UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of Earliest Event Reported): December 12, 2022

NURIX THERAPEUTICS, INC.
(Exact Name of Registrant as Specified in its Charter)

Delaware	**001-39398**	**27-0838048**
(State or Other Jurisdiction of Incorporation or Organization)	**(Commission File Number)**	**(IRS Employer Identification No.)**

1700 Owens Street, Suite 205 **San Francisco, California** **(Address of Principal Executive Offices)**	**94158** **(Zip Code)**

(415) 660-5320
(Registrant's Telephone Number, Including Area Code)

N/A
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol(s)	Name of each exchange on which registered
Common Stock, $0.001 par value per share	NRIX	Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On December 12, 2022, Nurix Therapeutics, Inc. (the "Company") issued a press release announcing the presentation at the 64th American Society of Hematology Annual Meeting and Exposition (the "ASH Annual Meeting") of positive clinical data from the Company's Phase 1 clinical trial of NX-2127. As previously announced, the Company will host a webcast at 9:30 p.m. ET on December 12, 2022, to review the data presented at the ASH Annual Meeting and the Company's progress in its degrader portfolio. Copies of the press release and the presentation materials for the webcast, which include the data presented at the ASH Annual Meeting, are attached hereto as Exhibit 99.1 and Exhibit 99.2, respectively, and are incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

The following exhibits are filed herewith and this list is intended to constitute the exhibit index:

99.1	Nurix Therapeutics, Inc. press release dated December 12, 2022.
99.2	Nurix Therapeutics, Inc. presentation dated December 12, 2022.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended the Registrant has duly caused this Report to be signed on its behalf by the undersigned hereunto duly authorized.

NURIX THERAPEUTICS, INC.

Date: December 12, 2022

By: /s/ Christine Ring
Christine Ring, Ph.D., J.D.
General Counsel and Secretary

Nurix Therapeutics Presents Positive Clinical Results from its Novel BTK Degrader (NX-2127) at the 64th American Society of Hematology (ASH) Annual Meeting

Treatment with NX-2127 provides clinically meaningful responses in heavily pretreated chronic lymphocytic leukemia (CLL) patients regardless of Bruton's tyrosine kinase (BTK) mutational status

BTK mutations conferring resistance to both covalent and non-covalent BTK inhibitors remain susceptible to degradation by NX-2127

Nurix will host a Key Opinion Leader (KOL) webcast event at 9:30 pm ET today to review data presented at ASH and progress in its degrader portfolio

SAN FRANCISCO, Dec. 12, 2022 – Nurix Therapeutics, Inc. (Nasdaq: NRIX), a clinical-stage biopharmaceutical company developing targeted protein modulation drugs designed to treat patients with hematologic malignancies and solid tumors, today presented additional positive clinical data from its Phase 1 clinical trial of NX-2127 in two oral sessions by Anthony Mato, M.D., MSCE, former director of the Chronic Lymphocytic (CLL) Program at Memorial Sloan Kettering Cancer Center, and Omar Abdel-Wahab, M.D., Chair of Sloan Kettering Institute (SKI) Molecular Pharmacology Program at Memorial Sloan Kettering Cancer Center. NX-2127 is a once daily, oral, investigational new drug that combines BTK degradation with immunomodulatory activity. The podium presentations took place at the 64th American Society of Hematology (ASH) Annual Meeting and Exposition which is being held in New Orleans, Louisiana.

"These early Phase 1 data demonstrate that NX-2127 effectively degrades BTK resulting in clinically meaningful responses independent of prior treatments or BTK mutational status and offering a potential new treatment modality for patients who have otherwise exhausted other approved and emerging treatment options," said Robert J. Brown, M.D., Nurix's executive vice president of clinical development.

The data presented by Dr. Mato demonstrate that treatment with NX-2127 results in sustained BTK degradation and clinically meaningful responses in heavily pretreated patients with relapsed/refractory CLL independent of prior treatments or BTK mutational status. These presentations included preliminary data from 36 adults with relapsed/refractory B-cell malignancies enrolled in the Phase 1a/b study, including 23 patients with CLL who had undergone and failed a median of five prior therapies including a BTK inhibitor. Approximately 78% of this group had previously received both BTK and BCL2 inhibitors and 35% had been

treated with the non-covalent BTK inhibitor pirtobrutinib. Of the CLL patients, 48% had one or more identified BTK resistance mutations prior to treatment with NX-2127. Following treatment with NX-2127 in this heavily pretreated CLL population, sustained BTK degradation and decreased B cell activation were observed regardless of prior treatment and baseline BTK mutation status with an overall response rate (ORR) of 33% (95% CI 12–62%). As of September 21, 2022, the data cut-off date, the median follow up was 5.6 months (0.3 to 15.7 months), and 14 of 23 patients remained on treatment. Importantly, the safety profile of NX-2127 was consistent with prior results from the Phase 1a portion of the trial and reports for BTK-targeted therapies in heavily pretreated patients with B cell malignancies.

“We are excited by the growing body of data generated in our Phase 1a/1b clinical trial of NX-2127 which highlights the significant differentiation and potential advantages of BTK degradation over BTK inhibition, especially in the setting of resistance to existing therapies,” said Arthur T. Sands, M.D., Ph.D., president and chief executive officer of Nurix. “We continue to explore the promise of this first-in-class targeted protein degrader of BTK as we enroll additional CLL patients in the ongoing expansion cohort and continue to enroll patients with non-Hodgkin lymphoma in the dose escalation. We look forward to additional clinical updates in 2023.”

The presentation by Dr. Abdel-Wahab highlighted critical scientific findings underlying the emergence of new BTK inhibitor resistance mutations that lack BTK’s enzymatic function but still drive tumor growth. These so-call “kinase deficient” and “kinase dead” mutations underscore the importance of BTK’s scaffolding function, which is uniquely addressable by the BTK degrader modality. In the presentation, five different clinically emergent BTK resistance mutations were analyzed and categorized as kinase proficient, kinase deficient, or kinase dead, each conferring a different spectrum of resistance to available therapies. NX-2127 was found to be broadly active against all these mutations. These findings translated into clinically meaningful BTK degradation in the Phase clinical 1 trial and clinical activity independent of baseline BTK mutations.

Webcast details

The live KOL webcast event, which will begin at 8:30 pm CT (9:30 pm ET) on Monday, December 12, 2022, and the subsequent replay, will be available in the Investors section of the Nurix website under Events and Presentations.

About the Phase 1, Study of NX-2127

The multicenter Phase 1 study is designed to evaluate safety, pharmacokinetics, pharmacodynamics and preliminary clinical activity of orally administered NX-2127 in adult patients with relapsed or refractory B-cell malignancies. The study is being conducted in two parts. The Phase 1a element is a dose-escalation study in which cohorts of patients will receive

ascending oral doses of NX-2127 once daily to determine the maximum tolerated dose (MTD) and/or the optimal Phase 1b dose based on safety and tolerability. The second portion of the study, Phase 1b, is a dose expansion phase in which cohorts of patients with specific cancers will receive NX-2127 to further evaluate the safety and clinical activity of the recommended dose. The study is expected to enroll eligible patients with the following cancers: chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), Waldenstrom macroglobulinemia (WM), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL), who have required and received prior systemic therapies. Additional information on the clinical trial can be accessed at ClinicalTrials.gov (NCT04830137).

About NX-2127

NX-2127 is a novel bifunctional molecule that degrades Bruton's tyrosine kinase (BTK) and cereblon neosubstrates Ikaros (IKZF1) and Aiolos (IKZF3). NX-2127 is currently being evaluated in a Phase 1 clinical trial in patients with relapsed or refractory B cell malignancies.

About Nurix

Nurix Therapeutics is a clinical stage biopharmaceutical company focused on the discovery, development and commercialization of small molecule and cell therapies based on the modulation of cellular protein levels as a novel treatment approach for cancer and other challenging diseases. Leveraging extensive expertise in E3 ligases together with proprietary DNA-encoded libraries, Nurix has built DELigase, an integrated discovery platform to identify and advance novel drug candidates targeting E3 ligases, a broad class of enzymes that can modulate proteins within the cell. Nurix's drug discovery approach is to either harness or inhibit the natural function of E3 ligases within the ubiquitin proteasome system to selectively decrease or increase cellular protein levels. Nurix's wholly owned pipeline includes targeted protein degraders of Bruton's tyrosine kinase, a B-cell signaling protein, and inhibitors of Casitas B-lineage lymphoma proto-oncogene B, an E3 ligase that regulates T cell activation. Nurix is headquartered in San Francisco, California. For additional information visit http://www.nurixtx.com.

Forward-Looking Statements

This press release contains statements that relate to future events and expectations and as such constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. When or if used in this press release, the words "anticipate," "believe," "could," "estimate," "expect," "intend," "may," "outlook," "plan," "predict," "should," "will," and similar expressions and their variants, as they relate to Nurix, may identify forward-looking statements. All statements that reflect Nurix's expectations, assumptions or projections about the future, other than statements of historical fact, are forward-looking

statements, including, without limitation, statements regarding the tolerability, safety profile, therapeutic potential and other advantages of NX-2127; the planned timing and conduct of the clinical trials for NX-2127; the planned timing for the provision of updates and findings from Nurix's clinical trials; and the extent to which Nurix's drug candidates and scientific approach may potentially address a broad range of diseases. Forward-looking statements reflect Nurix's current beliefs, expectations, and assumptions. Although Nurix believes the expectations and assumptions reflected in such forward-looking statements are reasonable, Nurix can give no assurance that they will prove to be correct. Forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and changes in circumstances that are difficult to predict, which could cause Nurix's actual activities and results to differ materially from those expressed in any forward-looking statement. Such risks and uncertainties include, but are not limited to: (i) whether Nurix will be able to successfully conduct Phase 1 clinical trials for NX-2127 and its other drug candidates and receive results on its expected timelines, or, at all; (ii) whether Nurix will be able to successfully complete clinical development for NX-2127 and its other drug candidates; (iii) the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; (iv) whether regulatory authorities will be satisfied with the results from Nurix's clinical studies; (v) whether Nurix will be able to obtain regulatory approval of and ultimately commercialize its drug candidates; (vi) whether Nurix will be able to fund development activities and achieve development goals; (vii) the impact of macroeconomic conditions, including as a result of the COVID-19 pandemic, inflation and rising interest rates on Nurix's clinical trials and operations; and (viii) other risks and uncertainties described under the heading "Risk Factors" in Nurix's Quarterly Report on Form 10-Q for the fiscal quarter ended August 31, 2022, and other SEC filings. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. The statements in this press release speak only as of the date of this press release, even if subsequently made available by Nurix on its website or otherwise. Nurix disclaims any intention or obligation to update publicly any forward-looking statements, whether in response to new information, future events, or otherwise, except as required by applicable law.

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Exhibit 99.2

nurix

Leader in Targeted Protein Modulation

Nurix Therapeutics

Blazing a New Path in Medicine

ASH Event Presentation

December 12, 2022

Important Notice and Disclaimers

This presentation contains statements that relate to future events and expectations and as such constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. When or if used in this presentation, the words “anticipate,” “believe,” “could,” “estimate,” “expect,” “intend,” “may,” “outlook,” “plan,” “predict,” “should,” “will,” and similar expressions and their variants, as they relate to Nurix Therapeutics, Inc. (“Nurix”, the “Company,” “we,” “us” or “our”), may identify forward-looking statements. All statements that reflect Nurix’s expectations, assumptions or projections about the future, other than statements of historical fact, are forward-looking statements, including, without limitation, statements regarding our future financial or business plans; our future performance, prospects and strategies; future conditions, trends, and other financial and business matters; our current and prospective drug candidates; the planned timing and conduct of the clinical trial programs for our drug candidates; the planned timing for the provision of clinical updates and initial findings from our clinical studies; the potential advantages of our DELigase™ platform and drug candidates; the extent to which our scientific approach and DELigase™ platform may potentially address a broad range of diseases; the extent animal model data predicts human efficacy; and the timing and success of the development and commercialization of our current and anticipated drug candidates. Forward-looking statements reflect Nurix’s current beliefs, expectations, and assumptions. Although Nurix believes the expectations and assumptions reflected in such forward-looking statements are reasonable, Nurix can give no assurance that they will prove to be correct. Forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and changes in circumstances that are difficult to predict, which could cause Nurix’s actual activities and results to differ materially from those expressed in any forward-looking statement. Such risks and uncertainties include, but are not limited to: (i) risks and uncertainties related to Nurix’s ability to advance its drug candidates, obtain regulatory approval of and ultimately commercialize its drug candidates; (ii) the timing and results of clinical trials; (iii) Nurix’s ability to fund development activities and achieve development goals; (iv) the impact of the COVID-19 pandemic on Nurix’s business, clinical trials, financial condition, liquidity and results of operations; (v) Nurix’s ability to protect intellectual property and (vi) other risks and uncertainties described under the heading “Risk Factors” in Nurix’s Quarterly Report on Form 10-Q for the fiscal quarter ended August 31, 2022, and other SEC filings. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. The statements in this presentation speak only as of the date of this presentation, even if subsequently made available by Nurix on its website or otherwise. Nurix disclaims any intention or obligation to update publicly any forward-looking statements, whether in response to new information, future events, or otherwise, except as required by applicable law.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company’s own internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal estimates and research are reliable, such estimates and research have not been verified by any independent source.

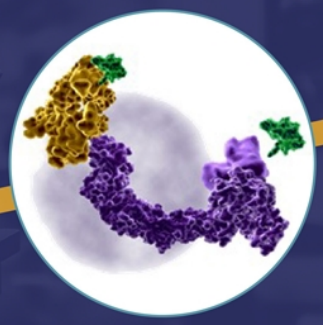
Nurix Drugs Engage Ligases for the Treatment of Cancer

Targeted Protein Modulation: TPM = TPD + TPE

A Powerful Cellular System

Targeted Protein Elevation (TPE)

Harness ligases to decrease specific protein levels



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

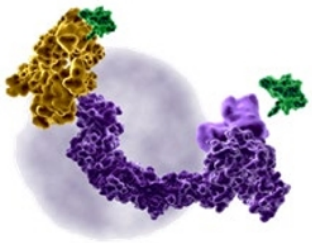
MOA	Drug program	Target/delivery	Therapeutic area	Preclinical	Phase 1	Phase 2	Phase 3
TPD	**NX-2127** Degrader	BTK-IKZF *Oral*	B-cell malignancies				
TPD	**NX-5948** Degrader	BTK *Oral*	B-cell malignancies				
TPE	**NX-1607** Inhibitor	CBL-B *Oral*	Immuno-Oncology				
TPE	**DeTIL-0255** Cell therapy	*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

Anthony Mato,[1] William G. Wierda,[2] Weiyun Ai,[3] Ian Flinn,[4] Michael Tees,[5] Manish R. Patel,[6] Krish Patel,[7] Susan O'Brien,[8] David Bond,[9] Lindsey E. Roeker,[1] Tanya Siddiqi,[10] Michael Wang,[2] Clare Sun,[11] Omar Abdel-Wahab,[1] Amanda Schwab,[12] May Tan,[12] Erin Meredith,[12] Melissa A. Gessner,[12] Adrian Wiestner,[11] Alexey Danilov[10]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]University of California San Francisco Medical Center, San Francisco CA, USA; [4]Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN, USA; [5]Colorado Blood Cancer Institute, Denver, CO, USA; [6]Florida Cancer Specialists, Sarah Cannon Research Institute, Sarasota, FL, USA; [7]Swedish Cancer Institute, Center for Blood Disorders and Cellular Therapy, Seattle, WA, USA; [8]Chao Family Comprehensive Cancer Center, University of California, Irvine, Orange, CA, USA; [9]The James Cancer Hospital at The Ohio State University, Columbus, OH, USA; [10]City of Hope National Medical Center, Duarte, CA, USA; [11]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA; [12]Nurix Therapeutics, Inc., San Francisco, CA, USA

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]

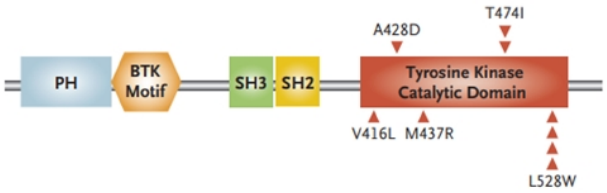
There is a need for a new treatment modality that can target both emerging resistant mutations and BTK scaffolding activity in patients who have otherwise, exhausted other approved and emerging treatment options

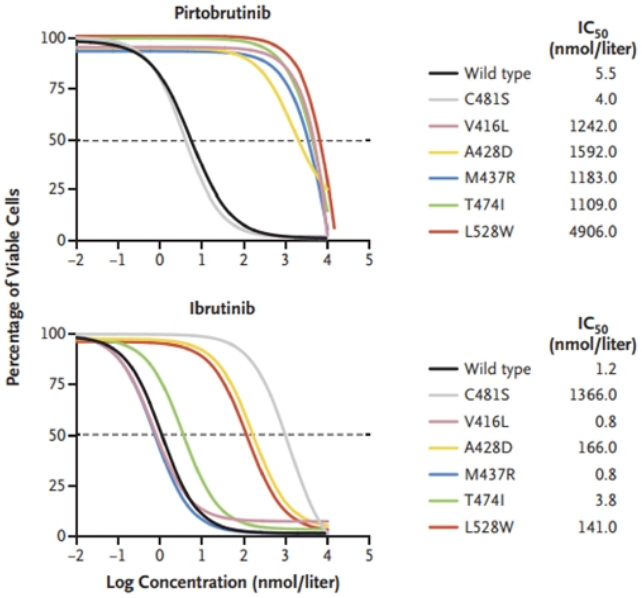
BCL2, B-cell lymphoma-2; **BTK,** Bruton tyrosine kinase; **CLL**, chronic lymphocytic leukemia; **NF-kB,** nuclear factor kappa-light-chain-enhancer of activated B cells

[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

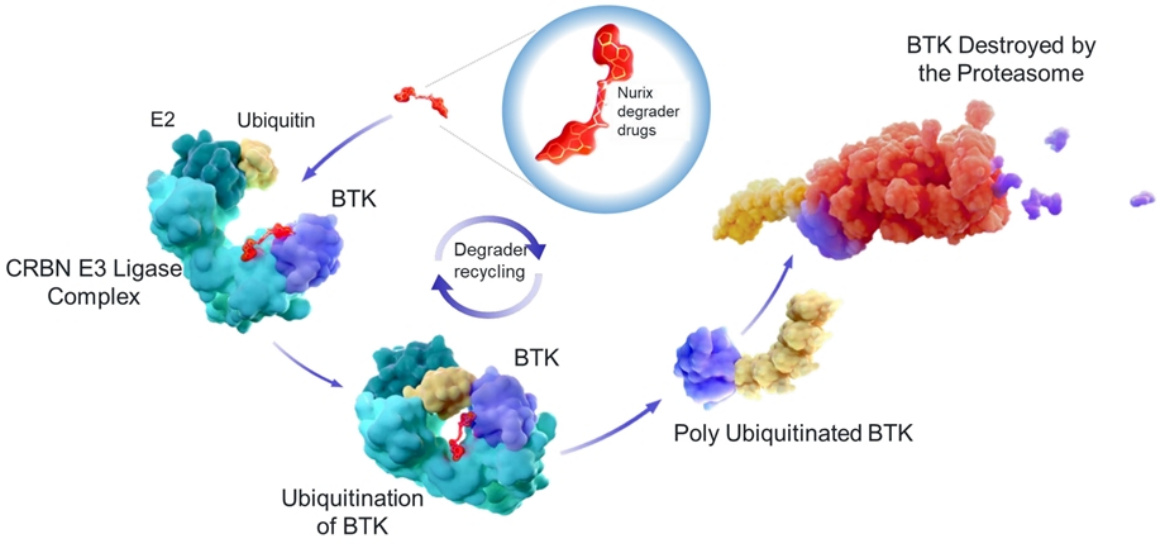




Wang et al. N Engl J Med 2022;386:735–43

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

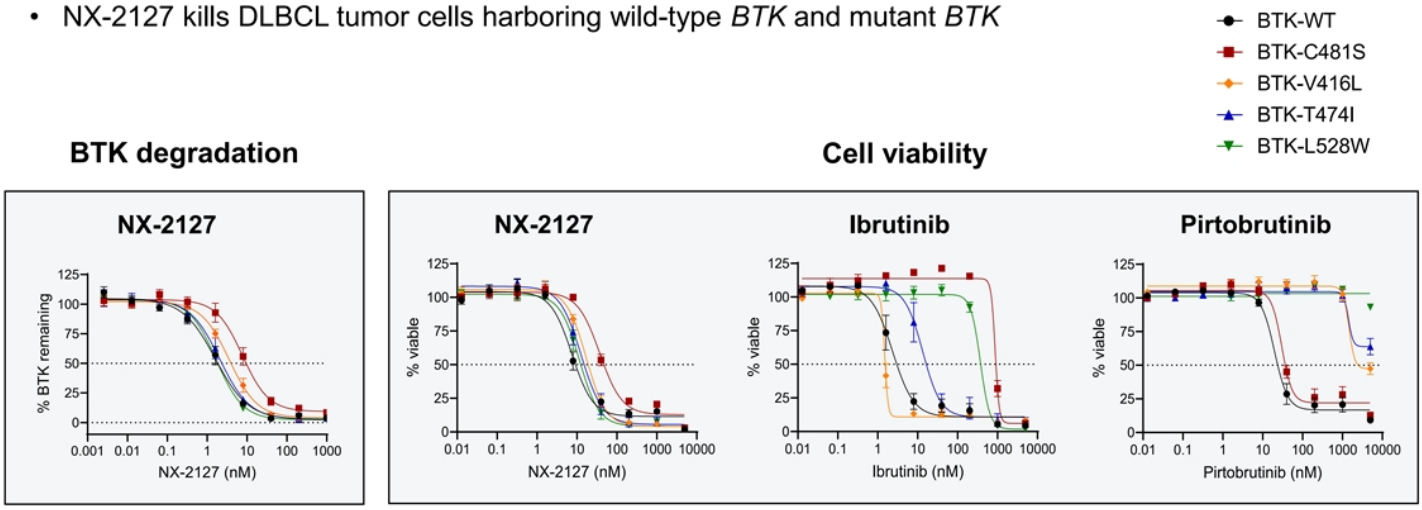
Utilizing the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in B-cell malignancies



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

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

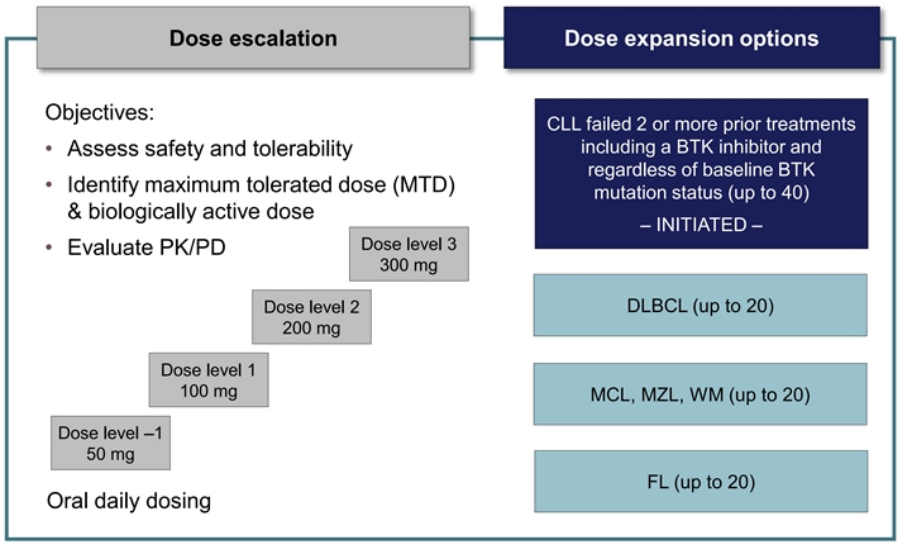
- NX-2127 degrades wild-type and mutant *BTK*, including the recently described kinase dead mutations
- NX-2127 kills DLBCL tumor cells harboring wild-type *BTK* and mutant *BTK*



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

NX-2127-001: trial design

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

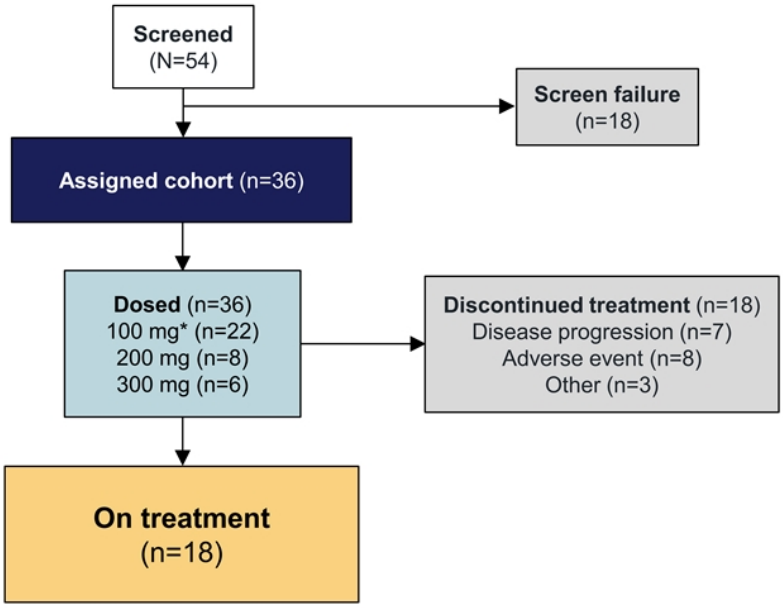


- CLL Phase 1b expansion cohort at 100 mg dose
  - MTD not established
  - 100 mg dose chosen as expansion dose based on PD, clinical activity and safety profile
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL (e.g. DLBCL, MCL, MZL, WM, FL)

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

Data cutoff: September 21, 2022

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 prior AF on ibrutinib (2 cases)

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

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

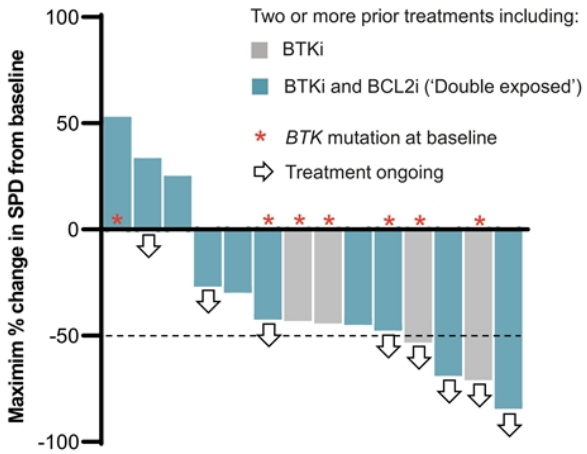
[a]Aggregate of "neutropenia" and "neutrophil count decreased" [b] Includes episodes of bruising and other similar verbatim terms [c]Aggregate of "thrombocytopenia" and "platelet count decreased" [d]Cases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases),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

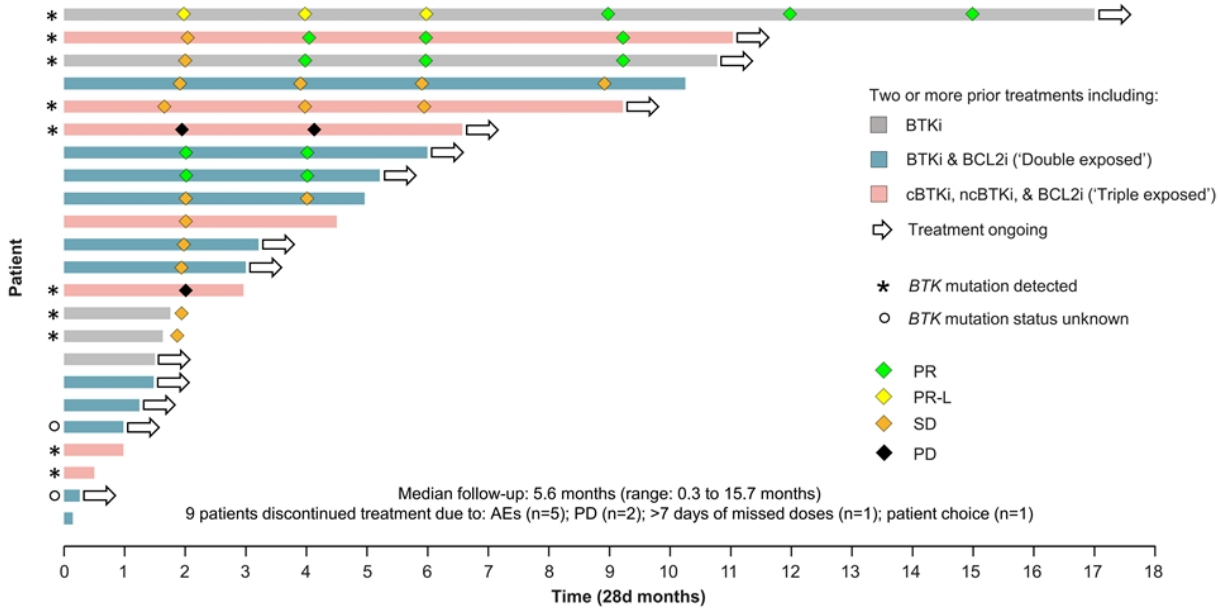


***One patient, not shown above, with prior BTKi and BCL2i treatment and with a *BTK* mutation detected at baseline, had no nodal disease at baseline. Their treatment is ongoing with a PR**

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

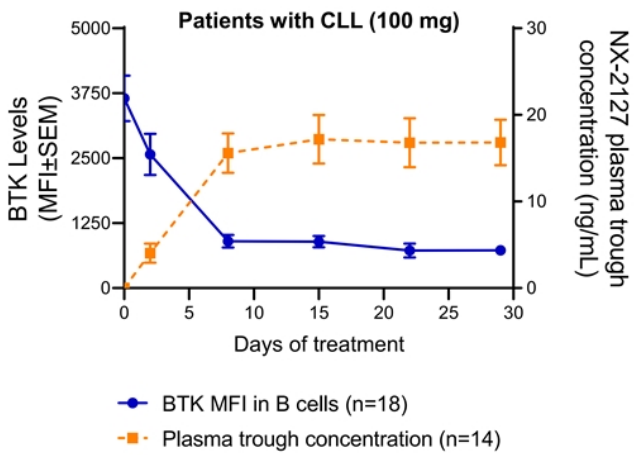
Outcomes and time on therapy with NX-2127 (patients with CLL)

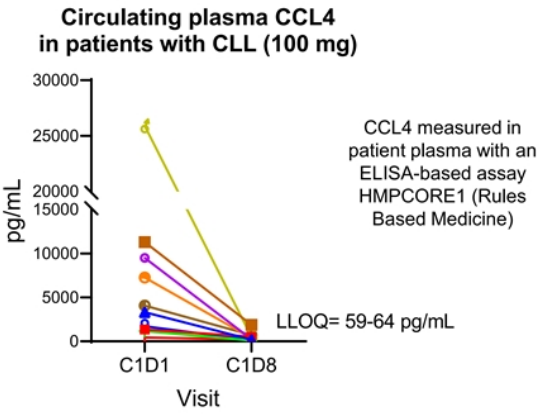
Responses seen in double and triple exposed patients



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

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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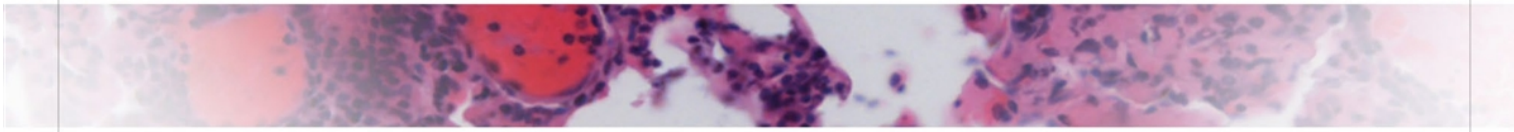
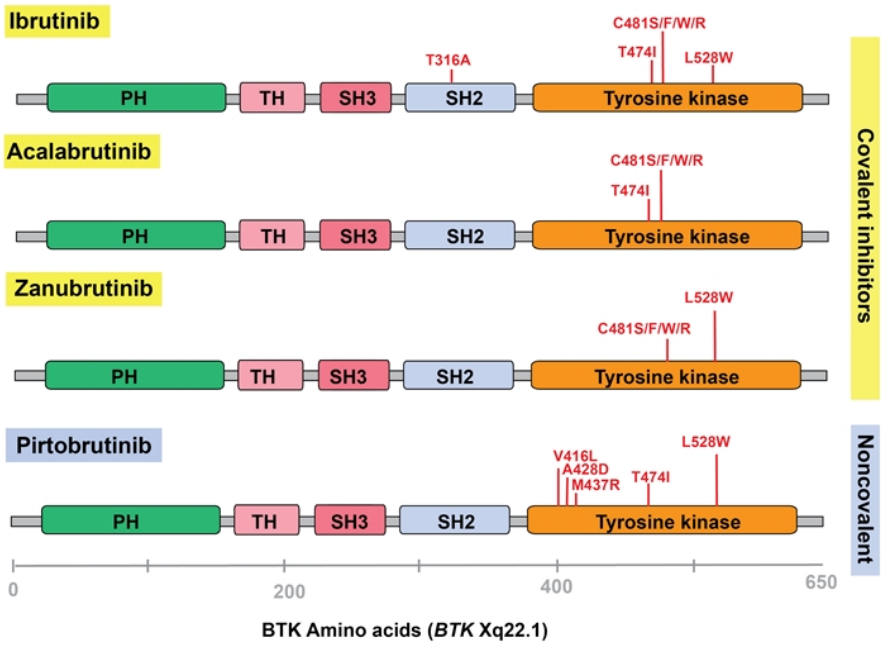


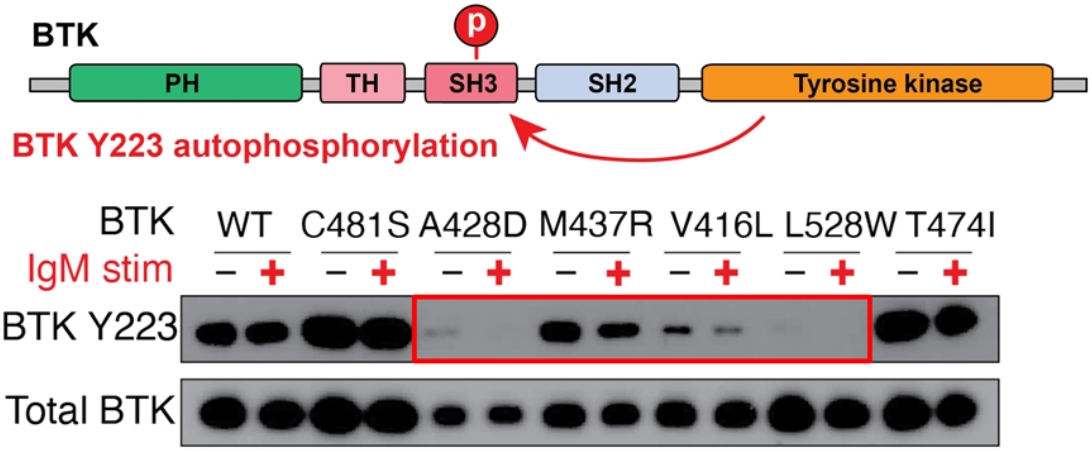
Kinase Dead BTK Mutations Confer Resistance to Covalent and Noncovalent BTK Inhibitors but Are Susceptible to Clinical Stage BTK Degraders

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



Several BTK mutations abrogate BTK phosphorylation



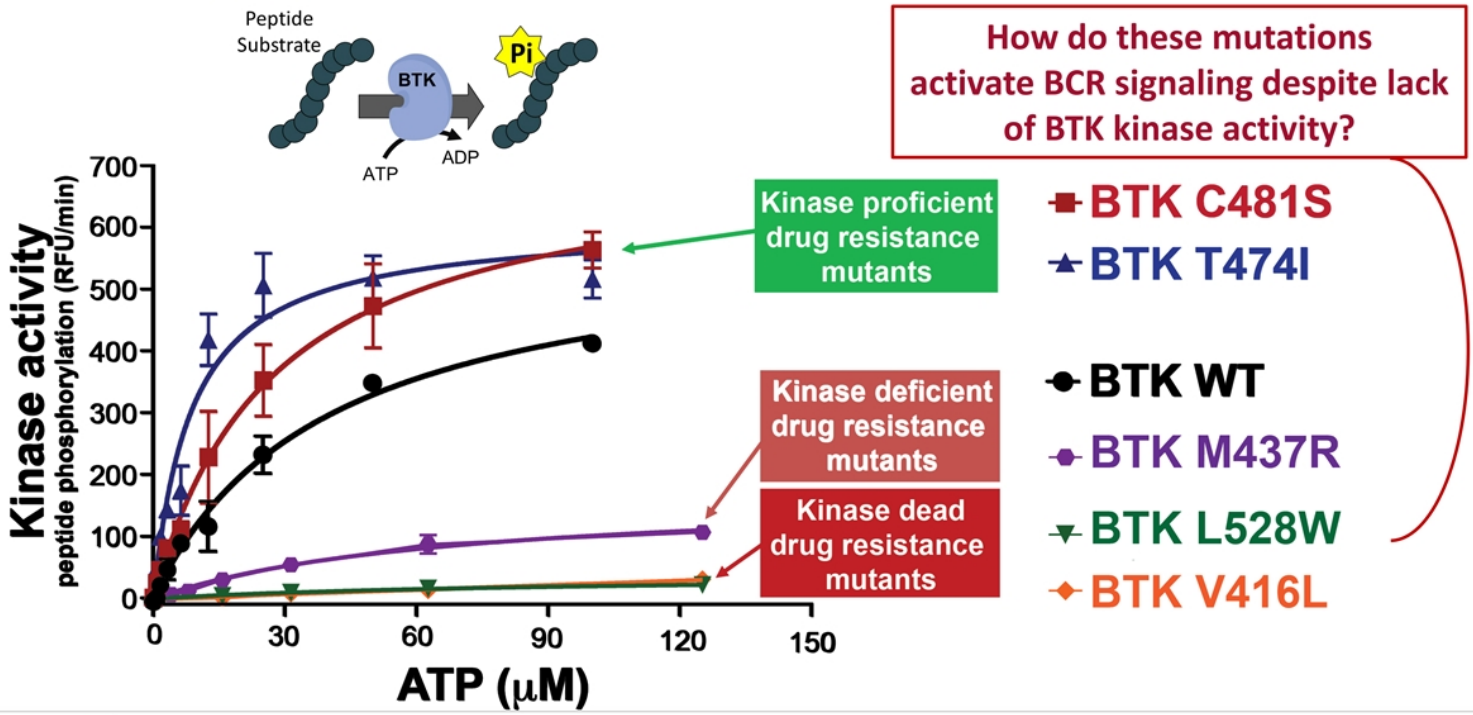
Questions:

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



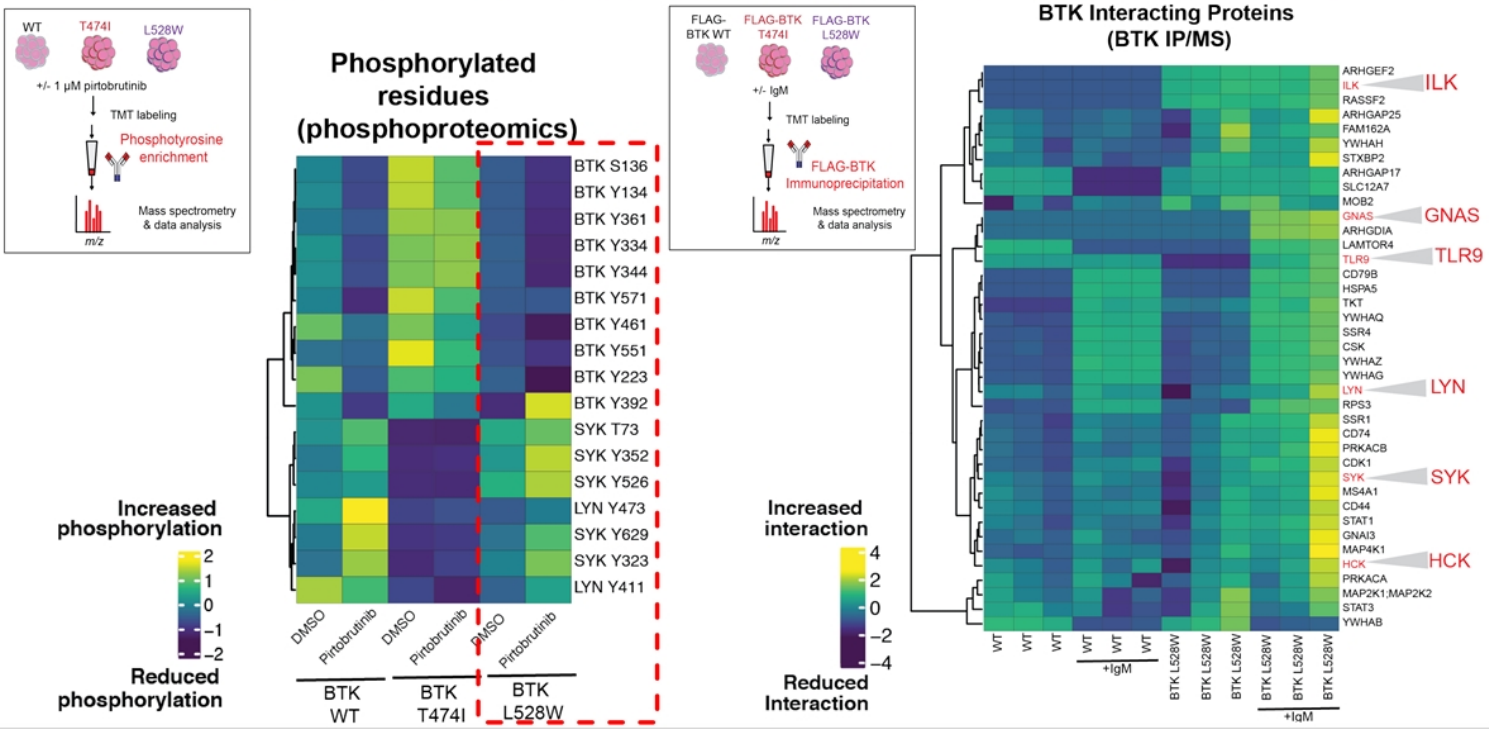
Proteomic characterization of BTK drug resistance mutants

Phosphoproteome

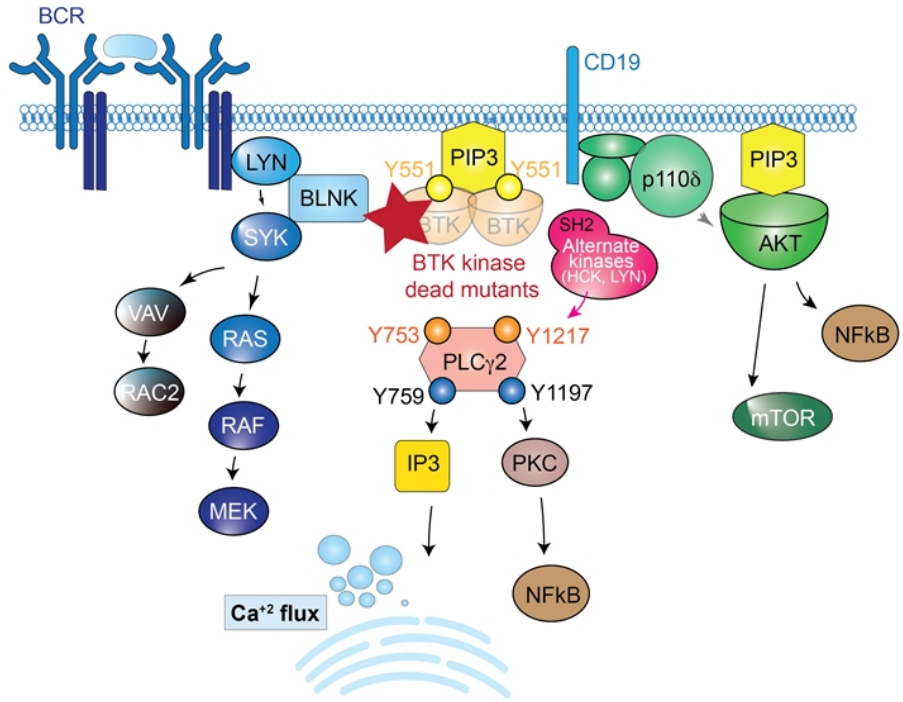
Kinome profiling using broad spectrum kinase inhibitors

BTK Immunoprecipitation/ mass spectrometry

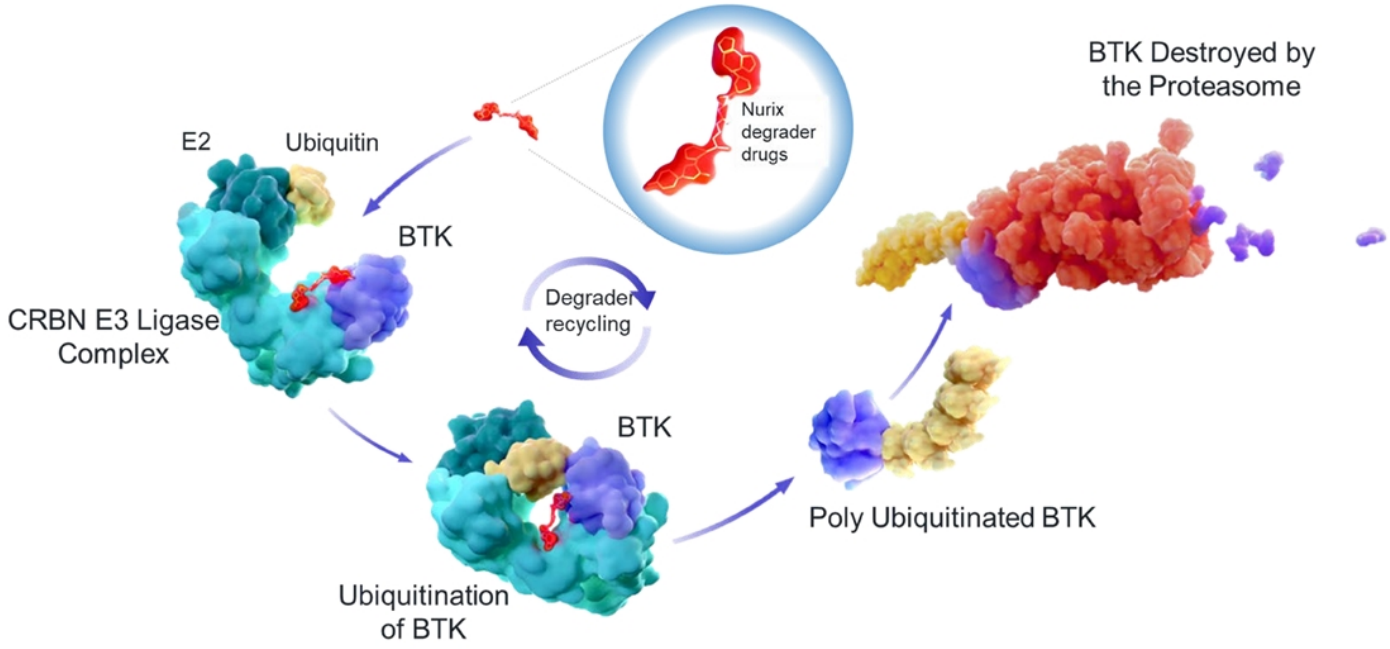
Kinase dead BTK mutants recruit unique interacting proteins



Can we target the scaffold function of BTK?



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



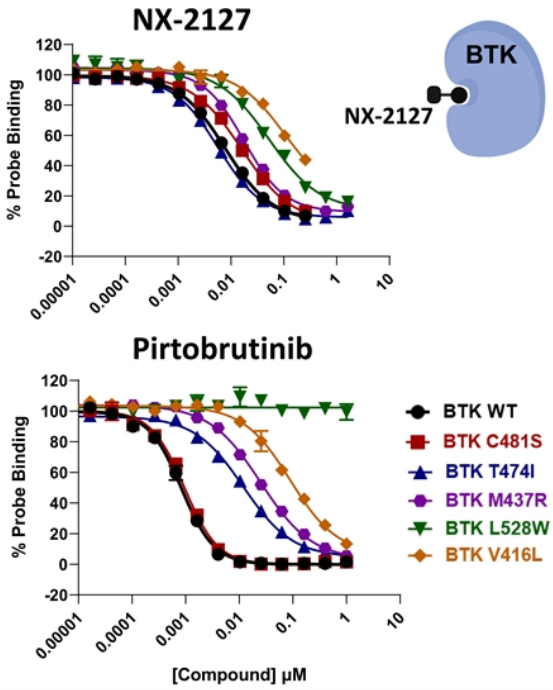
CRBN, cereblon

NX-2127 binds to BTKi resistance mutants

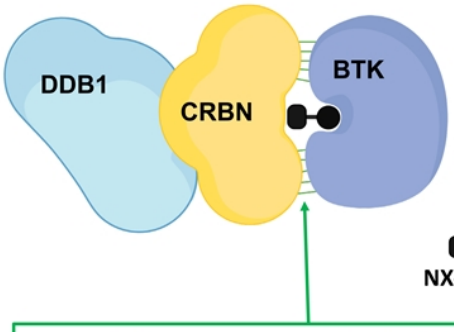
BTK Proteins	NX-2127 Degrader	Pirtobrutinib Non-covalent Inhibitor	Ibrutinib Covalent Inhibitor
	IC_{50} (nM)	IC_{50} (nM)	K_{inact}/K_i ($M^{-1}*s^{-1}$)
WT	9	0.7	2×10^5
C481S	19	0.8	6 nM (IC_{50})
T474I	7	11	1×10^5
M437R	22	30	3×10^6
L528W	66	No binding @ 1 µM	No binding @ 1 µM
V416L	111	98	6×10^4

>10x reduced binding

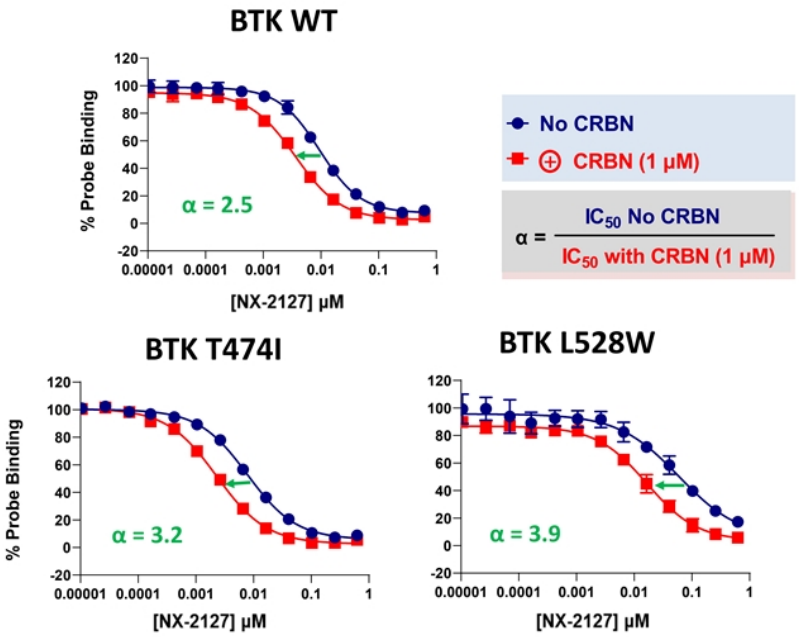
Compound binding measured in a FRET-based probe displacement assay



NX-2127 induces positive cooperativity between BTK and CRBN

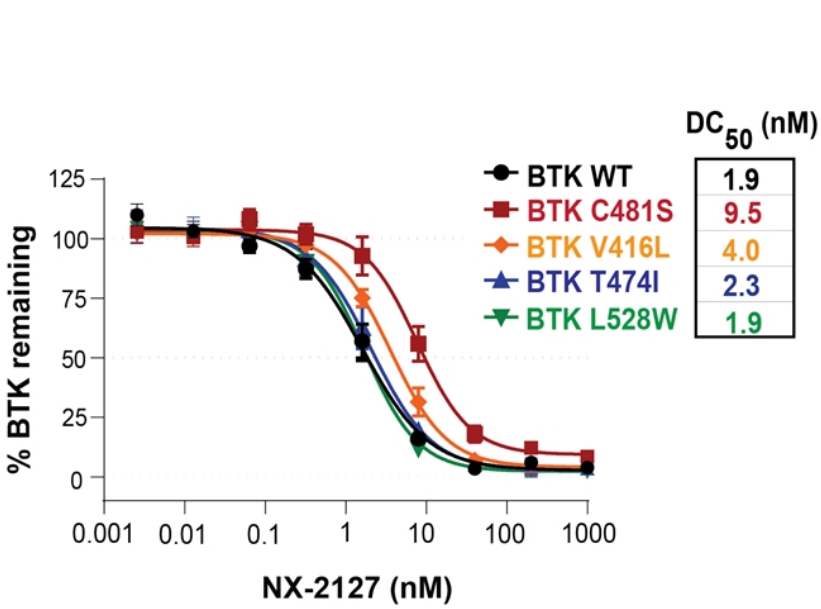


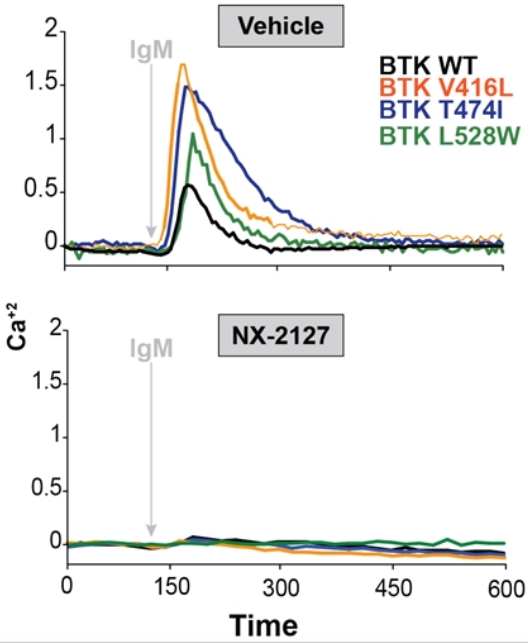
- Positive Cooperativity (α>1)
- Stable ternary complex
- Induced protein-protein interactions
- Greater tolerance for reduced binary affinity



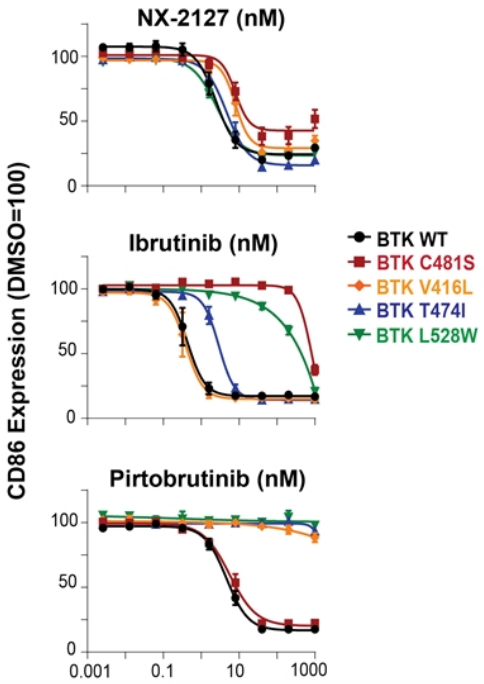
CRBN, cereblon; **DDB1**, DNA damage binding protein 1.

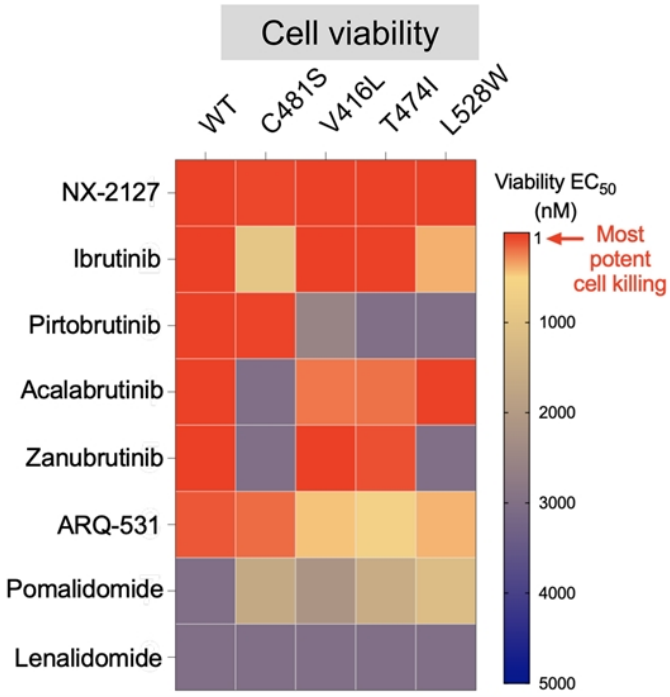
NX-2127 degrades both wild-type and kinase dead mutant BTK and suppresses Ca^{2+} signaling



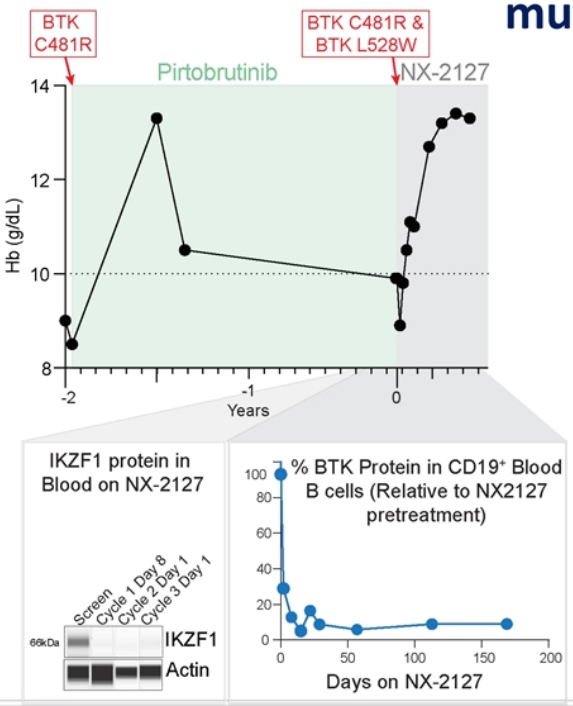


NX-2127 suppresses downstream biomarkers and displays potent cell killing



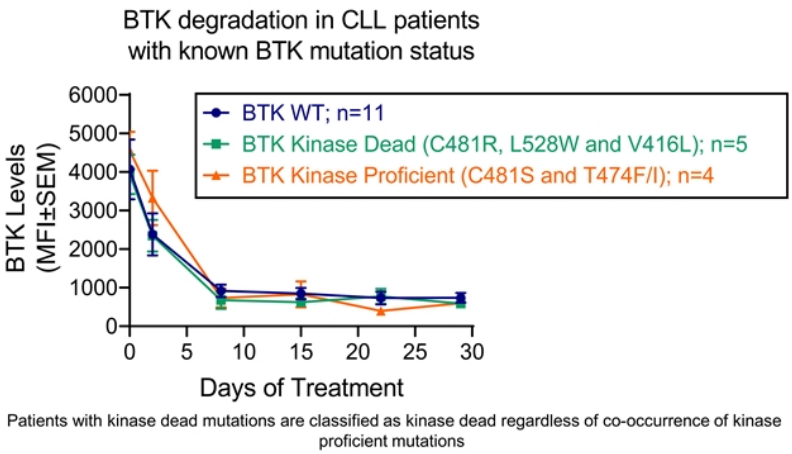


BTK degradation by NX-2127 overcomes pirtobrutinib resistance mutations in a patient

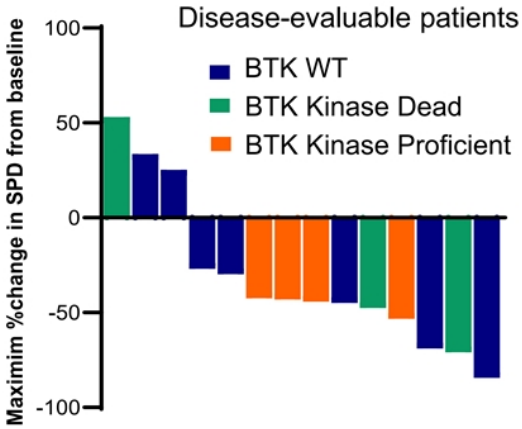


- 73 year-old man diagnosed with CLL at age 59.
- Treated with pirtobrutinib on clinical trial after prior treatment with FCR, ibrutinib and venetoclax.
- After initial response to pirtobrutinib had PD on therapy (due to acquisition of BTK L528W mutation).
- Treated with NX-2127 on phase I trial with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

nurix

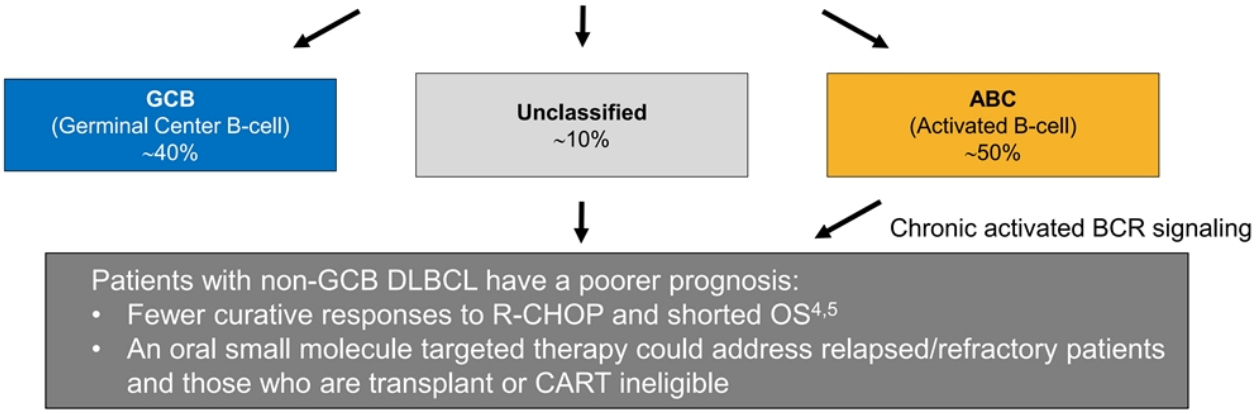
CASE STUDY

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]



Patients with non-GCB DLBCL have a poorer prognosis:
- Fewer curative responses to R-CHOP and shorted OS[4,5]
- An oral small molecule targeted therapy could address relapsed/refractory patients and those who are transplant or CART ineligible

[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

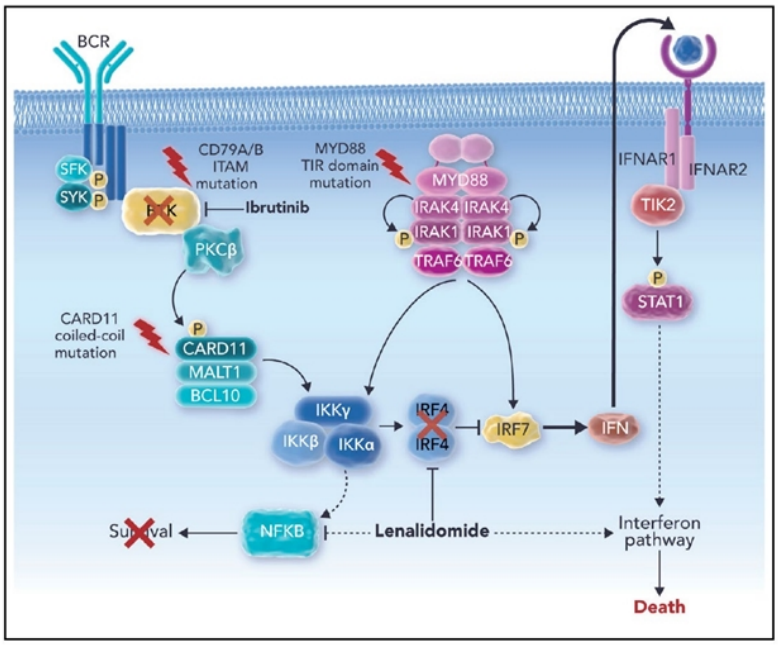
Comment on Goy et al, page 1024

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

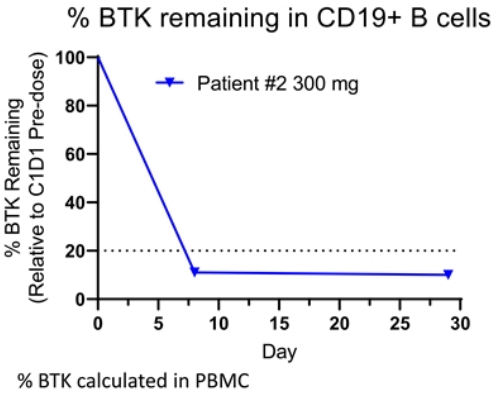
Patient #2	Baseline demographic and disease characteristics
Age; Relevant medical history	84; aortic regurgitation, diastolic dysfunction, aspergillosis sinus infection
Cancer Diagnosis	1988: Waldenstrom's macroglobulinemia (WM) 2015: Diffuse large B-cell lymphoma (DLBCL) ABC subtype
Prior treatments 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

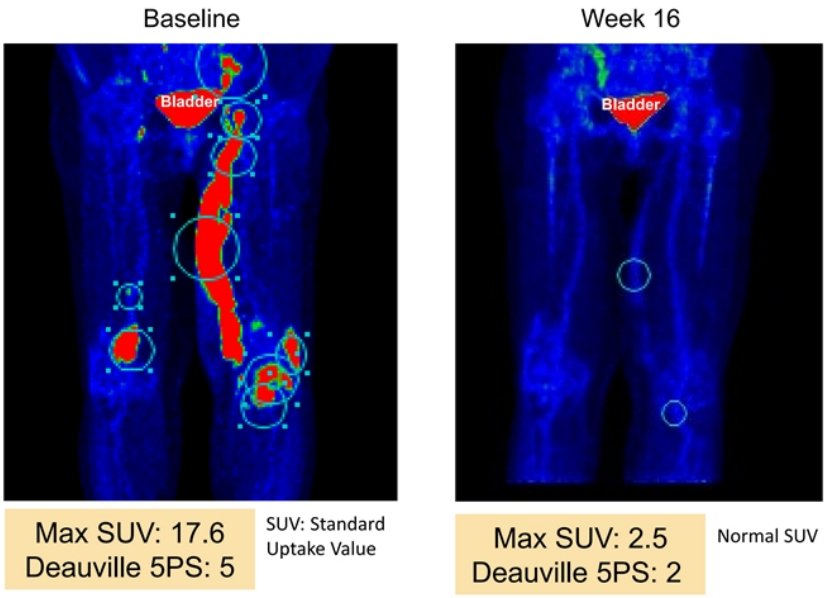
Rapid BTK Degradation and Confirmed Complete Response Following NX-2127 Therapy



% BTK calculated in PBMC

Significant Ikaros and Aiolos degradation also confirmed by day 8

FDG-PET CT Scan Disease Assessment



Max SUV: 17.6
Deauville 5PS: 5

SUV: Standard Uptake Value

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.

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 rationale mechanism to support the dual activity of NX-2127 in non-GCB DLBCL

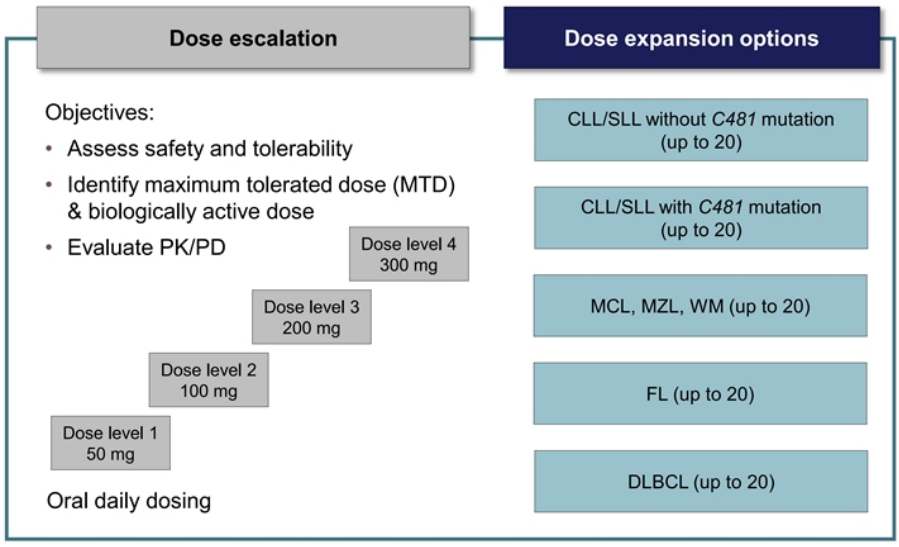
Next steps: Enrollment in Phase 1a is ongoing at the 200 mg and 300 mg doses in patients with NHL with a clinical update planned for 2023

NX-5948

Initial PK/PD data

NX-5948-301: Trial design

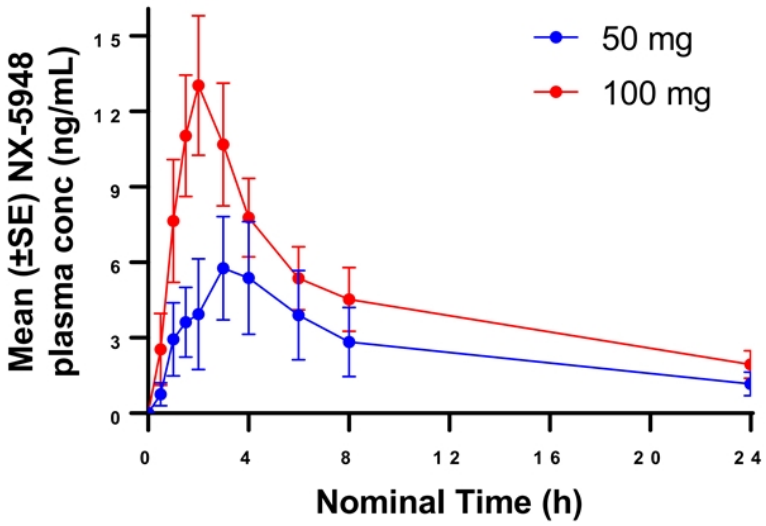
Phase 1 trial in adults with relapsed/refractory B-cell malignancies



- 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

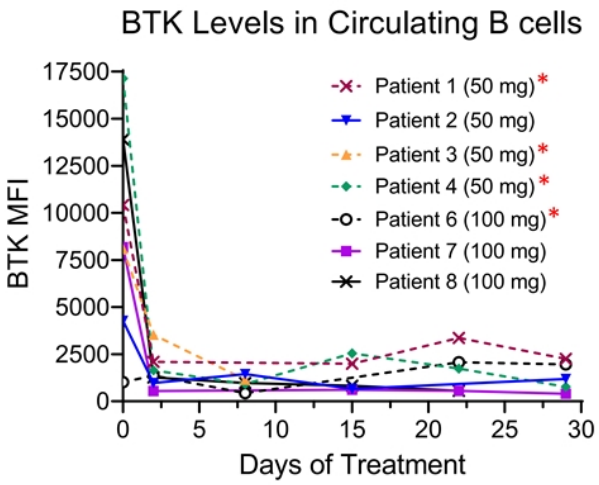
Preliminary Data Suggests NX-5948 Exhibits Linear PK and Supports Daily Dosing



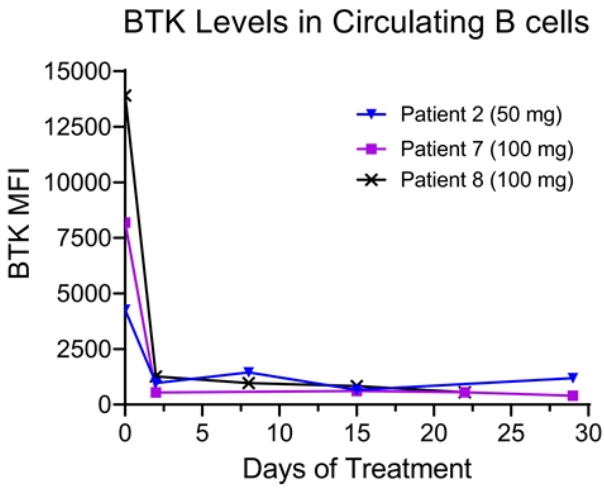
- Half-life ~12 hours
- T_{max} of 2-3 hours
- Exposures (both AUC and C_{max}) increase linearly with dose

nurix

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

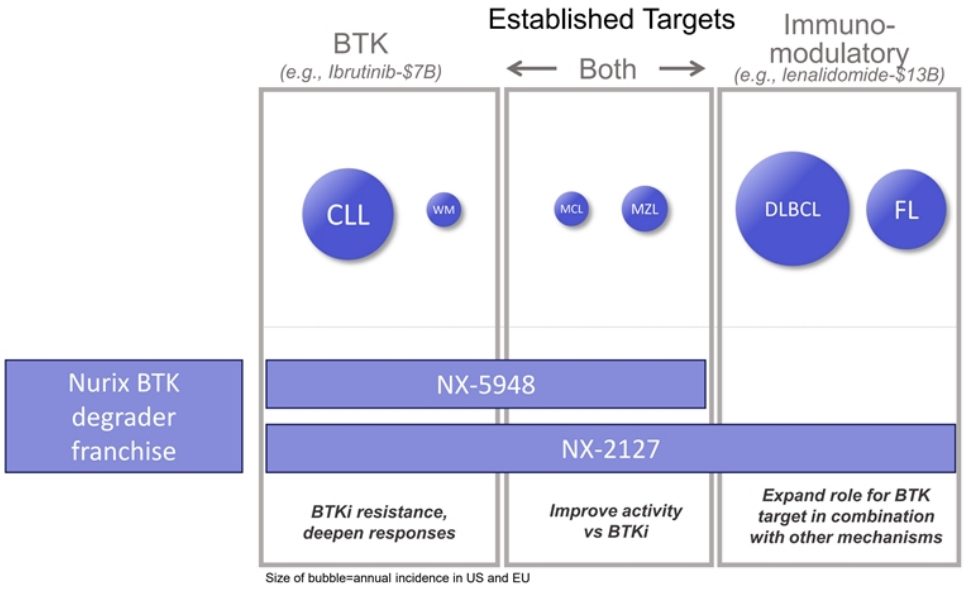
- Early evidence of target engagement
- Rapid and sustained BTK degradation in all patients
- No evidence of immunomodulatory associated adverse events (e.g. neutropenia)

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



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

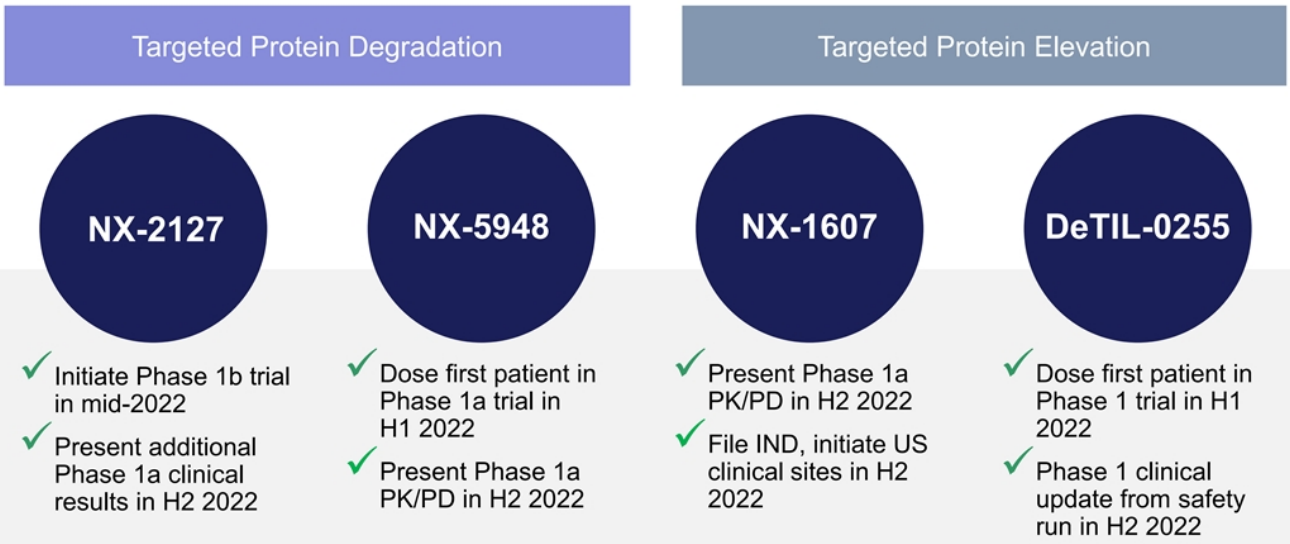
- Present Phase 1a PK/PD in H2 2022
- File IND, initiate US clinical sites in H2 2022

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



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