nurix

Leader in Targeted Protein Modulation

Nurix Therapeutics

Blazing a New Path in Medicine

ASH Event Presentation

December 12, 2022

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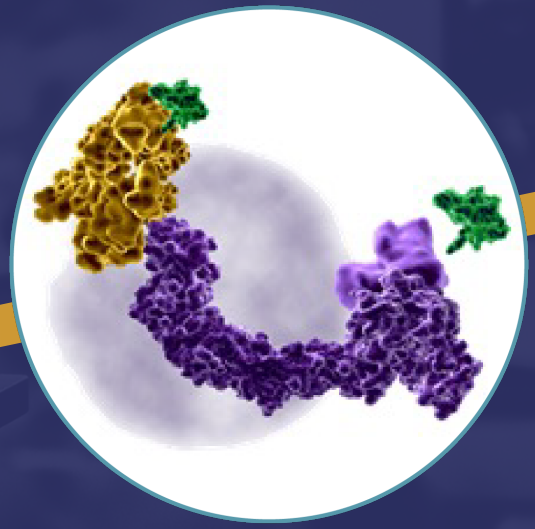
Nurix Drugs Engage Ligases for the Treatment of Cancer

Targeted Protein Modulation: TPM = TPD + TPE

Harness ligases
to decrease specific protein levels

A Powerful Cellular System



Targeted Protein Elevation (TPE)

Inhibit ligases
to increase specific protein levels

Targeted Protein Degradation (TPD)

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

Nurix is Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

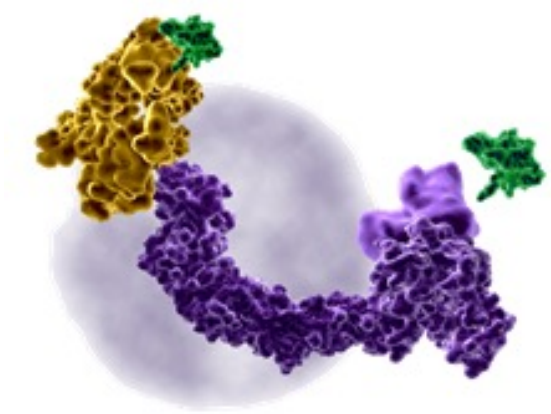
MOA	Drug program	Target/delivery	Therapeutic area	Preclinical	Phase 1	Phase 2	Phase 3
TPD	**NX-2127** Degrader	BTK-IKZF *Oral*	B-cell malignancies				
TPD	**NX-5948** Degrader	BTK *Oral*	B-cell malignancies				
TPE	**NX-1607** Inhibitor	CBL-B *Oral*	Immuno-Oncology				
TPE	**DeTIL-0255** Cell therapy	*Ex vivo CBL-B inhibition*	Gynecologic malignancies				
TPM	Wholly owned	5 targets	Multiple				
TPD	Gilead Sciences	5 targets	Multiple				
TPD	Sanofi	5 targets	Multiple				

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

NX-2127

BTK DEGRADATION
& IMMUNOMODULATION

- Active against clinically emergent BTK inhibitor-resistant mutations
- Robust BTK degradation and immunomodulatory activity observed across all dose levels to date
- Positive clinical activity in CLL patients, including responses in patients with BTK or BCL2 mutations
- Cohort expansion for CLL patients is ongoing
- Dose exploration in patients with NHL is ongoing



NX-5948

BTK DEGRADATION

- Active against clinically emergent BTK inhibitor-resistant mutations
- Crosses the blood brain barrier and degrades BTK in brain-resident lymphoma cells and microglia in animal models
- Activity in multiple models of autoimmune disease
- Phase 1a dose escalation is ongoing

Today's Agenda

NX-2127 Clinical Data: First Targeted Protein Degradation Drug in Hematologic Malignancies

NX-2127-001, a first-in-human trial of NX-2127, a Bruton's Tyrosine Kinase-targeted protein degrader, in patients with relapsed or refractory chronic lymphocytic leukemia and B-cell malignancies

Anthony Mato, M.D. MSCE
Former Director, CLL Program, Memorial Sloan Kettering Cancer Center

Kinase Dead BTK Mutations Confer Resistance to Covalent and Noncovalent BTK Inhibitors but Are Susceptible to Clinical Stage BTK Degraders

Gwenn M. Hansen, Ph.D.
Chief Scientific Officer

Recent update of NX-2127 in diffuse large B-cell lymphoma and initial PK/PD results for NX-5948

Robert J. Brown, M.D.
EVP, Head of Clinical Development

Q&A

NX-2127-001, a first-in-human trial of NX-2127, a Bruton's Tyrosine Kinase-targeted protein degrader, in patients with relapsed or refractory chronic lymphocytic leukemia and B-cell malignancies

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Acquired resistance to BTK inhibitors presents a new and growing challenge in the treatment of CLL

- Targeted therapy focusing on two key pathways (BTK/BCL2) is standard of care in CLL and has changed the treatment landscape in front-line and relapsed/refractory settings
- Emerging patterns of resistance and intolerance limit the utility of currently available therapies in later lines of treatment:[1]
  - Novel *BTK* mutations confer broad resistance to both covalent and noncovalent BTK inhibitors
  - Some mutations lead to 'kinase dead' *BTK* mutants with intact NF-kB signaling, pointing to a potential scaffolding function of BTK
- Dual resistance to BTKi and BCL2i is occurring at increasing frequency adding to the treatment challenge in the relapsed setting[2,3]

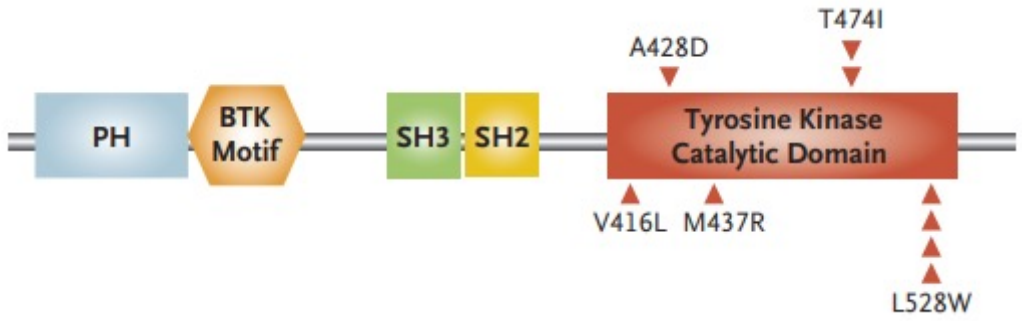
There is a need for a new treatment modality that can target both emerging resistant mutations and BTK scaffolding activity in patients who have otherwise, exhausted other approved and emerging treatment options

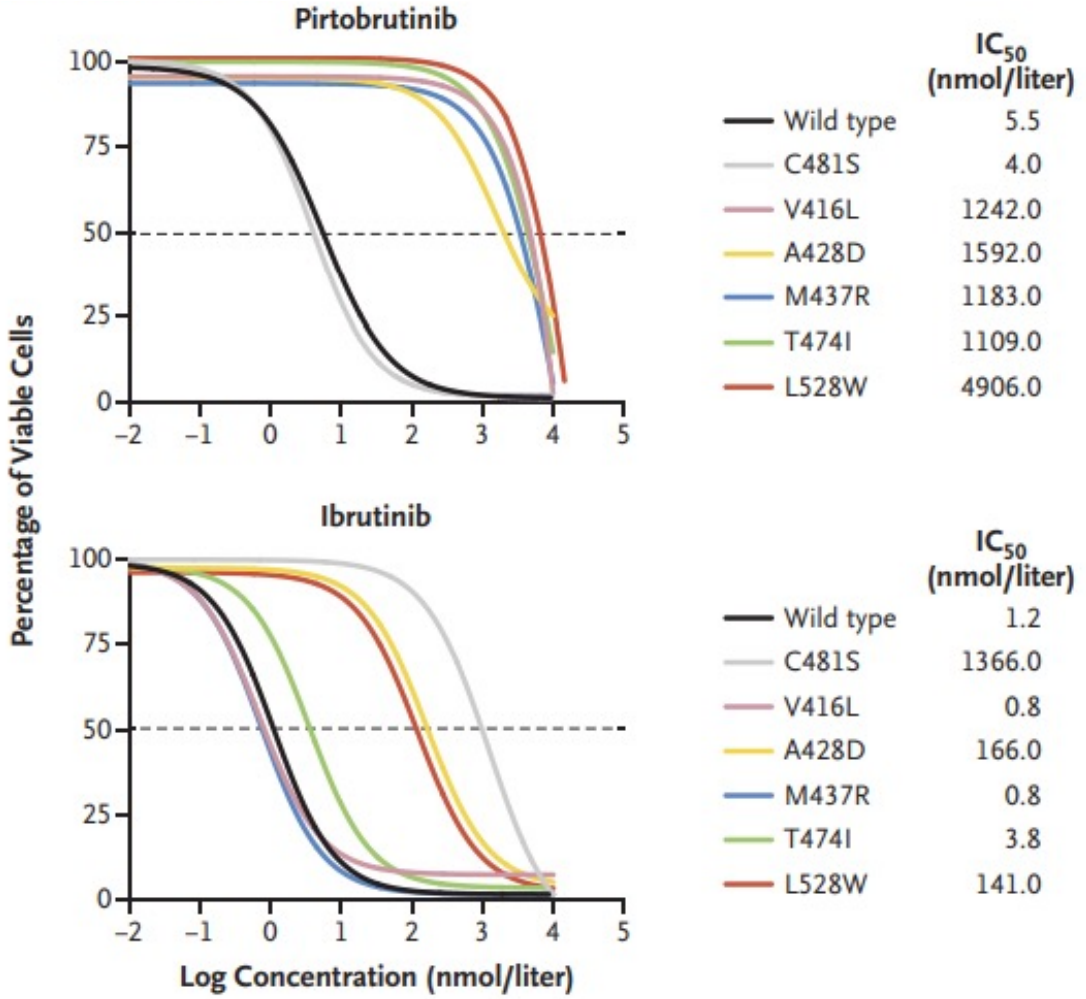
BCL2, B-cell lymphoma-2; **BTK,** Bruton tyrosine kinase; **CLL**, chronic lymphocytic leukemia; **NF-kB,** nuclear factor kappa-light-chain-enhancer of activated B cells

[1]Wang et al. N Engl J Med 2022;386:735–43; [2]Mato A et al. Clin Cancer Res 2020;26:3589–96; [3]Lew TE, et al. Blood Adv 2021;5:4054–8

Resistance to non-covalent BTK inhibitors presents a new and growing challenge to treatment

BTK mutations identified from patients progressing on the non-covalent inhibitor pirtobrutinib

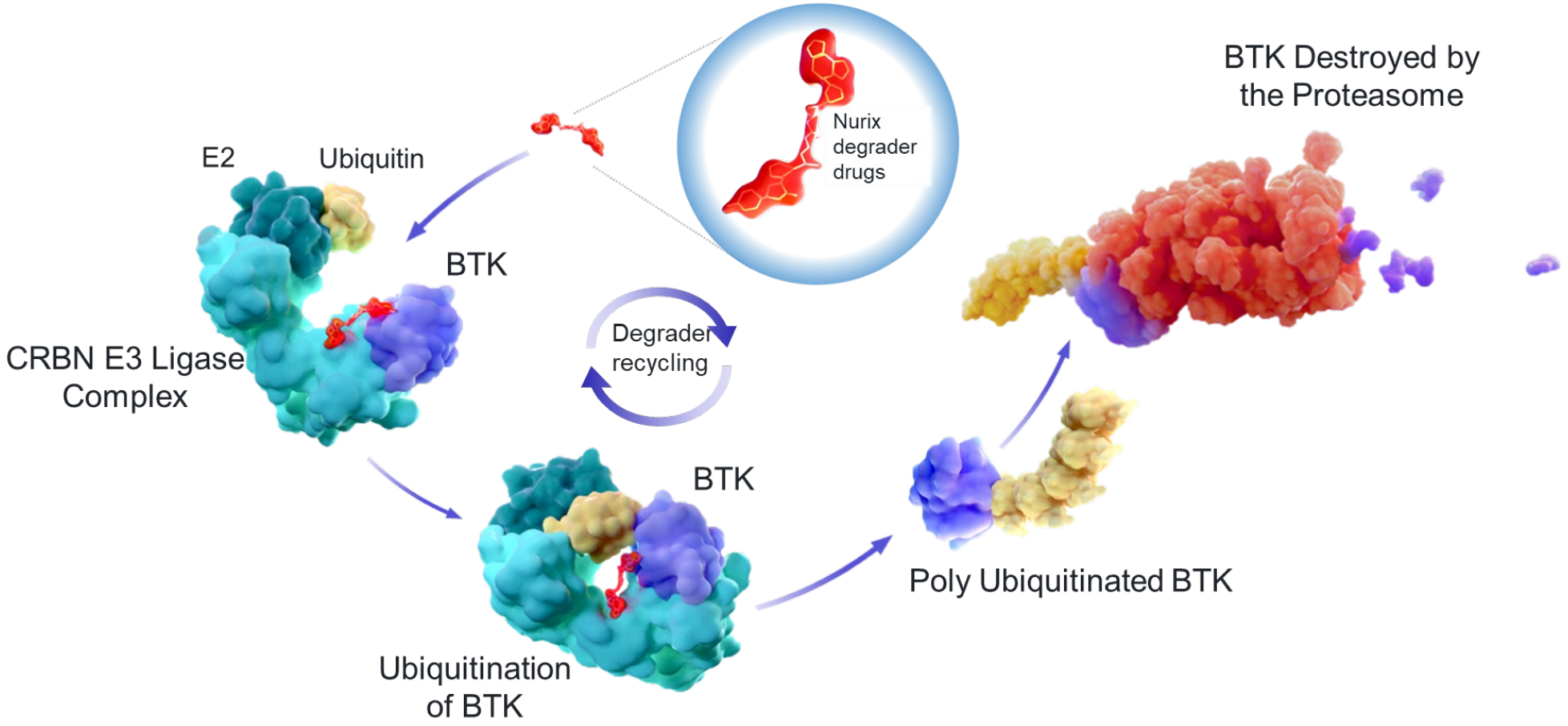




Wang et al. N Engl J Med 2022;386:735–43

NX-2127: first-in-class targeted protein degrader of BTK

Utilizing the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in B-cell malignancies



BTK, Bruton tyrosine kinase; **CRBN,** cereblon

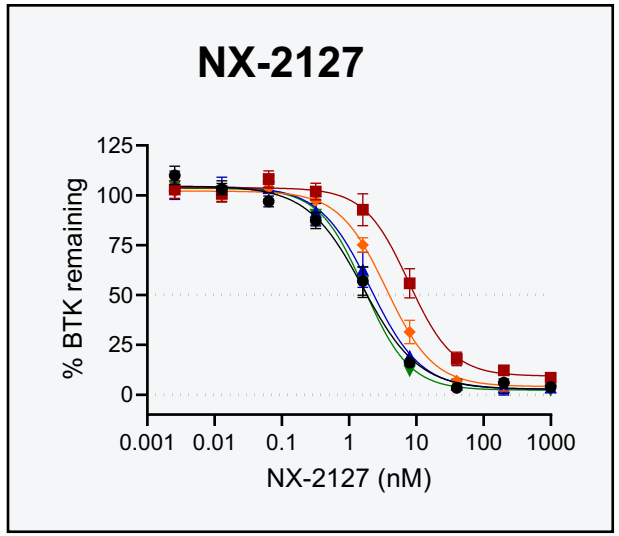
NX-2127 has the potential to address emerging *BTK* mutations

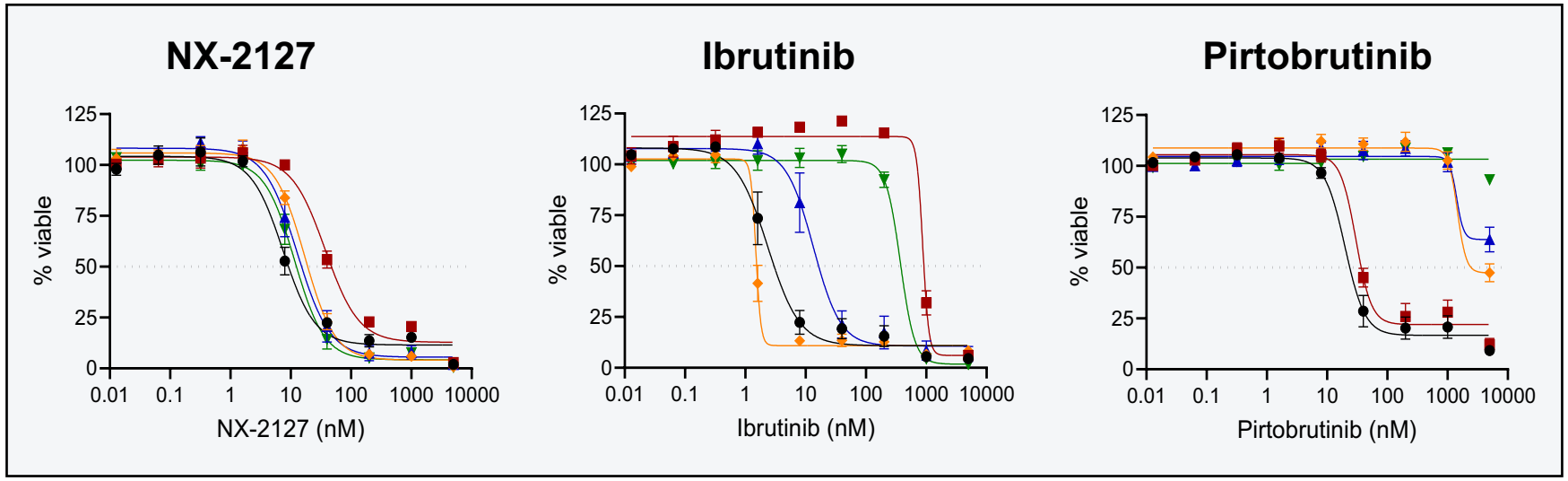
- NX-2127 degrades wild-type and mutant *BTK*, including the recently described kinase dead mutations
- NX-2127 kills DLBCL tumor cells harboring wild-type *BTK* and mutant *BTK*

BTK-WT
BTK-C481S
BTK-V416L
BTK-T474I
BTK-L528W

BTK degradation

Cell viability

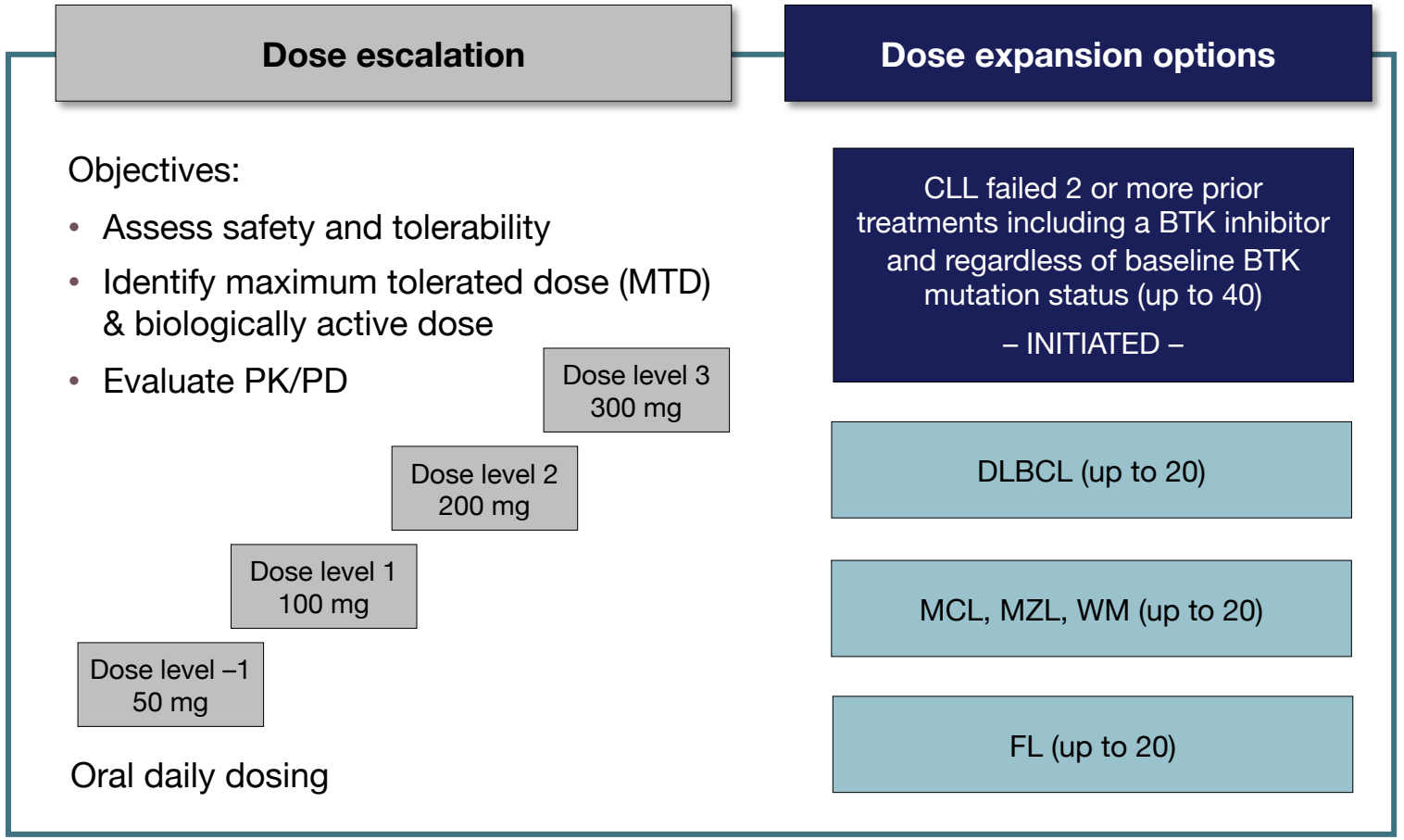




Montoya S, et al. ASH 2022 (abstract #750)

NX-2127-001: trial design

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

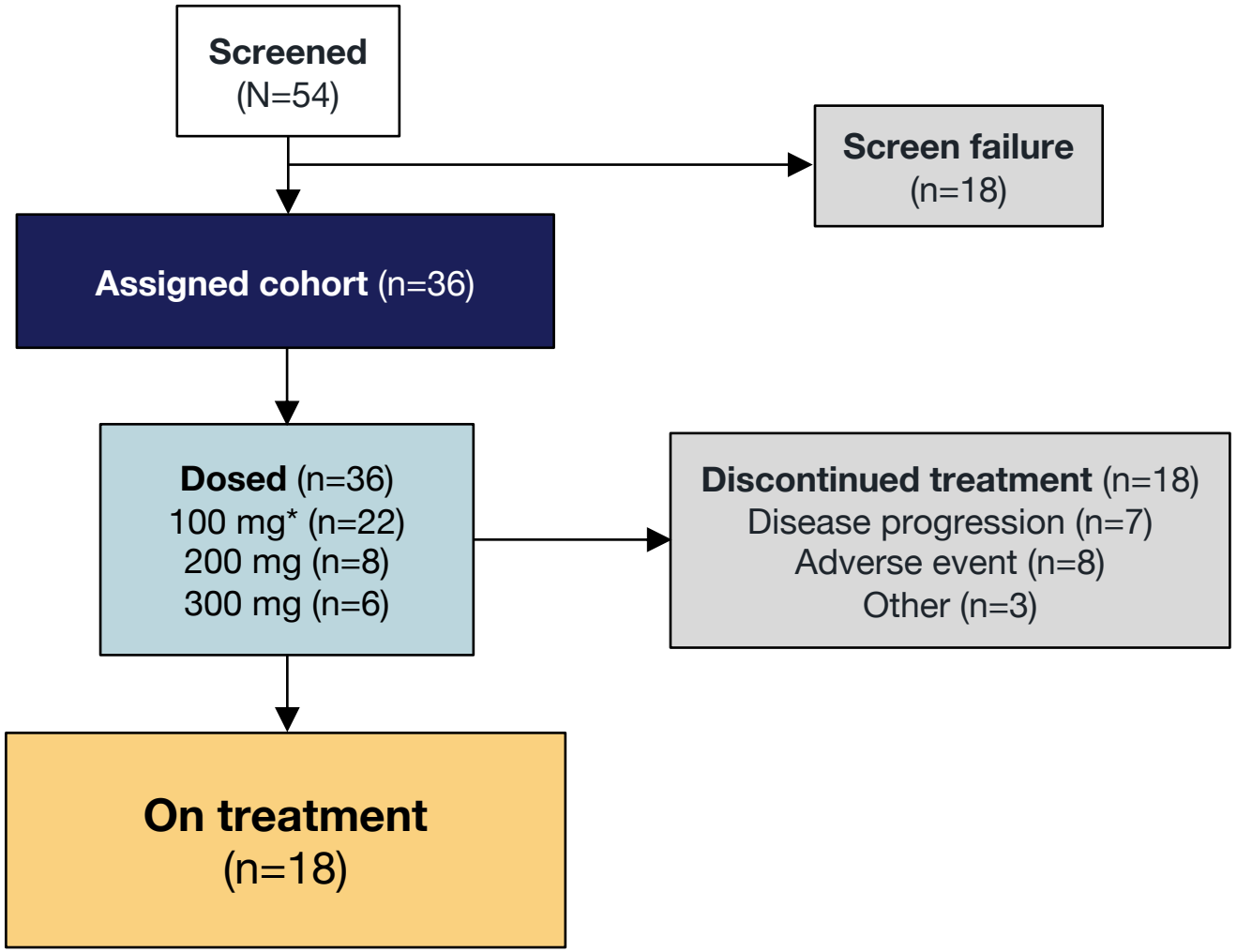


- CLL Phase 1b expansion cohort at 100 mg dose
  - MTD not established
  - 100 mg dose chosen as expansion dose based on PD, clinical activity and safety profile
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL (e.g. DLBCL, MCL, MZL, WM, FL)

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

NX-2127-001: patient disposition

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



- **Causes for screen failure:**
  - Inadequate organ reserve (n=5)
  - Subject withdrawal (n=3)
  - Disease progression/other cancer (n=2)
  - Administration of prohibited medications (n=2)
  - Other (n=6)

- **Patients dosed include:**
  - CLL (n=23)
  - DLBCL (n=4)
  - WM (n=3)
  - FL (n=1)
  - MCL (n=4)
  - MZL (n=1)

*100 mg dose includes patients from Phase 1a and Phase 1b

Baseline characteristics

Elderly population with multiple prior lines of targeted therapies and acquired mutations

Characteristics	CLL (n=23)	Overall population (N=36)
Median age, years (range)	75 (61–90)	75 (50–92)
Female, n (%)	9 (39.1)	13 (36.1)
Male, n (%)	14 (60.9)	23 (63.9)
Lines of prior therapy, median (range)	5 (2–11)	4 (2–11)
BTKi, n (%)	23 (100)	31 (86.1)
Pirtobrutinib, n (%)	8 (34.8)	11 (30.6)
BTKi and BCL2i, n (%)	18 (78.3)	19 (52.8)
cBTKi, ncBTKi, and BCL2i, n (%)	7 (30.4)	7 (19.4)
***BTK* mutation present**[a], n (%)	10 (48)	11 (35)
C481	5 (24)	5 (16)
L528W	4 (19)	4 (13)
T474	3 (14)	4 (13)
V416L	1 (5)	1 (3)
***BCL2* mutation present**[a], n (%)	4 (19)	4 (13)
***PLCG2* mutation present**[a], n (%)	0 (0)	1 (3.2)

[a]Specific mutations are not additive as some patients have multiple *BTK* mutations
Mutations were tested by NGS centrally in those patients with available samples (n=31 in total population; n=21 in CLL population)

Data cutoff: September 21, 2022

NX-2127 safety summary (TEAEs >15% in all patients)

Treatment-emergent AEs occurring in >15% of total population, n (%)	Any grade (N=36)	Grade 3+ (N=36)	SAE (N=36)
Fatigue	19 (52.8)	–	-
Neutropenia[a]	14 (38.9)	13 (36.1)	-
Contusion[b]	10 (27.8)	–	1 (2.8)
Thrombocytopenia[c]	9 (25)	3 (8.3)	-
Anemia	8 (22.2)	4 (11.1)	1 (2.8)
Hypertension	9 (25.0)	1 (2.8)	-
Constipation	7 (19.4)	–	-
Dyspnea	7 (19.4)	1 (2.8)	-
Pruritis	7 (19.4)	–	-
Atrial fibrillation/Atrial flutter[d]	6 (16.7)	3 (8.3)	2 (5.6)
Diarrhea	6 (16.7)	–	-
Petechiae	6 (16.7)	–	-
Rash	6 (16.7)	–	-

[a]Aggregate of "neutropenia" and "neutrophil count decreased" [b]Contusion includes episodes of bruising and other similar terms [c]Aggregate of "thrombocytopenia" and "platelet count decreased" [d]Cases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases), male sex (3 cases), and history of

1 DLT of cognitive disturbance was observed at 300 mg (CLL); MTD not reached

AE, adverse event; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event

Data cutoff: September 21, 2022

NX-2127 safety summary (all participants) by dose

AEs: all grades, n (%)	All doses (n=36)	100 mg* (n=22)	200 mg (n=8)	300 mg (n=6)
Fatigue	19 (53)	13 (59)	5 (63)	1 (17)
Neutropenia[a]	14 (39)	5 (23)	5 (63)	4 (67)
Contusion[b]	10 (28)	4 (18)	3 (38)	3 (50)
Thrombocytopenia[c]	9 (25)	5 (23)	2 (25)	2 (33)
Hypertension	9 (25)	5 (23)	2 (25)	2 (33)
Anemia	8 (22)	6 (27)	2 (25)	0
Constipation	7 (19)	7 (32)	0	0
Dyspnea	7 (19)	4 (18)	3 (38)	0
Pruritis	7 (19)	5 (23)	1 (13)	1 (17)
Atrial fibrillation/Atrial flutter[d]	6 (17)	3 (14)	2 (25)	1 (17)
Diarrhea	6 (17)	5 (23)	1 (13)	0
Petechiae	6 (17)	4 (18)	1 (13)	1 (17)
Rash	6 (17)	5 (23)	1 (13)	0

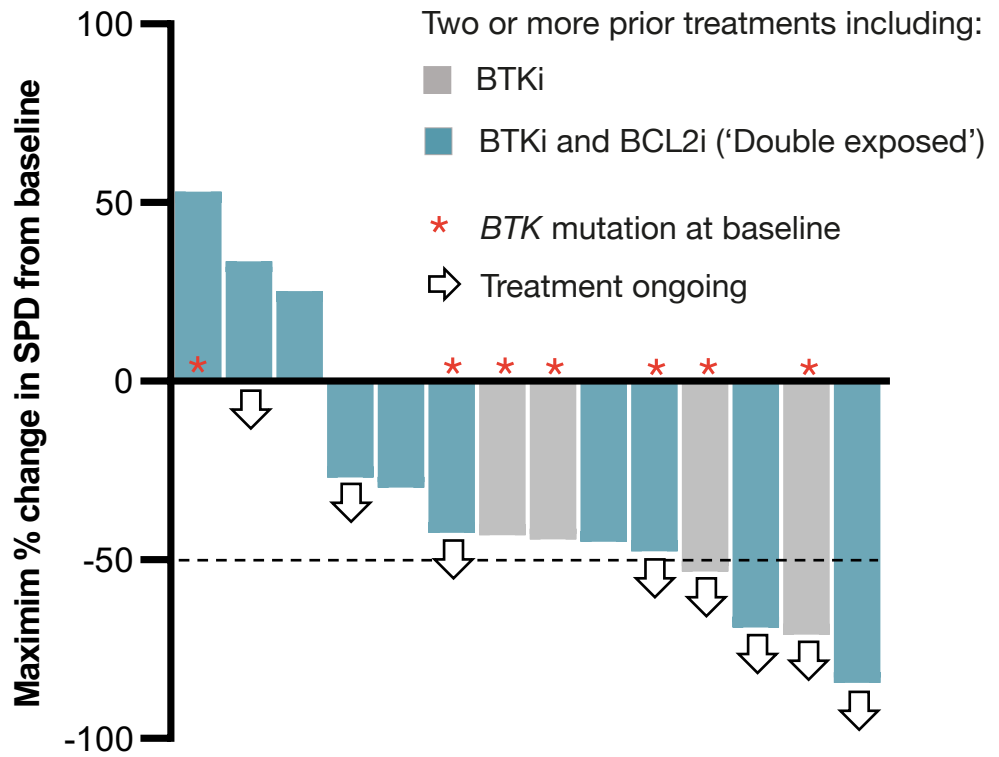
[a]Aggregate of "neutropenia" and "neutrophil count decreased" [b] Includes episodes of bruising and other similar verbatim terms [c]Aggregate of "thrombocytopenia" and "platelet count decreased" [d]Cases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases), male sex (3 cases), and history of prior AF on ibrutinib (2 cases)
*18 of the 22 patients treated at the 100 mg qd dose had CLL

Data cutoff: September 21, 2022

NX-2127 preliminary efficacy (patients with CLL)

Disease-evaluable patients	n=15
Objective response rate,[a] % (95% CI)	33 (12–62)
Best response, n (%)	
CR	0 (0)
PR	5 (33.3)
SD	5 (33.3)
PD	2 (13.3)
NE[b]	3 (20)

[a]Objective response rate includes CR + CRi + nPR + PR-L + PR
[b]Patients who discontinued after a single assessment of SD are considered as NE



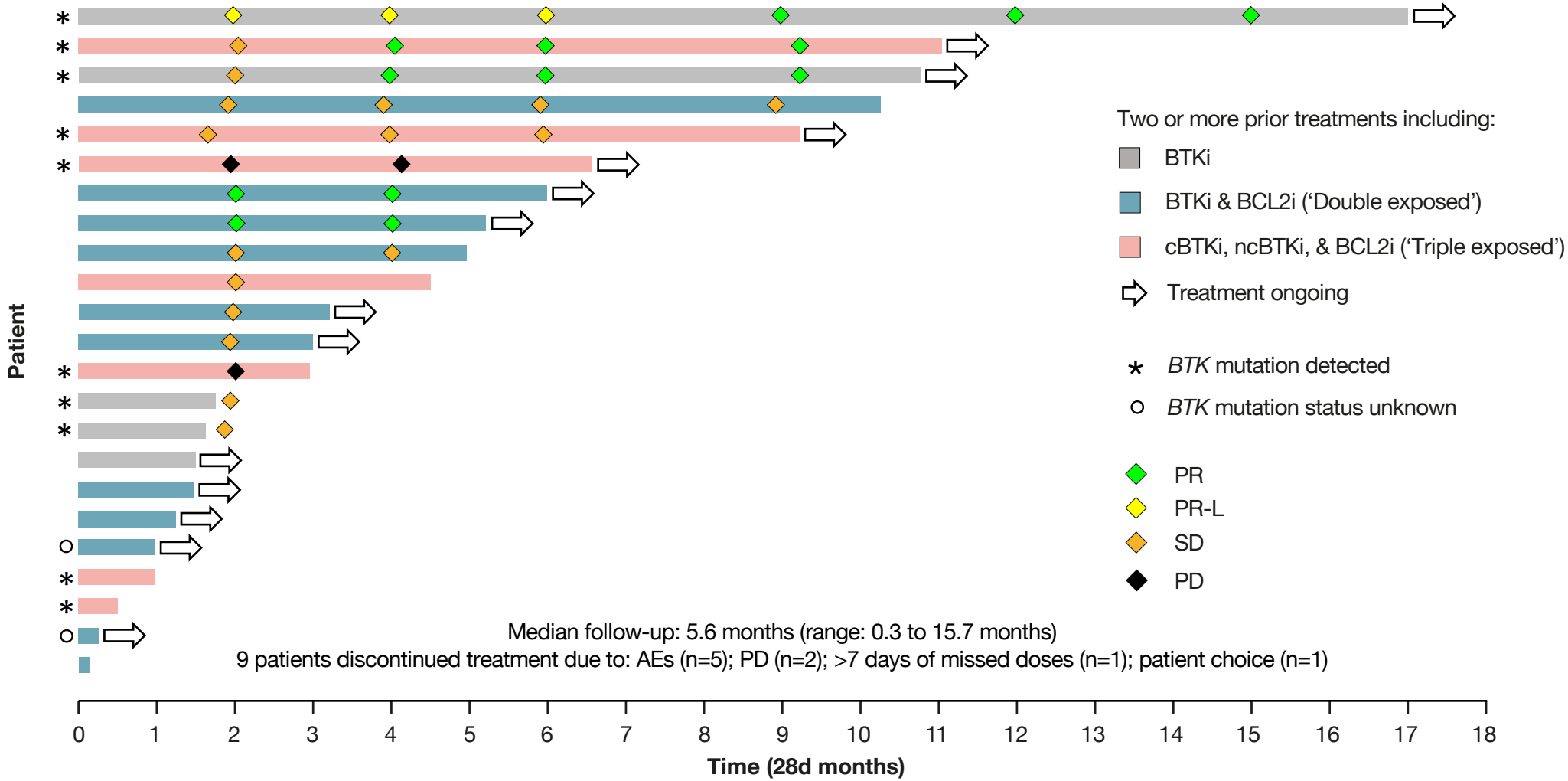
***One patient, not shown above, with prior BTKi and BCL2i treatment and with a *BTK* mutation detected at baseline, had no nodal disease at baseline. Their treatment is ongoing with a PR**

BCL2i, B-cell lymphoma-2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CR**, complete response; **CRi**, complete response with incomplete count recovery; **NE**, not evaluable; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease

Data cutoff: September 21, 2022

Outcomes and time on therapy with NX-2127 (patients with CLL)

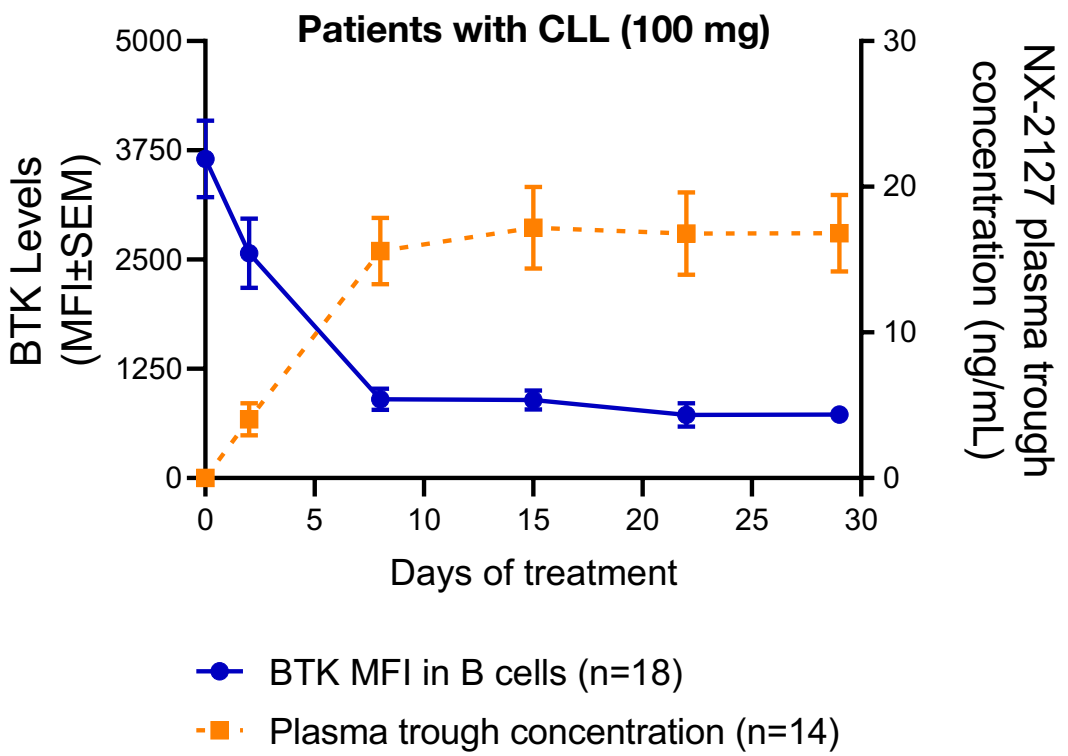
Responses seen in double and triple exposed patients

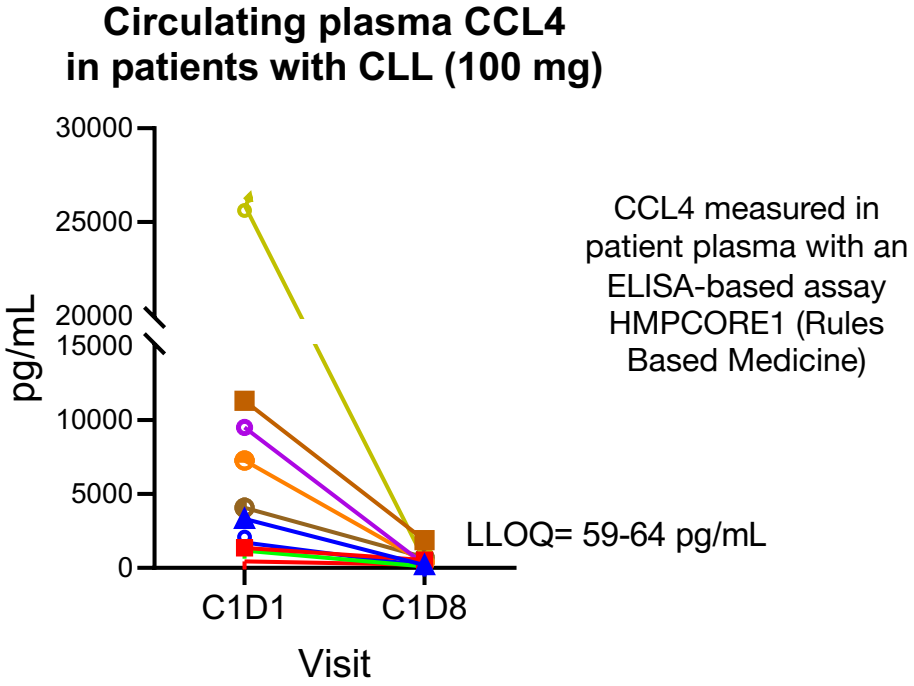


AE, adverse event; **BCL2i,** B-cell lymphoma-2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTK inhibitor; **ncBTKi**, non-covalent BTK inhibitor; **PD**, progressive disease; **PR**, partial response; **PR-L**, partial response with lymphocytosis; **SD**, stable disease

Data cutoff: September 21, 2022

NX-2127 leads to robust BTK degradation and decrease in B-cell activation





- Daily treatment with NX-2127 resulted in a fast and sustained suppression of BTK (CD19+) as measured in patient whole blood using a flow cytometry assay. BTK suppression target of 80% reached consistently (data not shown here)
- Robust decrease of plasma CCL4 by Cycle 1 Day 8 and suppression was maintained through Cycle 2 Day 1, consistent with clinically observed lymphocytosis occurring in majority of patients with nodal disease by Cycle 1 Day 8
- NX-2127 treatment also resulted in degradation of cereblon neo-substrate Ikaros

BTK, Bruton's tyrosine kinase; **CCL4**, C–C motif ligand 4; **LLOQ**, lower limit of quantification

Conclusions

- Early Phase 1 data of NX-2127, a first-in-class BTK degrader with immunomodulatory activity, demonstrates BTK degradation and clinically meaningful responses independent of prior treatments or *BTK* mutational status
  - ORR 33% (95% CI 12–62%) in heavily pre-treated patients with relapsed/refractory CLL with median follow up of 5.6 months (range 0.3 to 15.7 months)
  - Treatment duration up to 15.7 months (with 14 of 23 CLL patients remaining on treatment)
  - Safety profile consistent with previous reports for BTK-targeted therapies in heavily pretreated patients with B-cell malignancies (Grade 3 neutropenia, thrombocytopenia, anemia, and atrial fibrillation/flutter)
  - Sustained BTK degradation and decreased B-cell activation in double and triple exposed CLL population

American Society of Hematology
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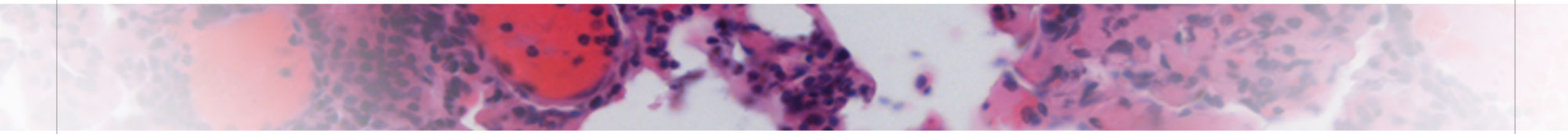
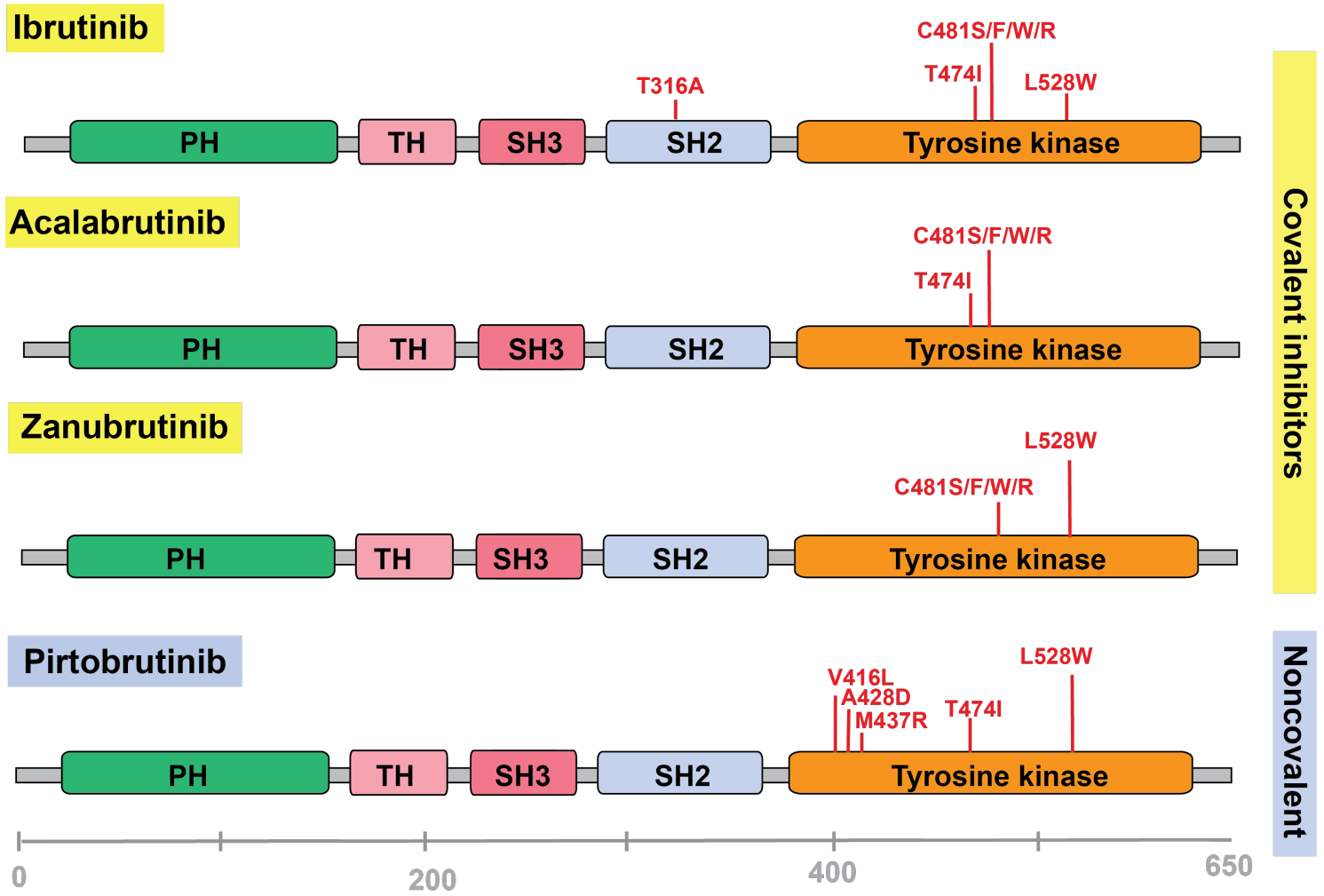


Kinase Dead BTK Mutations Confer Resistance to Covalent and Noncovalent BTK Inhibitors but Are Susceptible to Clinical Stage BTK Degraders

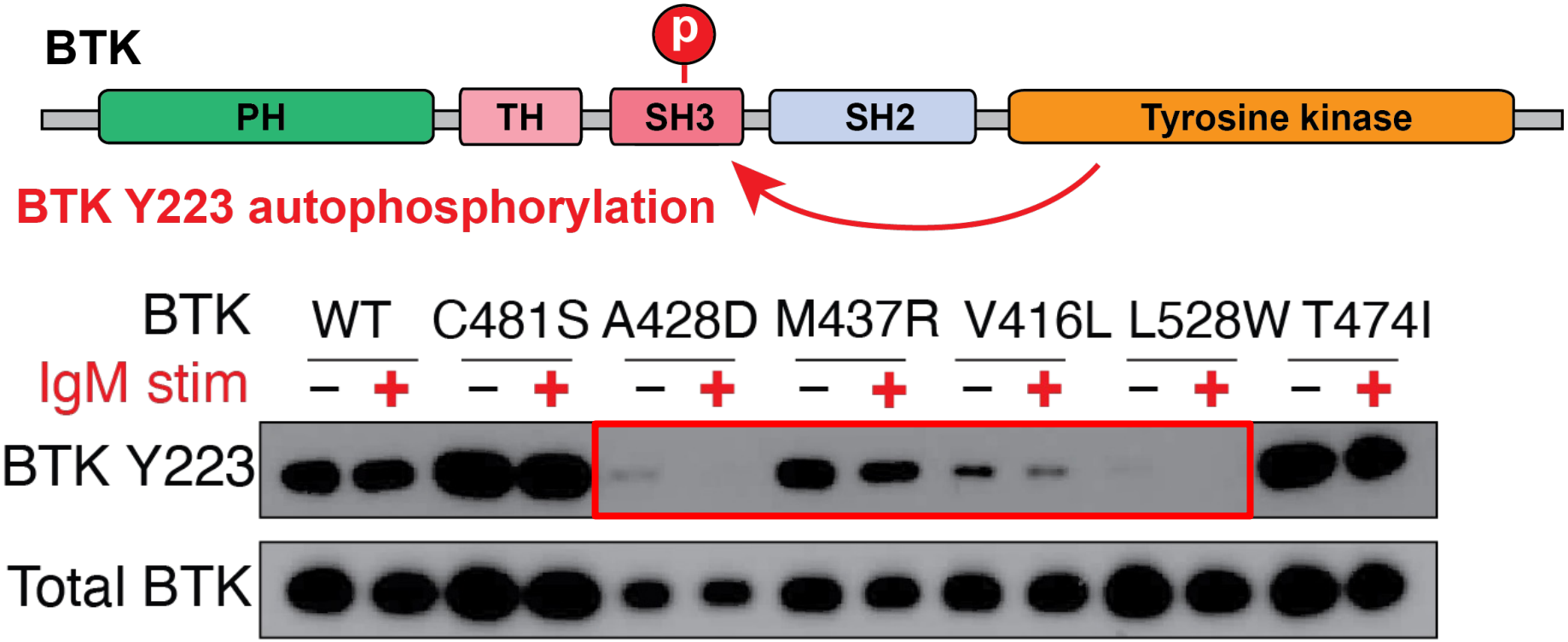
Skye Montoya, Jessie Bourcier, Meghan C. Thompson, Mark Noviski, May Tan, Eric Wang, Xiaoli Mi, Nivetha Brathaban, Carla Barrientos Risso, Daniel Tsai, Jordan Ye, Jacob Jahn, Gabriel Pardo, Ryan Notti, Alejandro Pardo, Maurizio Affer, Stephanie Yung, James N. Iuliano, Janine Powers, Daniel W Robbins, Vindhya Nawaratne, Tulasigeri M Totiger, Camila Pena-Velasquez, Joanna M. Rhodes, Andrew D. Zelenetz, Lindsey E. Roeker, Hao Lu, Adam Linley, Anthony R. Mato, Omar Abdel-Wahab, and Justin Taylor

Diverse BTK mutations cause resistance to covalent & non-covalent BTK inhibitors



BTK Amino acids (*BTK* Xq22.1)

Several BTK mutations abrogate BTK phosphorylation



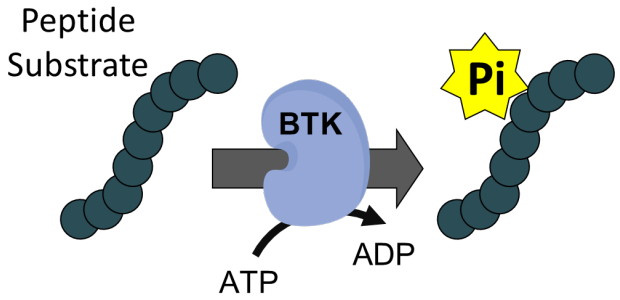
Questions:

1. What is the impact of BTK drug resistant mutants on BTK enzymatic activity & BCR signaling?

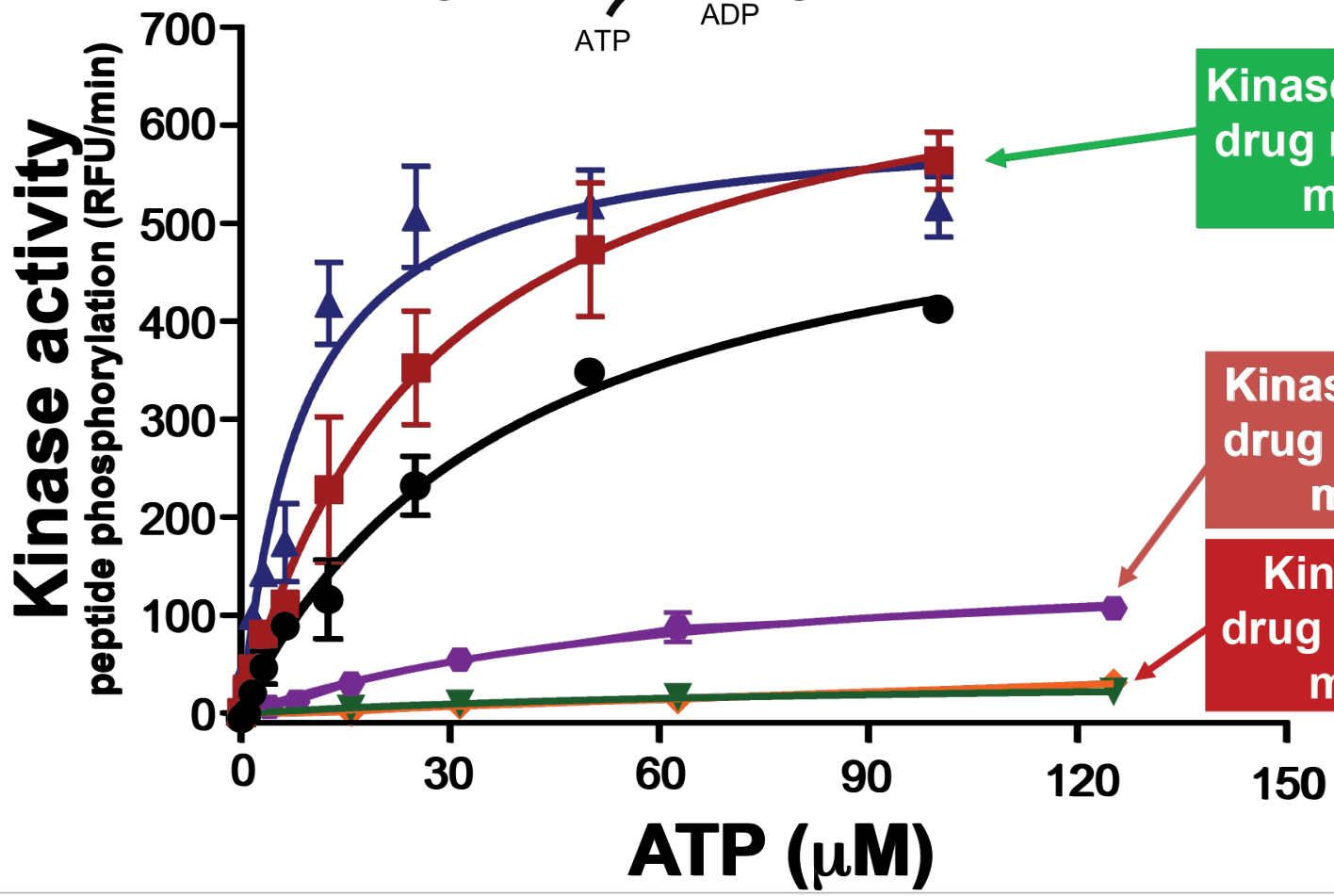
2. How can we overcome resistance to BTK enzymatic inhibitors?

Wang, Mi, Thompson, *et al. NEJM* 2022

Emerging BTKi-resistant mutations abolish BTK kinase activity



How do these mutations activate BCR signaling despite lack of BTK kinase activity?



Kinase proficient drug resistance mutants

- BTK C481S
- BTK T474I

Kinase deficient drug resistance mutants

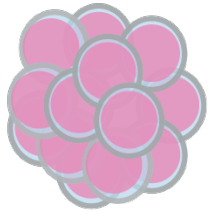
- BTK WT
- BTK M437R

Kinase dead drug resistance mutants

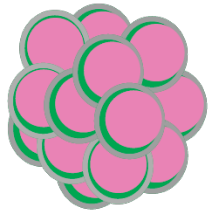
- BTK L528W
- BTK V416L

Proteomic characterization of BTK drug resistance mutants

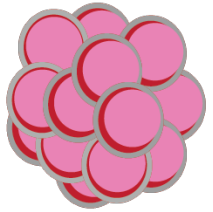
BTK WT



BTK T474I



BTK L528W

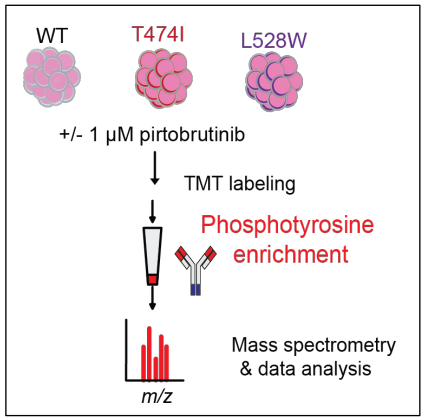


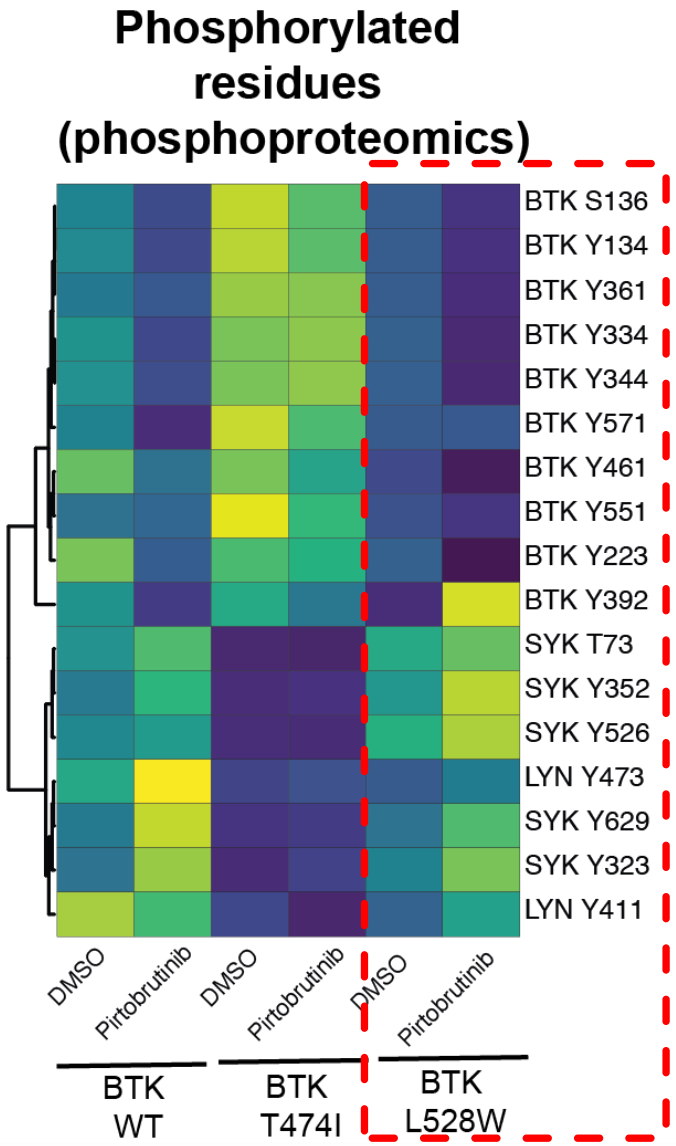
Phosphoproteome

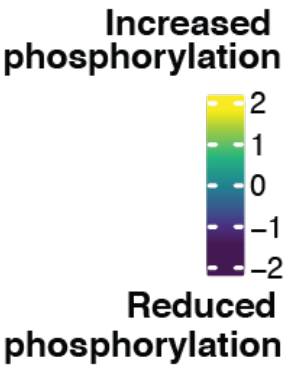
Kinome profiling using broad spectrum kinase inhibitors

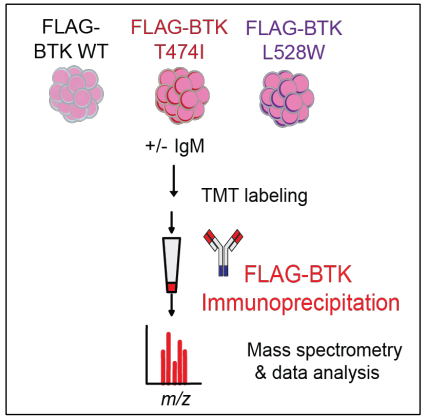
BTK Immunoprecipitation/ mass spectrometry

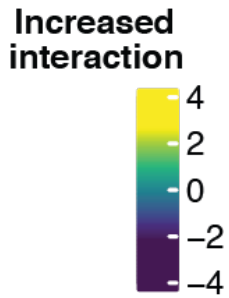
Kinase dead BTK mutants recruit unique interacting proteins

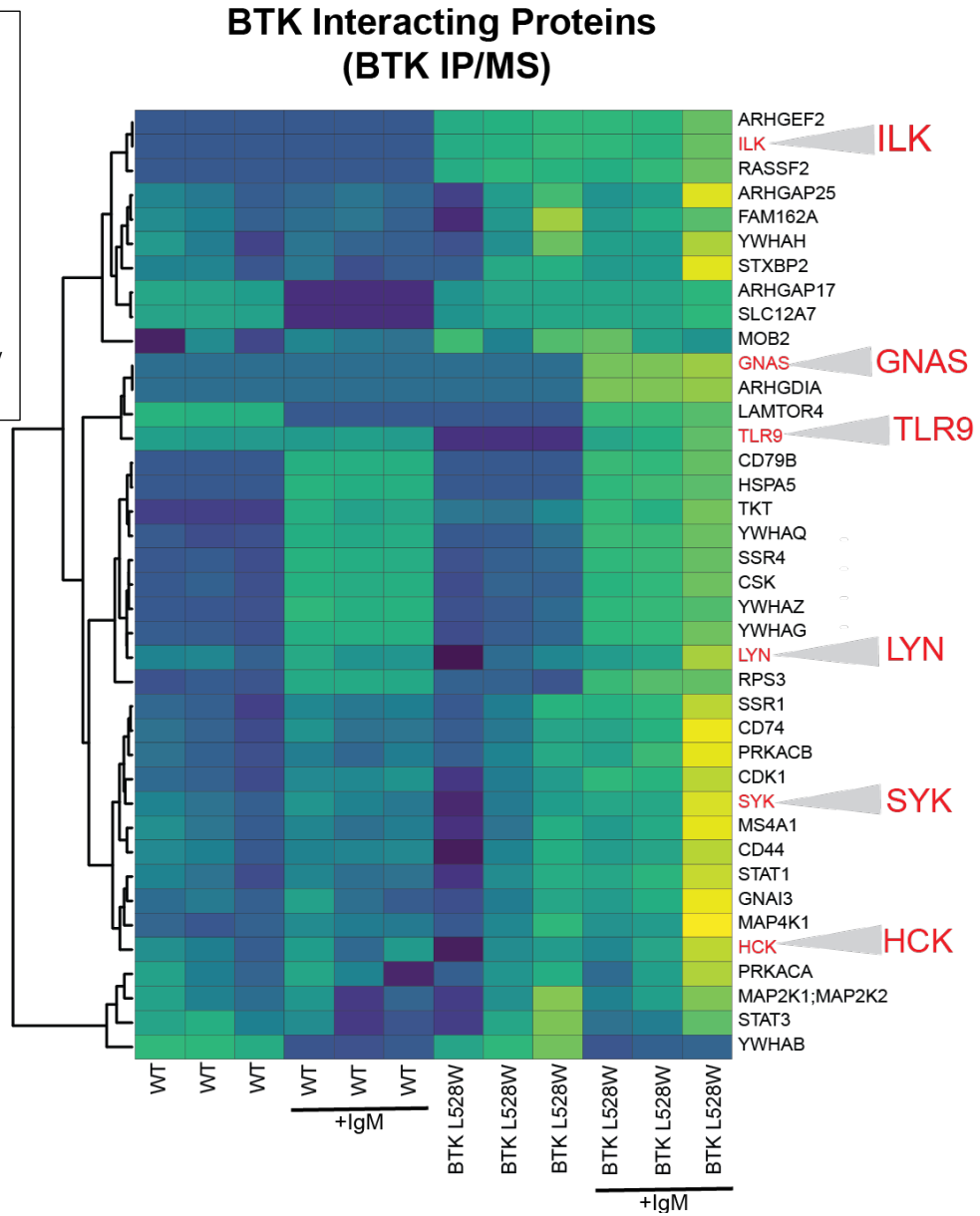




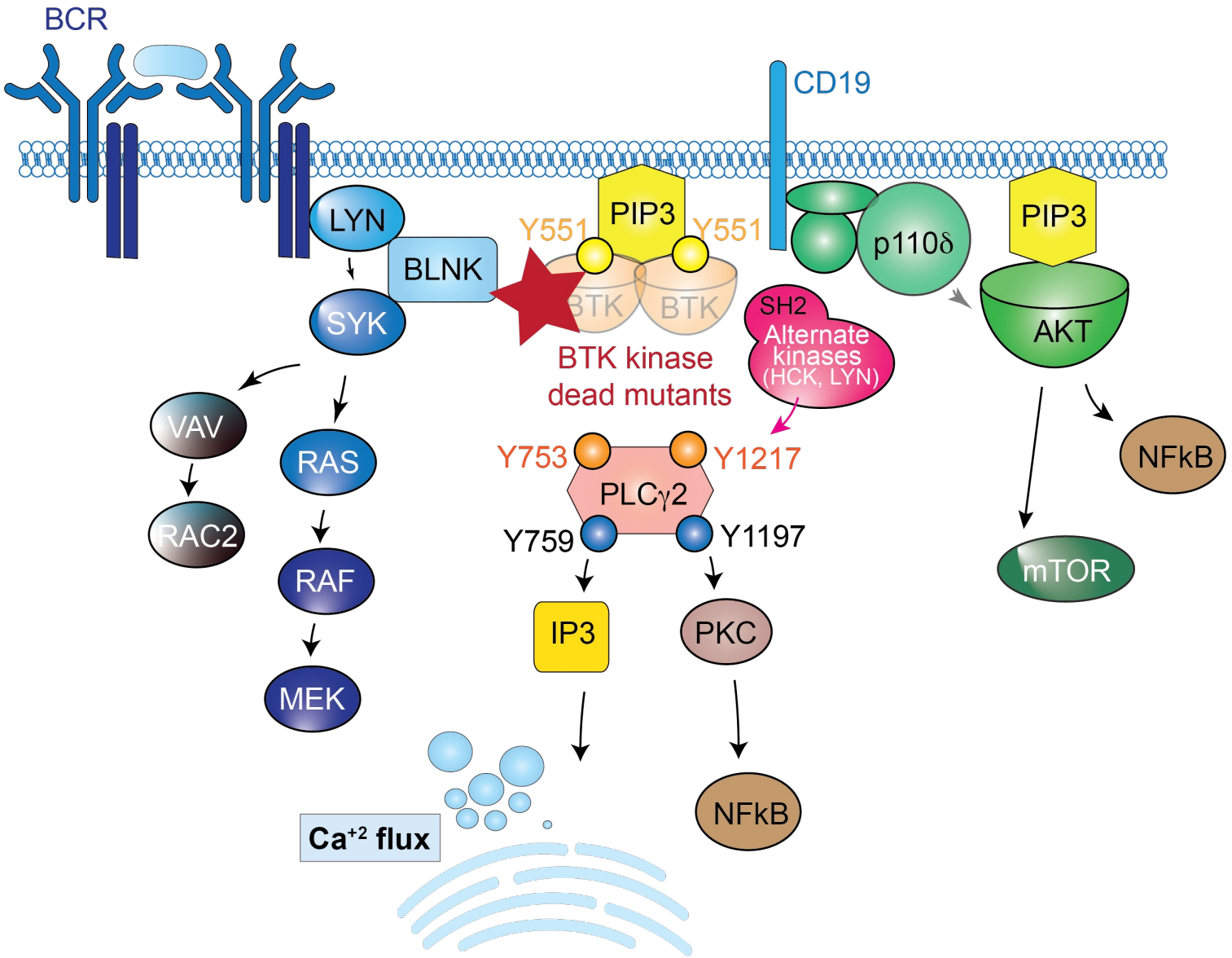




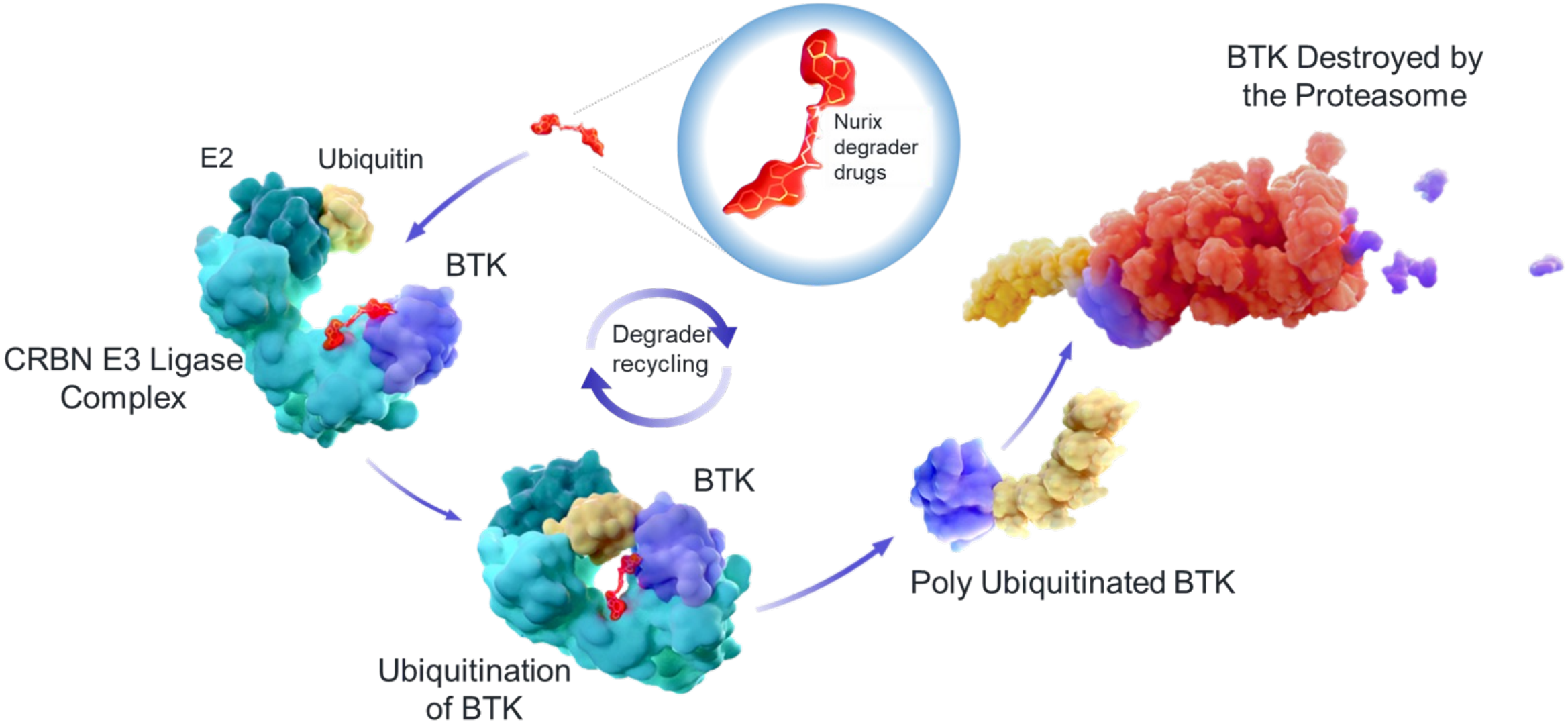




Can we target the scaffold function of BTK?



NX-2127: a first-in-class targeted protein degrader of BTK



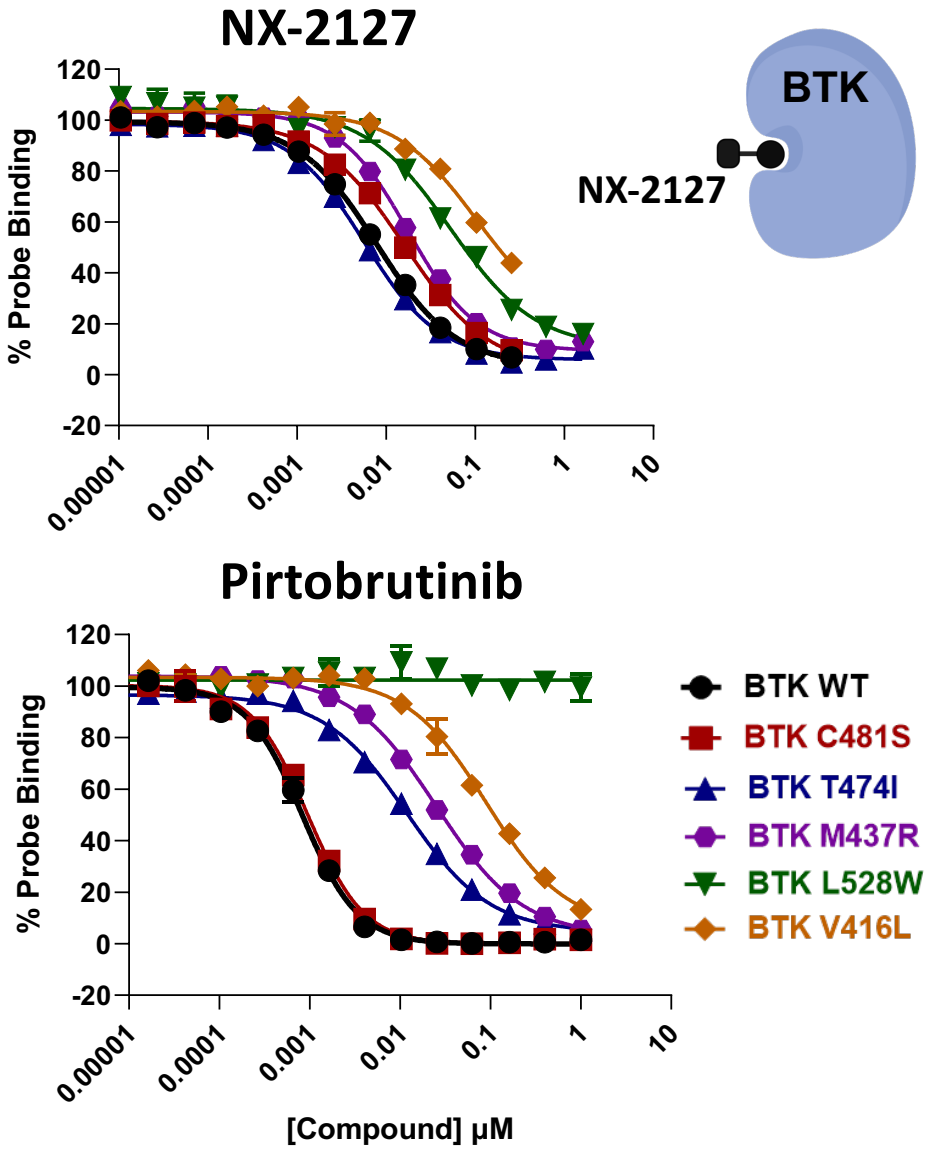
CRBN, cereblon

NX-2127 binds to BTKi resistance mutants

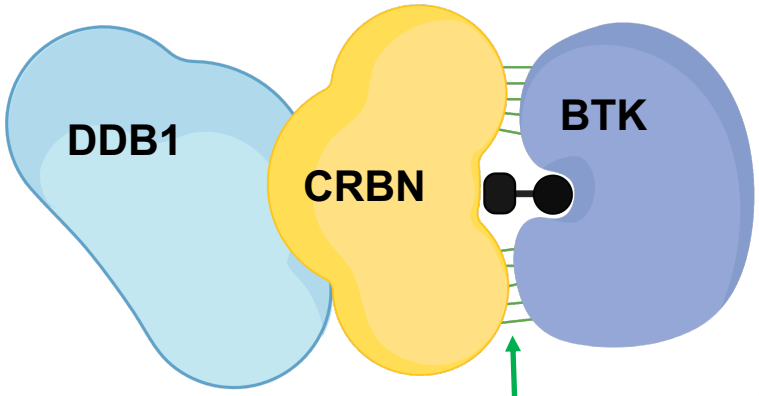
BTK Proteins	NX-2127 Degrader	Pirtobrutinib Non-covalent Inhibitor	Ibrutinib Covalent Inhibitor
	IC_{50} (nM)	IC_{50} (nM)	K_{inact}/K_i ($M^{-1}*s^{-1}$)
WT	9	0.7	2×10^5
C481S	19	0.8	6 nM (IC_{50})
T474I	7	11	1×10^5
M437R	22	30	3×10^6
L528W	66	No binding @ 1 µM	No binding @ 1 µM
V416L	111	98	6×10^4

>10x reduced binding

Compound binding measured in a FRET-based probe displacement assay

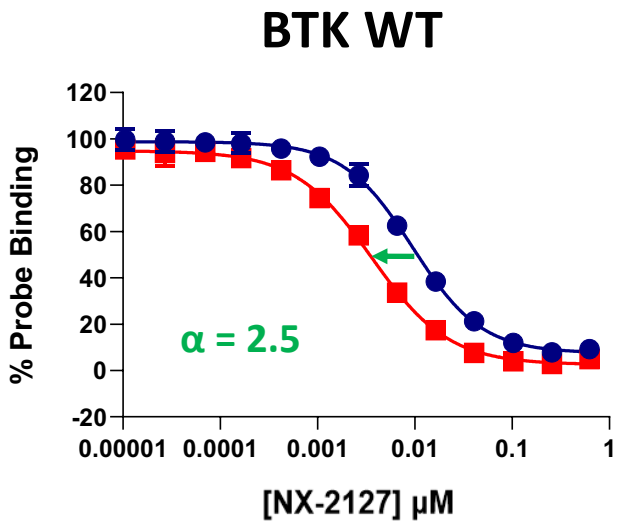


NX-2127 induces positive cooperativity between BTK and CRBN



NX-2127

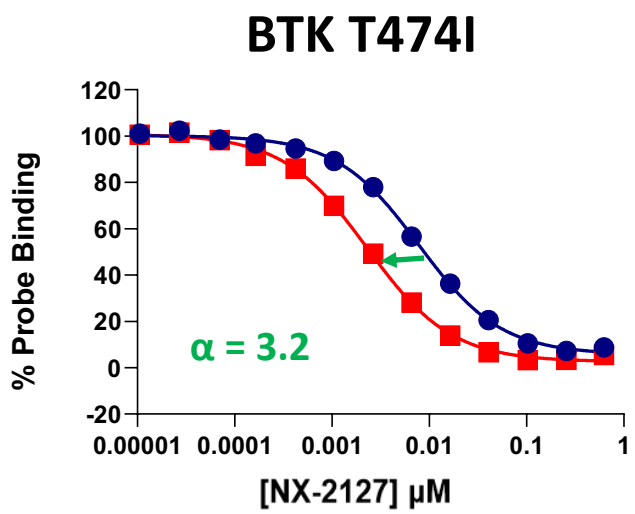
- Positive Cooperativity (α>1)
- Stable ternary complex
- Induced protein-protein interactions
- Greater tolerance for reduced binary affinity

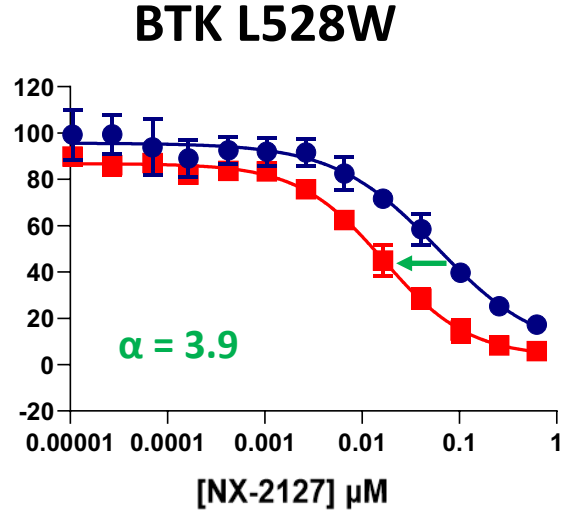


No CRBN

⊕ CRBN (1 μM)

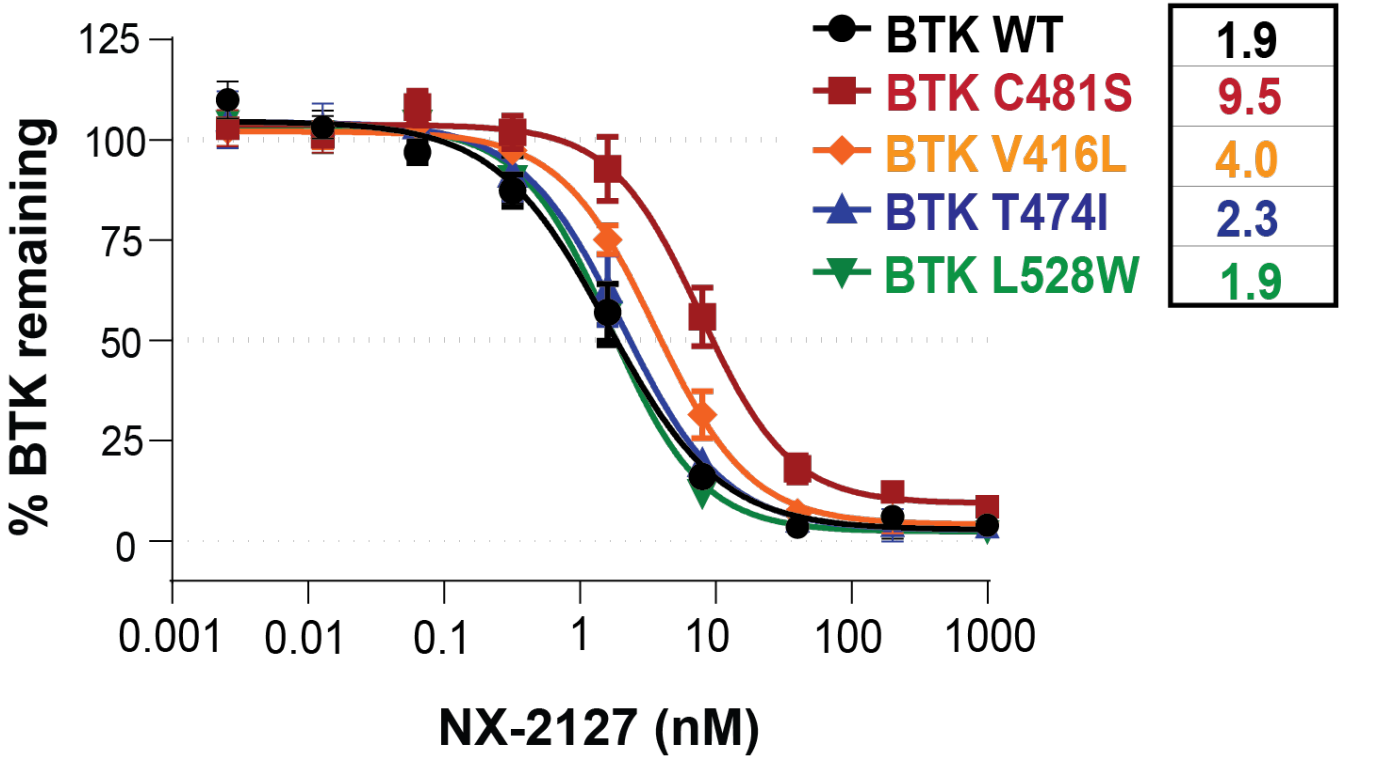
$$\alpha = \frac{IC_{50}\ \text{No CRBN}}{IC_{50}\ \text{with CRBN (1 μM)}}$$



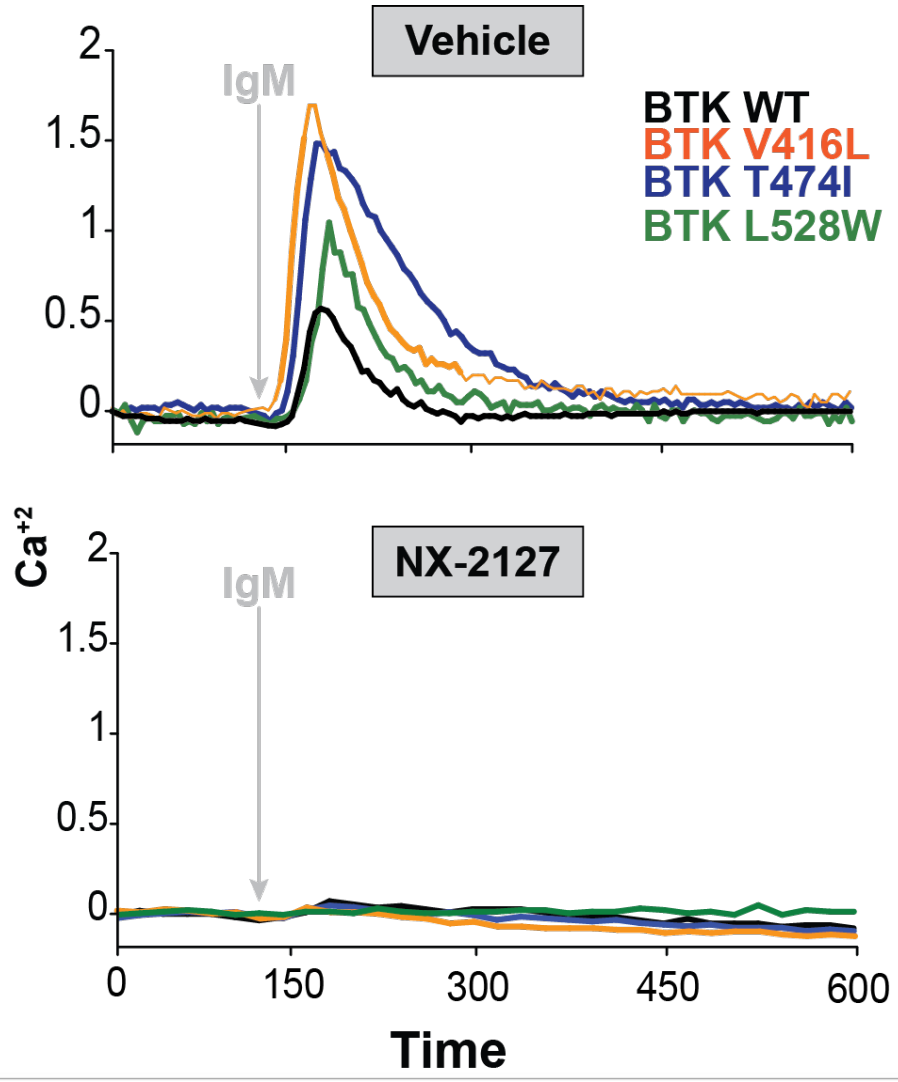


CRBN, cereblon; **DDB1**, DNA damage binding protein 1.

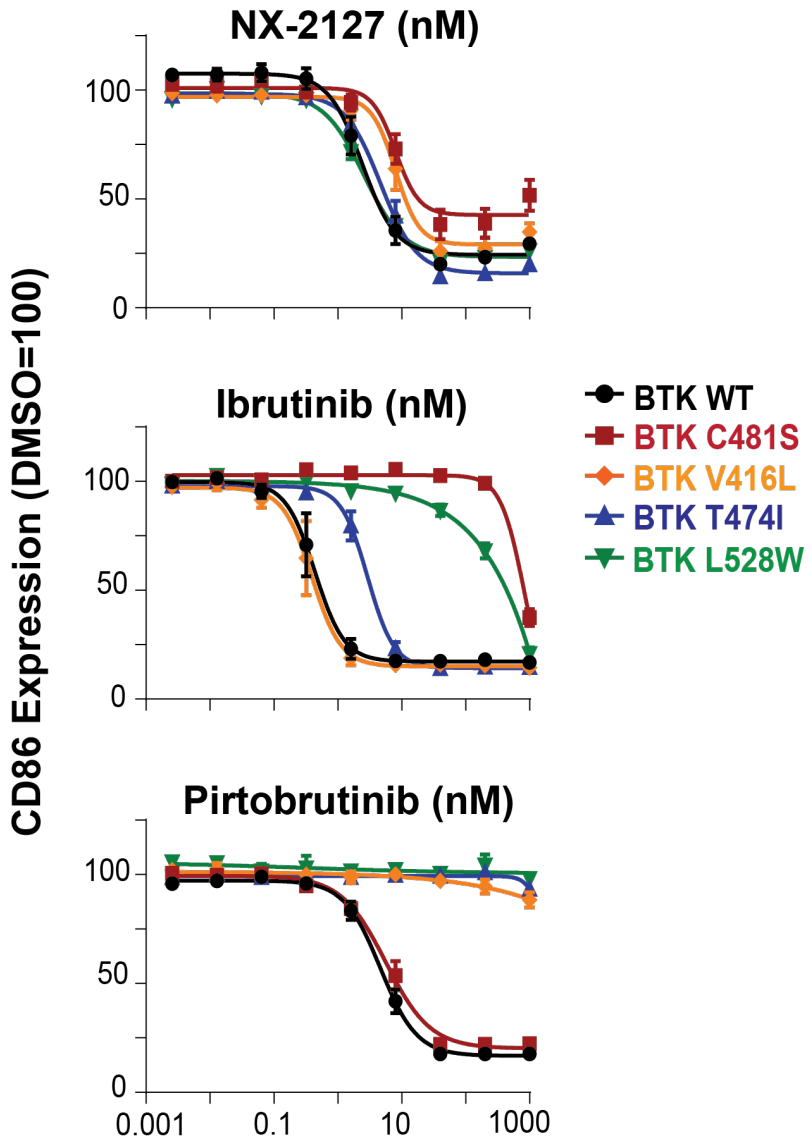
NX-2127 degrades both wild-type and kinase dead mutant BTK and suppresses Ca^{2+} signaling

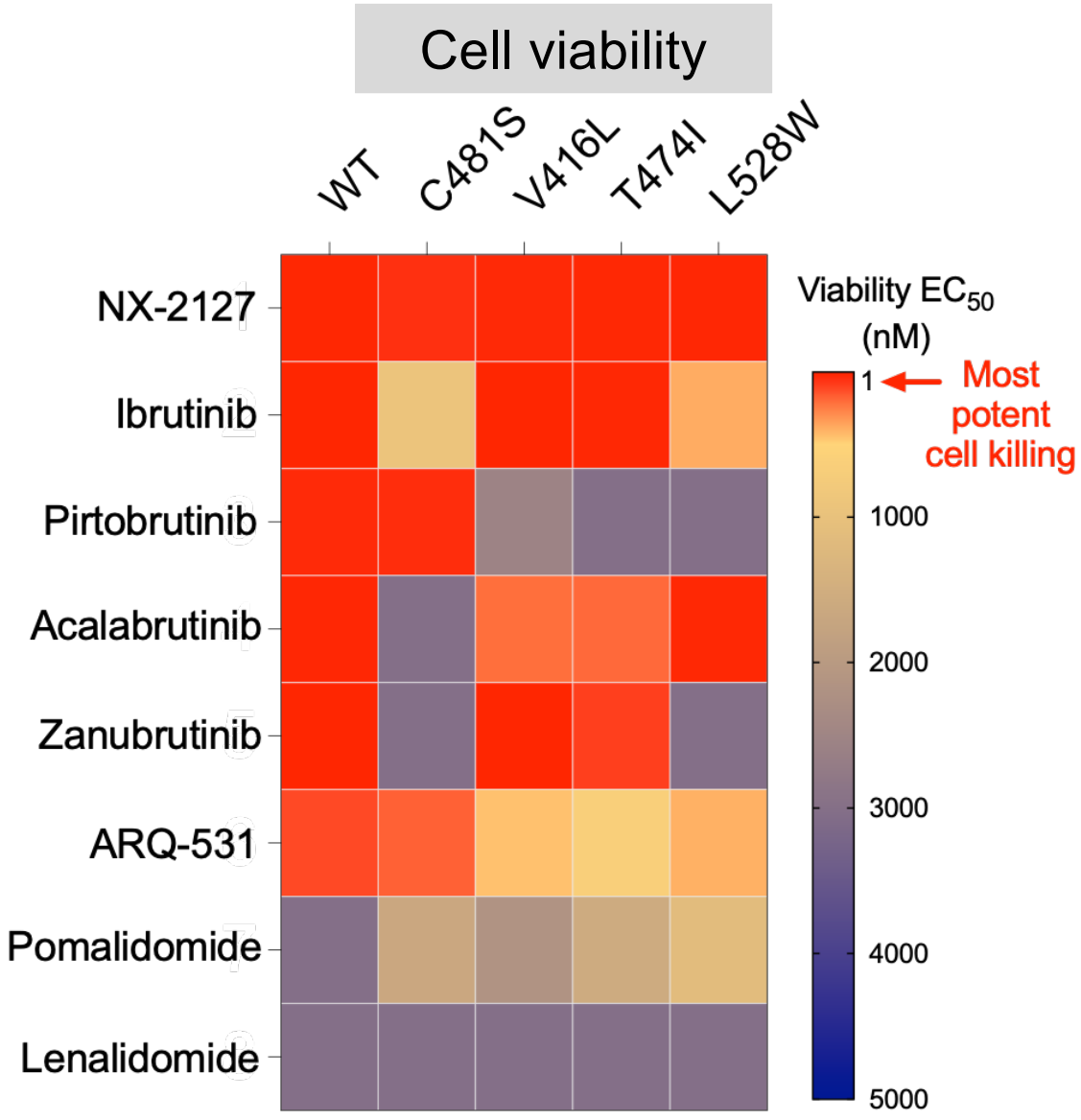


DC_{50} (nM)
1.9
9.5
4.0
2.3
1.9

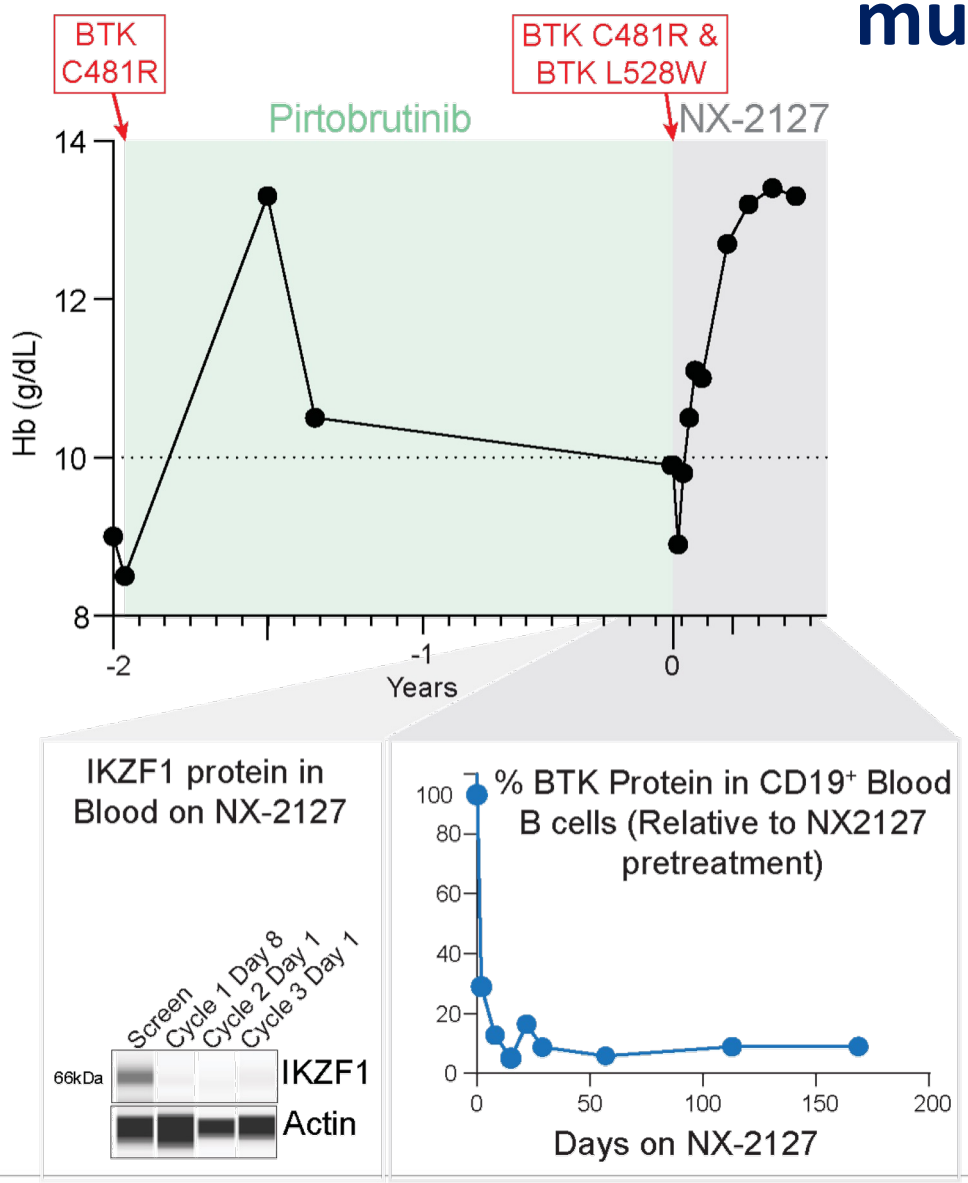


NX-2127 suppresses downstream biomarkers and displays potent cell killing



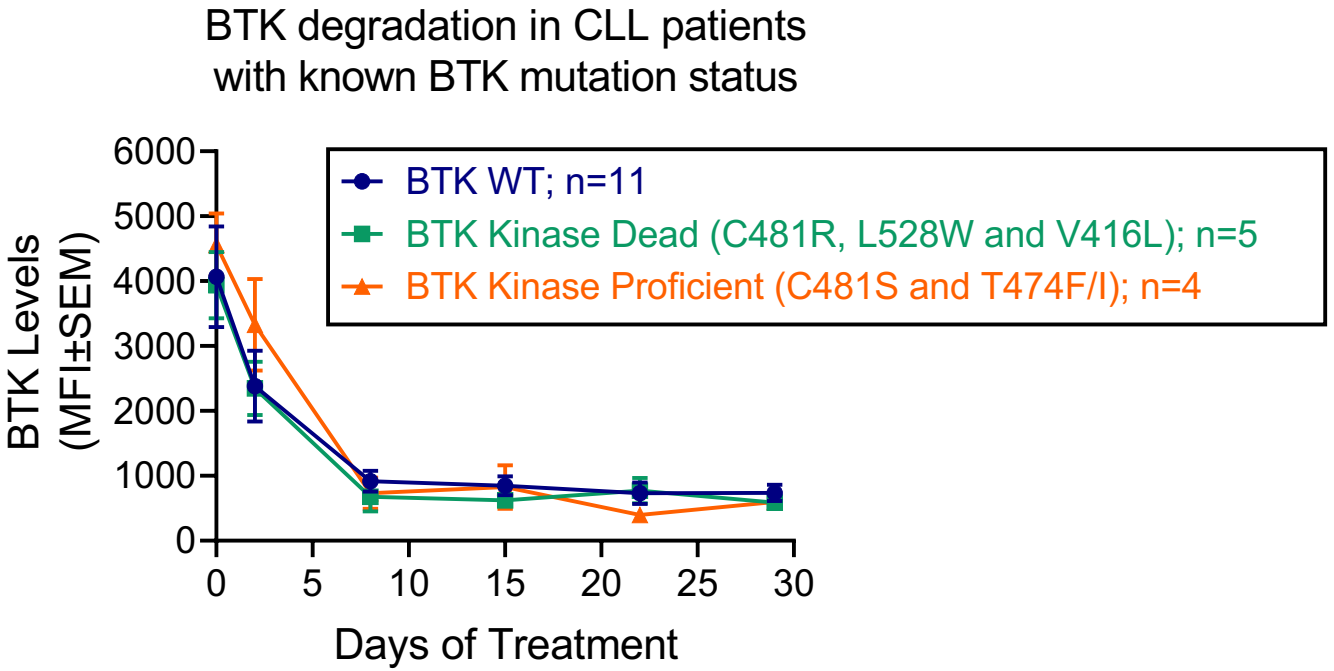


BTK degradation by NX-2127 overcomes pirtobrutinib resistance mutations in a patient

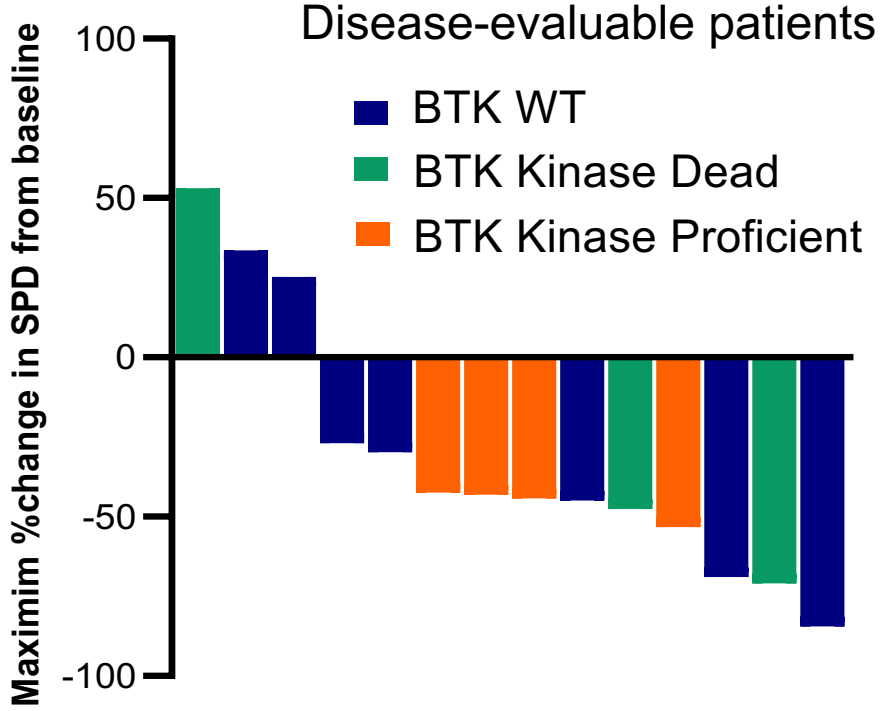


- 73 year-old man diagnosed with CLL at age 59.
- Treated with pirtobrutinib on clinical trial after prior treatment with FCR, ibrutinib and venetoclax.
- After initial response to pirtobrutinib had PD on therapy (due to acquisition of BTK L528W mutation).
- Treated with NX-2127 on phase I trial with best overall response of PR on NX-2127 with >90% BTK and IKZF1 degradation in blood.

Treatment with NX-2127 leads to BTK degradation and clinical response irrespective of mutation status in CLL patients



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



- BTK degradation of 80% achieved in CLL patients including those harboring BTK C481, T474, L528, and V416 resistance mutations
- Clinical data for NCT04830137 first in human trial assessing NX-2127 in B Cell malignancies will be presented by Dr. Anthony Mato (ABSTRACT 965)

Conclusions

- Multiple BTK mutations (including L528W, V416L, M437R, and T474I) confer resistance to noncovalent and covalent BTK inhibitors.
- We define distinct classes of BTK alterations based on enzymatic activity and a differential interactome.
- Kinase dead BTK mutations interact with other kinases to allow persistent downstream B-cell receptor signaling.
- Clinical grade BTK degraders bind & degrade mutant forms of BTK.
- NX-2127 can overcome BTK inhibitor resistance in CLL patients with kinase dead BTK mutations.

NHL Update

Initial experience in non-GCB DLBCL patients

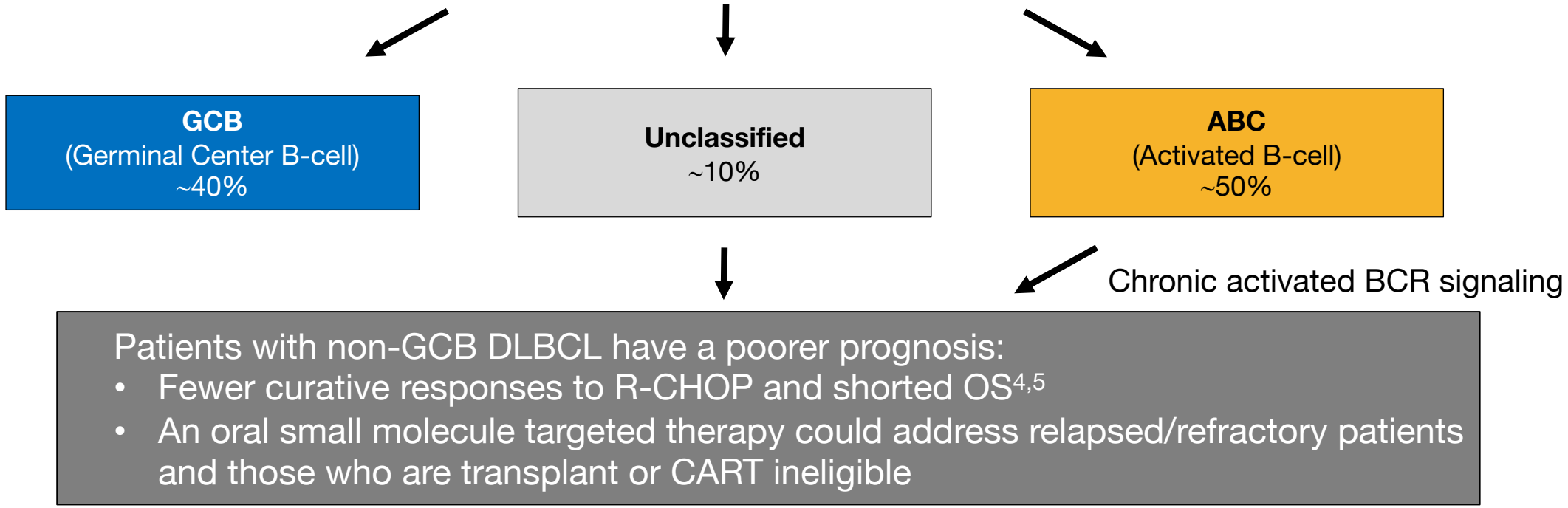
CASE STUDY

First Report of Targeted Protein Degrader NX-2127 in Diffuse Large B cell Lymphoma (DLBCL)

Non-GCB DLBCL Represents an Important Unmet Medical Need

- DLBCL is the most common form of lymphoma, representing ~30% of all NHL diagnoses[1,2]
- ~24,000 people diagnosed in the United States each year, with ~65% 5-year survival[1,2,3]

DLBCL treatments are the same for all patients, even though it is a biologically heterogeneous disease[4]



[1]American Cancer Society. Cancer Facts & Figures 2022. Atlanta, Ga: American Cancer Society; 2022. https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/key-statistics.html#references
[2]NCCN, B-Cell Lymphomas; April 2021 https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf; [3]https://seer.cancer.gov/statfacts/html/dlbcl.html
[4]Mareschal et al. Hematologica 2011;96:1888–90; [5]Schmitz et al. N Engl J Med 2018;378:1396–407

Mechanistic Rationale for Dual Degrader in DLBCL

CLINICAL TRIALS AND OBSERVATIONS

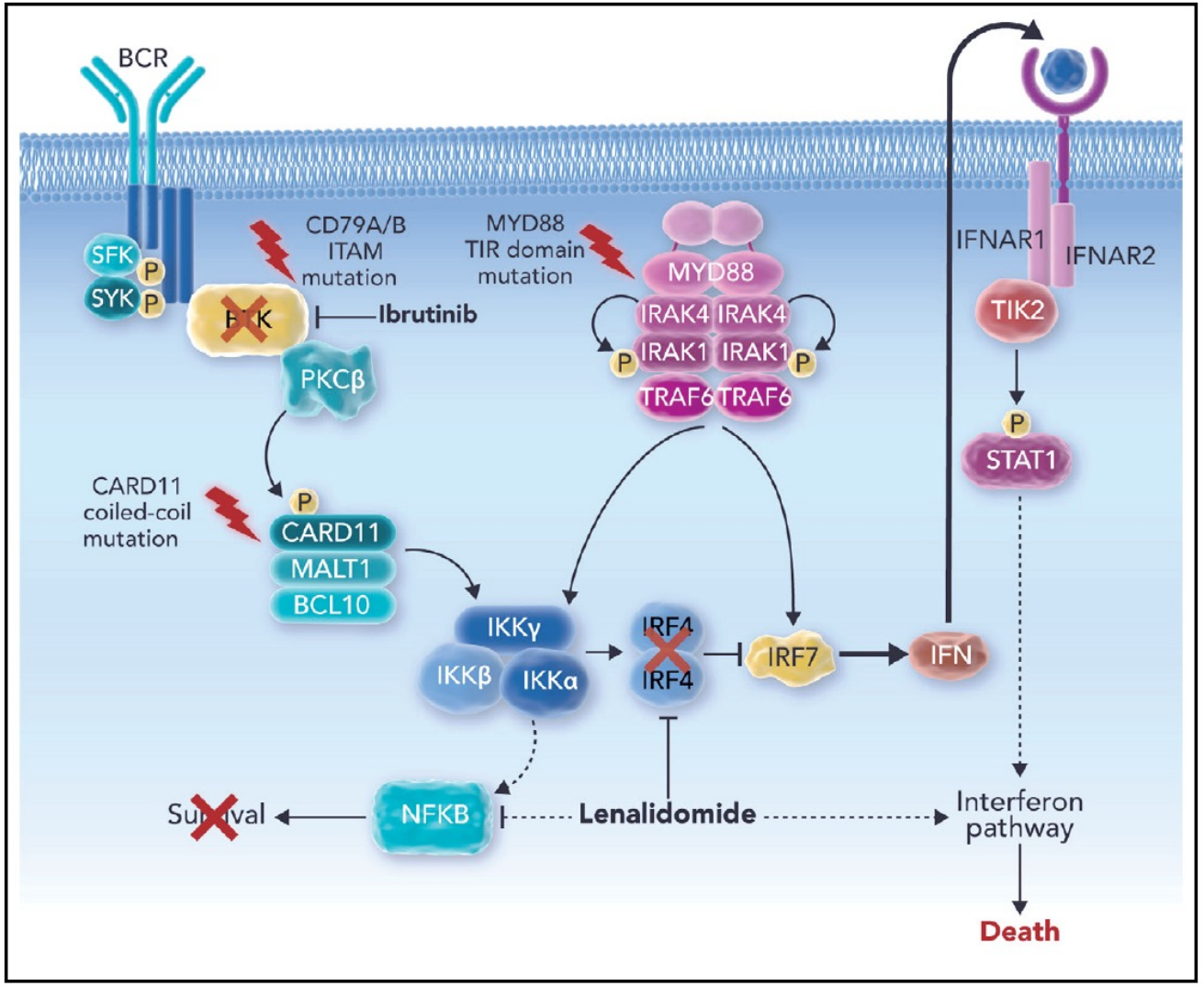
Comment on Goy et al, page 1024

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

Two Heavily Pre-Treated Patients with Non-GCB DLBCL Enrolled in NX-2127 Phase 1 Dose-Escalation

	Patient #1	Patient #2
Subtype	Non-GCB (ABC subtype) Double-hit, BCL2/BCL6	Non-GCB (ABC subtype)
Dose	100 mg	300 mg
Time on Study	3.5 months	5 months and ongoing
Priors	4	4
Response(s)	Stable Disease (SD) at 8w → Progressive Disease (PD)	Complete Response (CR)* at 8w confirmed at 16w

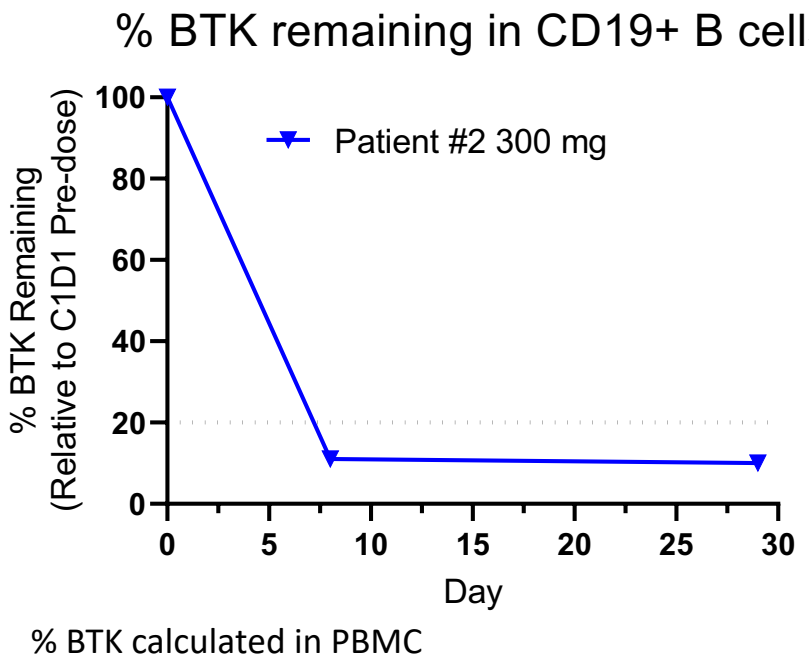
Patient #2	Baseline demographic and disease characteristics
Age; Relevant medical history	84; aortic regurgitation, diastolic dysfunction, aspergillosis sinus infection
Cancer Diagnosis	1988: Waldenstrom's macroglobulinemia (WM) 2015: Diffuse large B-cell lymphoma (DLBCL) ABC subtype
Prior treatments for DLBCL	2015: Rituximab + CHOP followed by focal axillary irradiation 2017: Rituximab + ICE 2018: Rituximab, mogamulizumab (anti-CCR4), and magrolimab (anti-CD47) 2019: Rituximab, ibrutinib, and lenalidomide (RIL)
Disease features at study entry	Stage IV, MYD88 mutated and CXCR4 mutated
Time on study	Ongoing, Cycle #6 (5 months)

nurix

Data as reported October 26, 2022

*CR per Lugano criteria

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



% BTK calculated in PBMC

Significant Ikaros and Aiolos degradation also confirmed by day 8

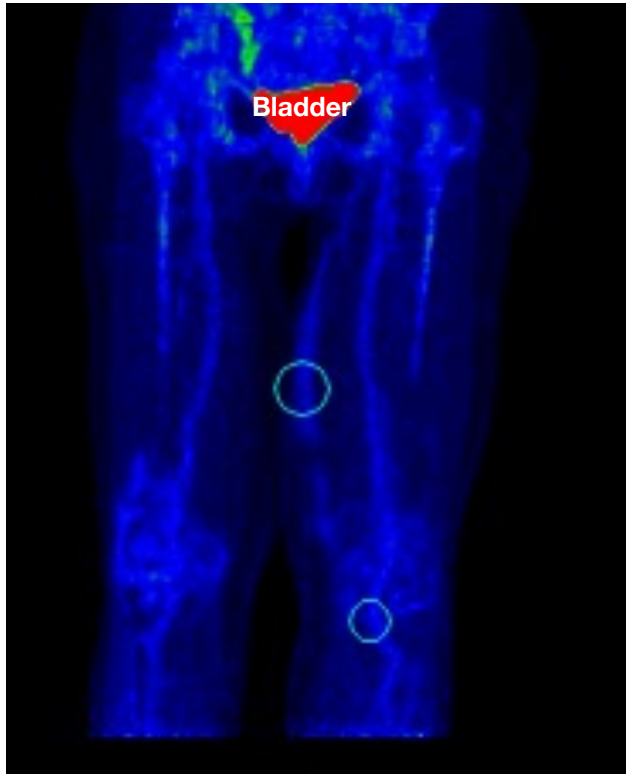
FDG-PET CT Scan Disease Assessment

Baseline

Max SUV: 17.6
Deauville 5PS: 5

SUV: Standard Uptake Value

Week 16



Max SUV: 2.5
Deauville 5PS: 2

Normal SUV

- Complete response at first assessment (Week 8) and confirmed at subsequent assessment (Week 16)
- Safety: No DLT or SAE. Grade 3 neutropenia without infection, resolved with G-CSF. No Rx interruptions.

nurix

Data as reported October 26, 2022

NX-2127: First-in-Class BTK Degrader Demonstrates Early Signs of Meaningful Clinical Activity in Both CLL and NHL

Chronic lymphocytic leukemia (CLL)

- Objective responses observed in heavily pretreated CLL patients including those receiving prior covalent BTK inhibitors, non-covalent BTK inhibitors, and BCL2 inhibitors
- Objective responses observed in patients whose tumors harbor BTK mutations known to cause resistance to both covalent and non-covalent BTK inhibitors

Next steps: Enrollment in Phase 1b is ongoing and we anticipate defining a regulatory strategy in CLL in 2023 based on a mature set of data from our ongoing Phase 1a/1b trial

Non-Hodgkin lymphoma (NHL)

- Rapid and complete response in a patient with advanced relapsed/refractory non-GCB DLBCL
- A rational mechanism to support the dual activity of NX-2127 in non-GCB DLBCL

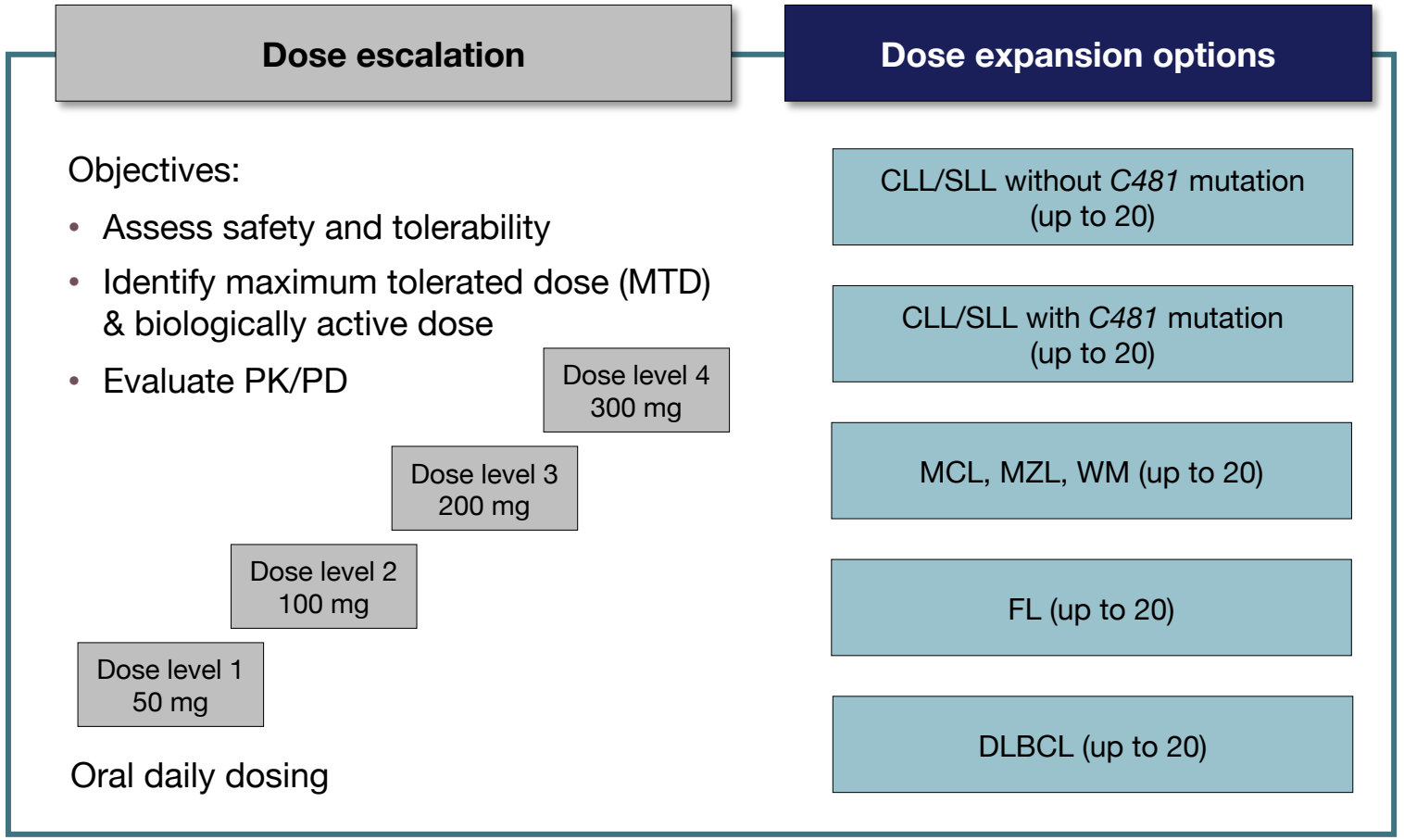
Next steps: Enrollment in Phase 1a is ongoing at the 200 mg and 300 mg doses in patients with NHL with a clinical update planned for 2023

NX-5948

Initial PK/PD data

NX-5948-301: Trial design

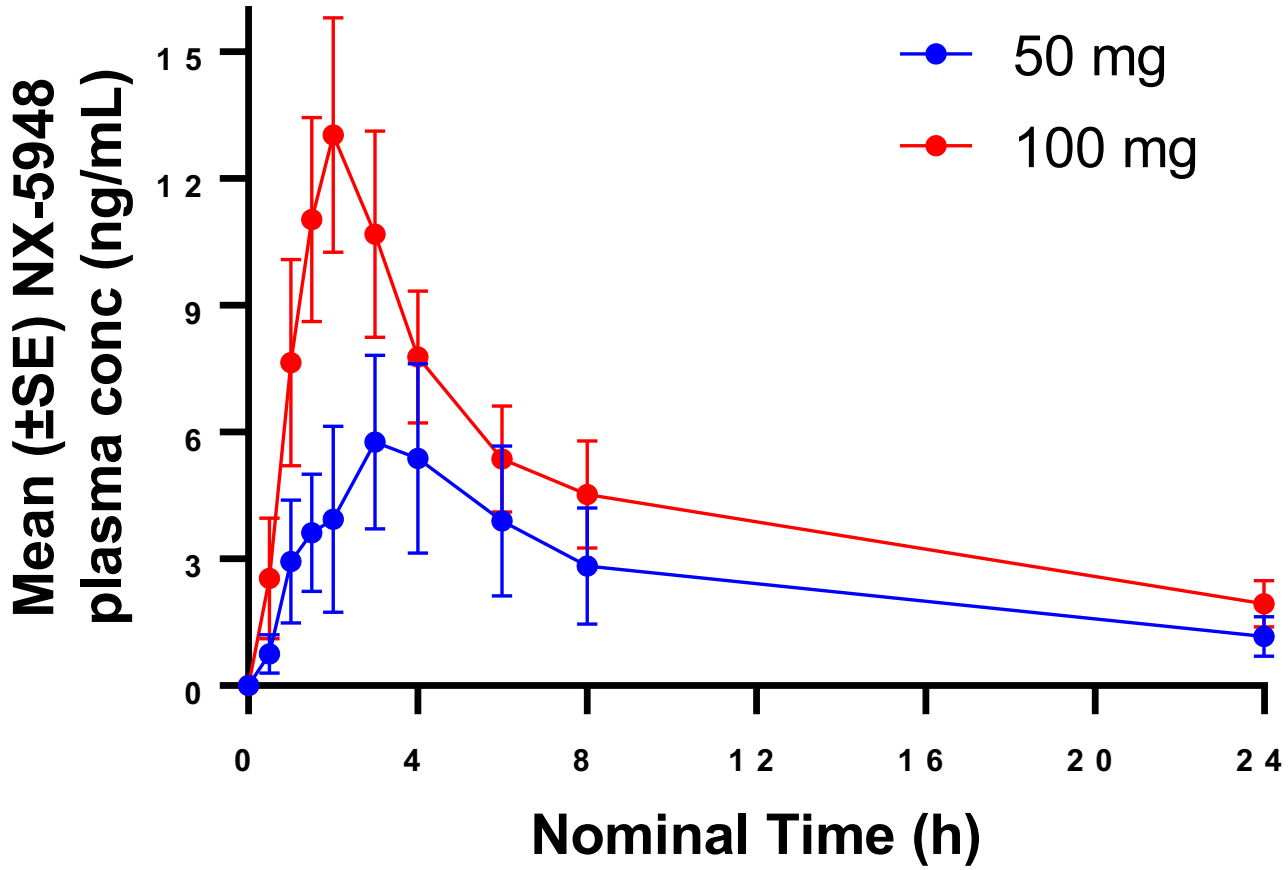
Phase 1 trial in adults with relapsed/refractory B-cell malignancies



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

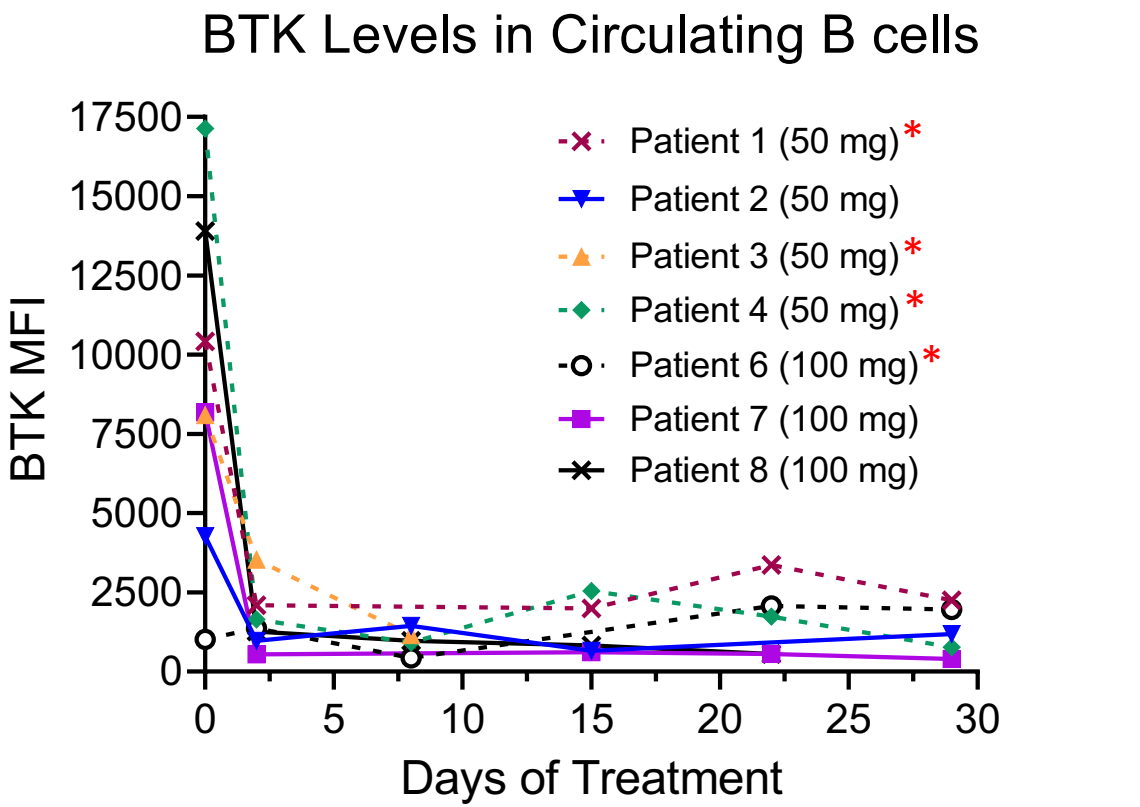
CLL, chronic lymphocytic leukemia; **DLBCL**, diffuse large B-cell lymphoma; **FL**, follicular lymphoma; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **PD,** pharmacodynamics; **PK,** pharmacokinetics; **WM**, Waldenstrom's macroglobulinemia

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

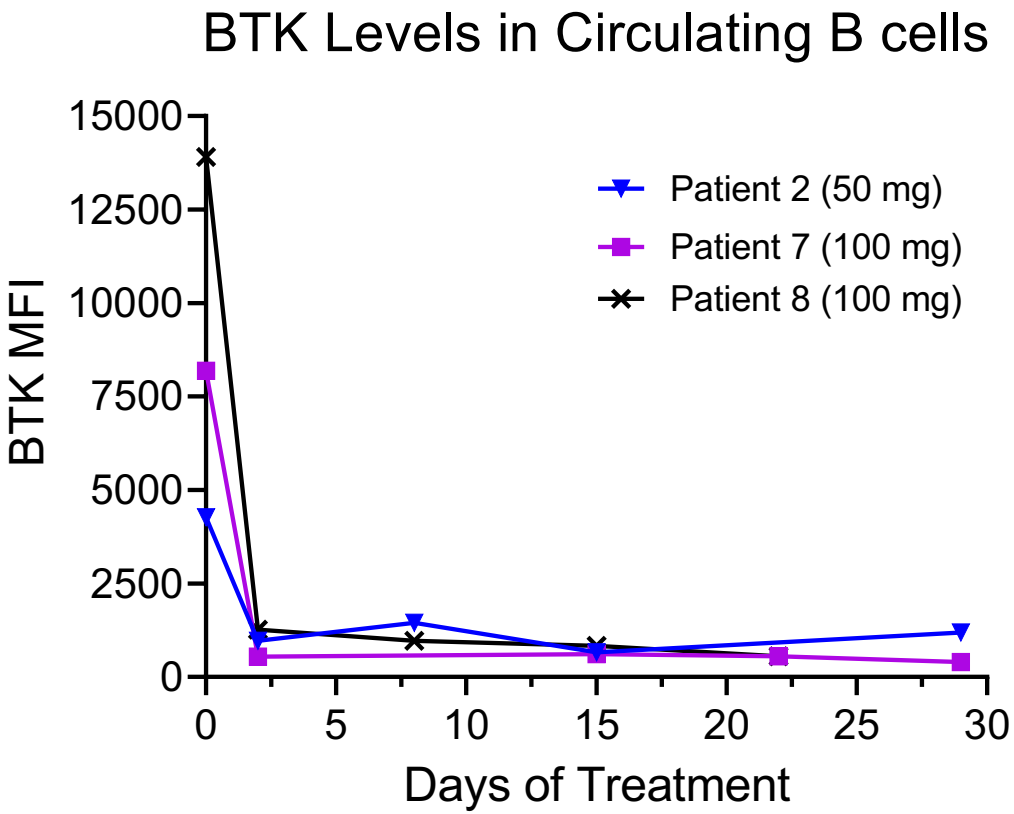


- Half-life ~12 hours
- T_{max} of 2-3 hours
- Exposures (both AUC and C_{max}) increase linearly with dose

NX-5948 Induces Rapid and Robust BTK Degradation in All Patients



* BTK MFI measured on low number of CD19+B cells (<500 events); low confidence in the MFI value



Patients with adequate circulating B cells for high confidence in MFI measurements

NX-5948: BTK Degrader Without Immunomodulatory Activity Demonstrates Rapid and Sustained BTK Degradation

Phase 1a Dose Escalation

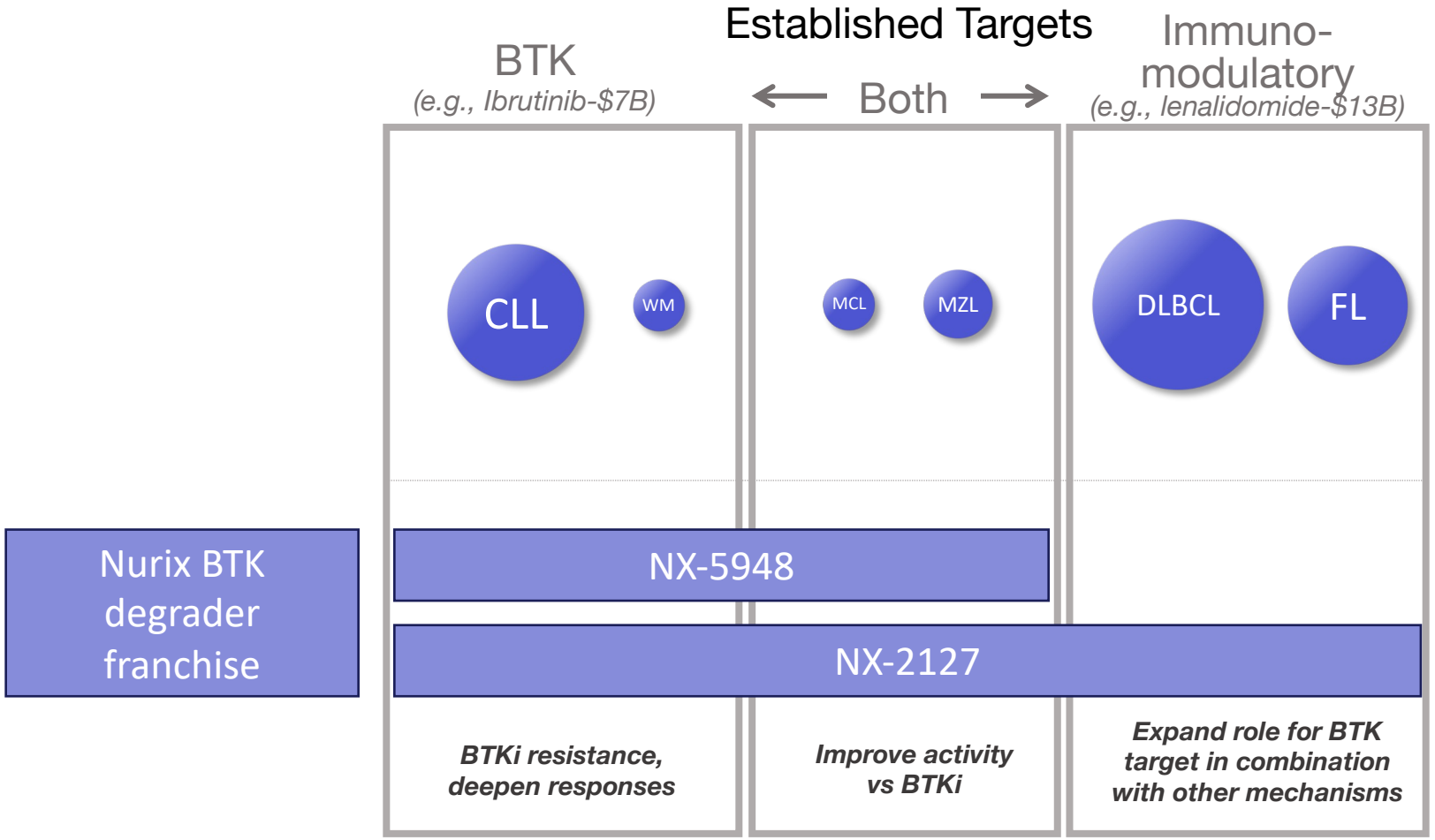
- Early evidence of target engagement
- Rapid and sustained BTK degradation in all patients
- No evidence of immunomodulatory associated adverse events (e.g. neutropenia)

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

Wrap up

NX-2127 Combines Activity of Two Blockbuster MOAs: BTK Inhibition and Immunomodulation



Size of bubble=annual incidence in US and EU

B-CELL MALIGNANCIES ANNUAL INCIDENCE (US & EU)	
Chronic Lymphocytic Leukemia (CLL)	39,700
Diffused Large B-Cell Lymphoma (DLBCL)	55,100
Follicular Lymphoma (FL)	26,200
Mantle cell lymphoma (MCL)	6,200
Marginal Zone Lymphoma (MZL)	10,700
Waldenstrom's macroglobulinemia (WM)	6,300

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

- NX-2127 has potential to address BTK inhibitor resistance arising through multiple pathways, and indications that require combination therapy
- NX-5948 may address BTK resistance mutations and be the degrader of choice for single-target therapy with potential in autoimmunity

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

Delivering Key Clinical Milestones in 2022

Targeted Protein Degradation

NX-2127

- Initiate Phase 1b trial in mid-2022
- Present additional Phase 1a clinical results in H2 2022

NX-5948

- Dose first patient in Phase 1a trial in H1 2022
- Present Phase 1a PK/PD in H2 2022

Targeted Protein Elevation

NX-1607

- Present Phase 1a PK/PD in H2 2022
- File IND, initiate US clinical sites in H2 2022

DeTIL-0255

- Dose first patient in Phase 1 trial in H1 2022
- Phase 1 clinical update from safety run in H2 2022

Note: All anticipated timing is based on calendar-year periods

Delivering Key Clinical Milestones in 2022

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DeTIL-0255

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Note: All anticipated timing is based on calendar-year periods

Nurix Today

- World-class small molecule discovery capabilities focused on ligase-based medicines
- Four wholly owned and internally developed Phase 1 clinical assets and five preclinical programs
- Pharma partners dedicated to pursuing first-in-class and best-in-class drugs funding an additional ten programs
- Clinical investigators from top academic institutions with strong track records of developing innovative drugs
- Well funded to progress pipeline through important clinical milestones in 2023 and 2024

Q&A