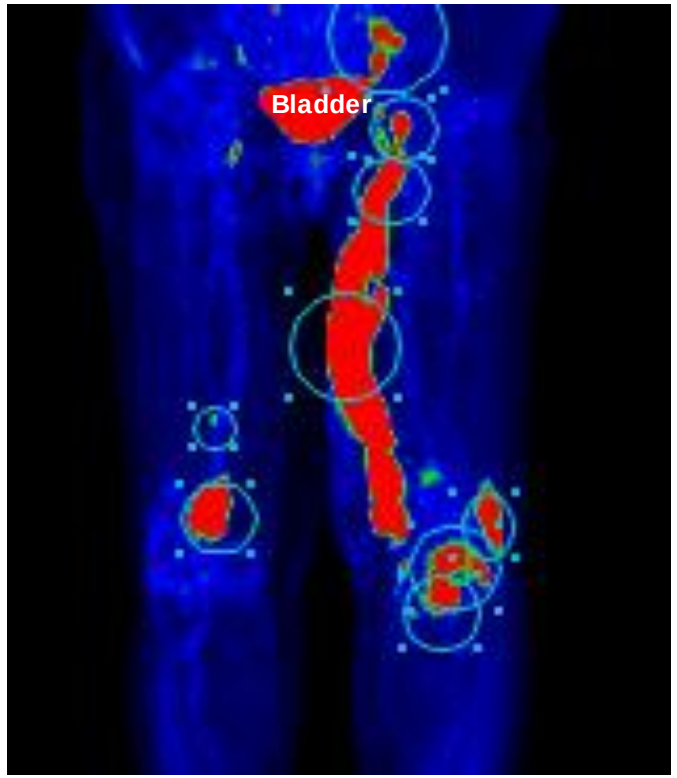

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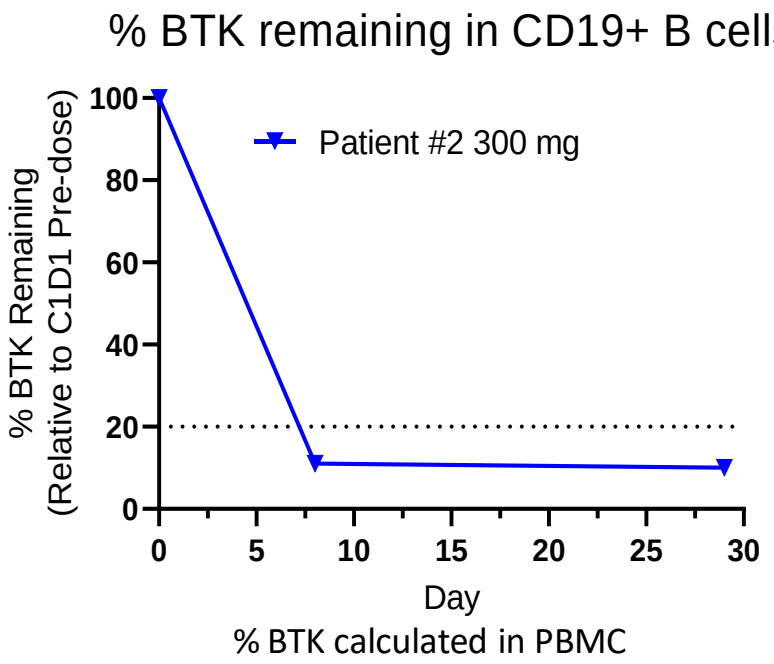


- 84-year-old woman with multiply relapsed ABC-DLBCL following 4 lines of aggressive therapy (including combination of Rituximab, Ibrutinib, and Lenalidomide).

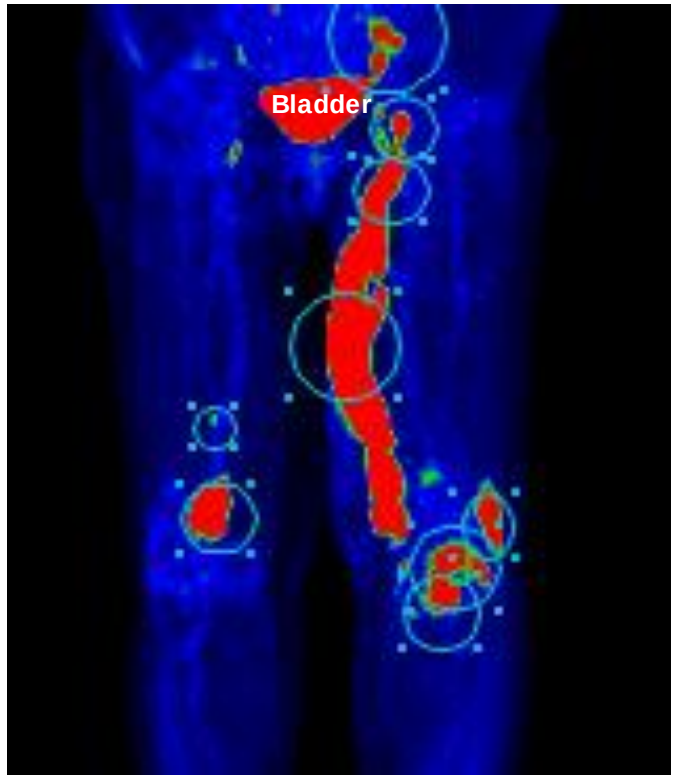
Significant IKZF1 and IKZF3 degradation also confirmed by day 8

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

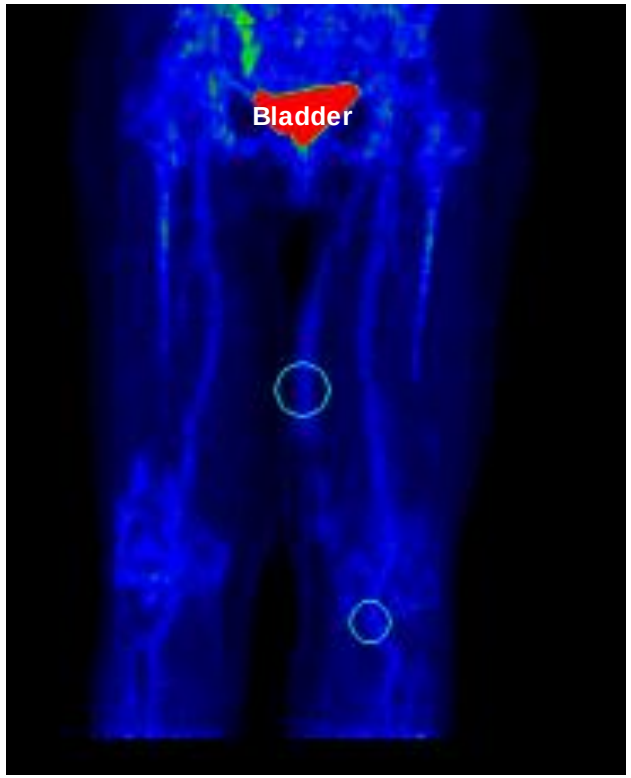
Baseline



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.

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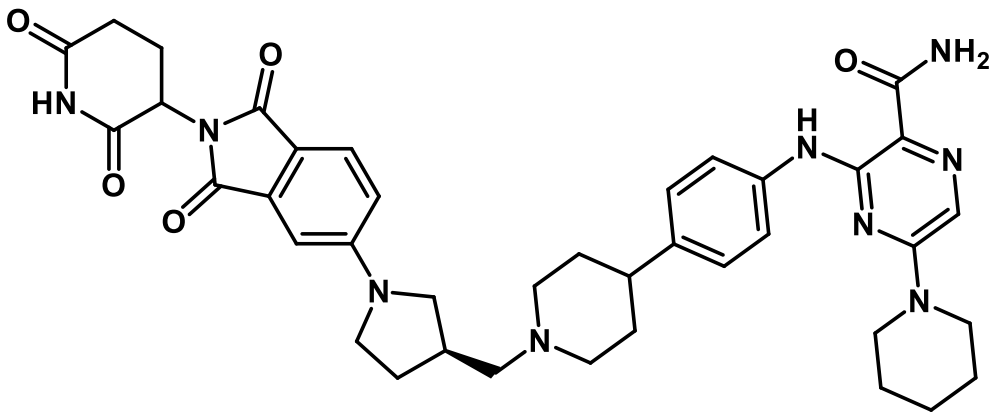
Data as reported TPD October 26, 2022

NX-2127 overcomes resistance in the clinic



Overcome resistance

Degrader activity against resistance mutations to both covalent and non-covalent BTKi

Address scaffolding function

Degradation blocks all downstream signaling including kinase-dead BTK mutants

Dual degrader activity

Immunomodulatory activity retained from cereblon binder adds second anti-tumor mechanism

Thank you!