Leader in Targeted Protein Modulation

Nurix Therapeutics

Blazing a New Path in Medicine

R&D Day
New York, NY
May 26, 2022

Welcome and Introduction

Arthur T Sands, MD, PhD
President, CEO and Board Director
Nurix Therapeutics

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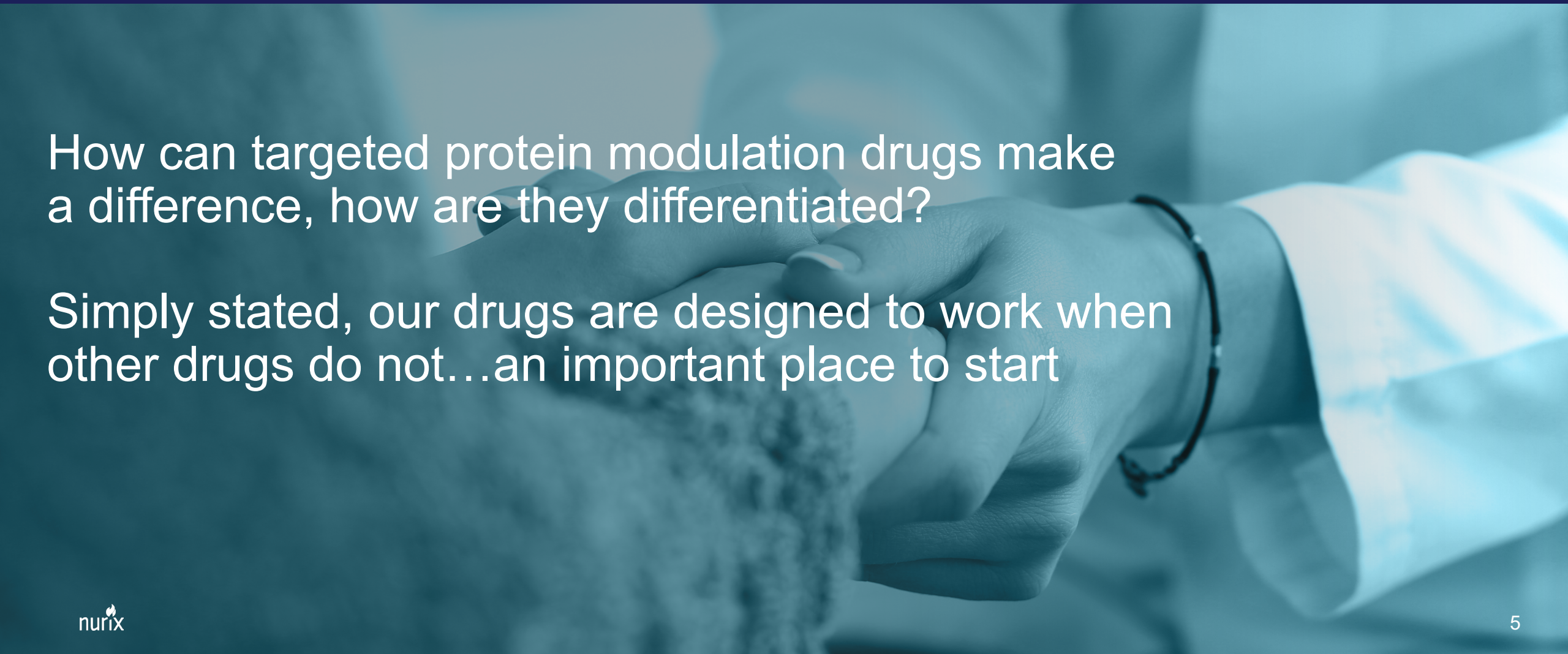
Cancer Connects Us All

602,350 Deaths From Cancer in 2020 in the United States

Nurix is committed to building a patient-focused, science-driven oncology company powered by our leadership position in Targeted Protein Modulation

Cancer Connects Us All

602,350 Deaths From Cancer in 2020 in the United States

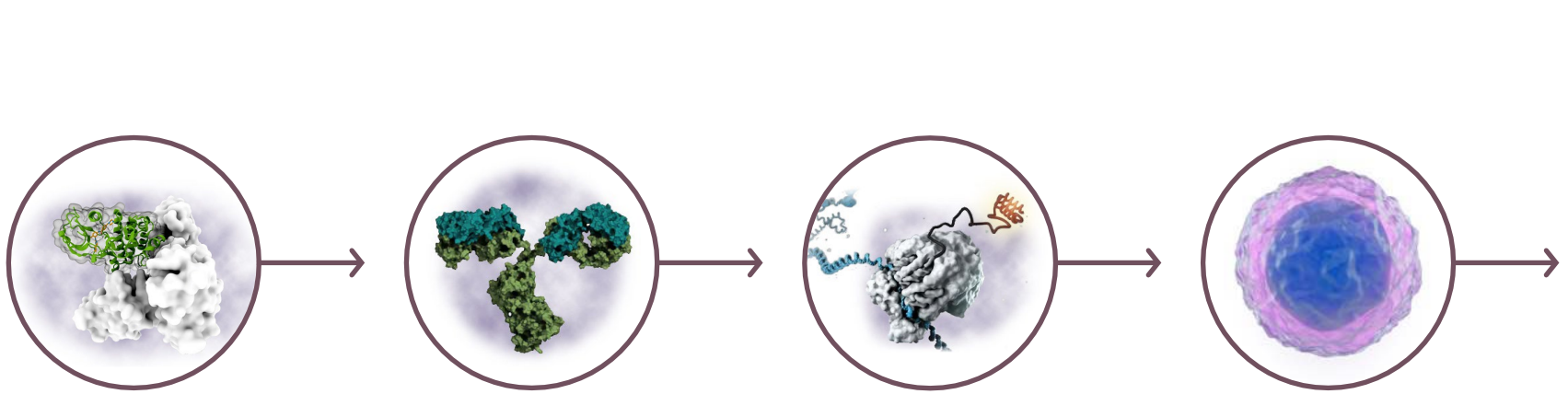


How can targeted protein modulation drugs make a difference, how are they differentiated?

Simply stated, our drugs are designed to work when other drugs do not…an important place to start

The War on Cancer Has a New Weapon

Nurix is the Pioneer and Leader in Targeted Protein Modulation



Small Molecule Inhibitors

Antibodies

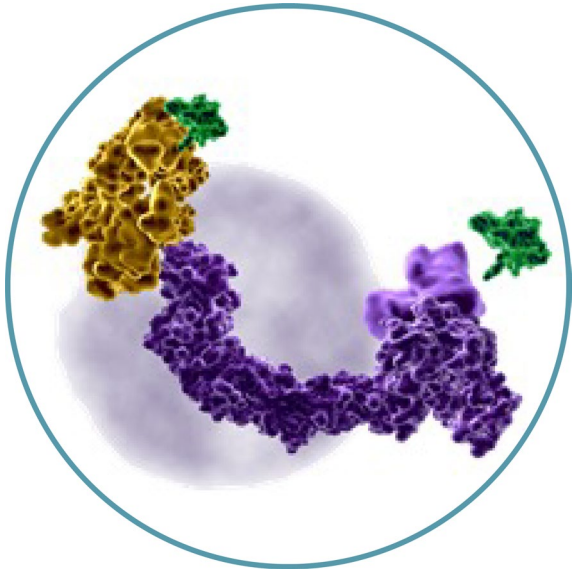
Therapeutic Proteins

Nucleic Acid-Based Therapies

Antisense, RNAi
Gene Therapy
CRISPR

Adoptive Cell Therapy

DeTIL



Targeted Protein Modulation (TPM) to *Increase* or *Decrease* Specific Protein Levels

Small Molecule E3 Ligase Modulators

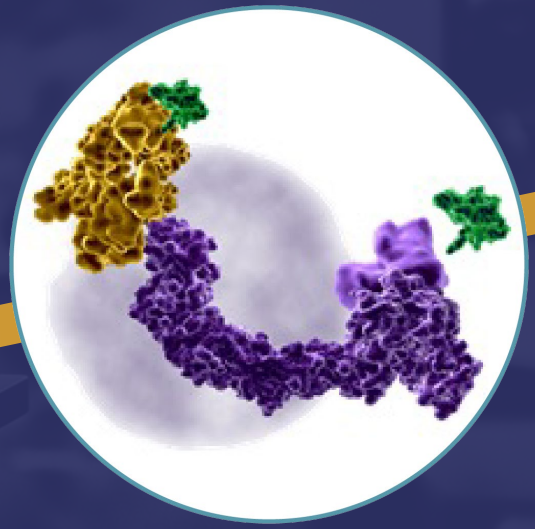
Nurix Drugs Engage Ligases for the Treatment of Cancer

Targeted Protein Modulation: TPM = TPD + TPE

Harness ligases
to decrease specific protein levels

Targeted Protein Degradation (TPD)

A Powerful Cellular System

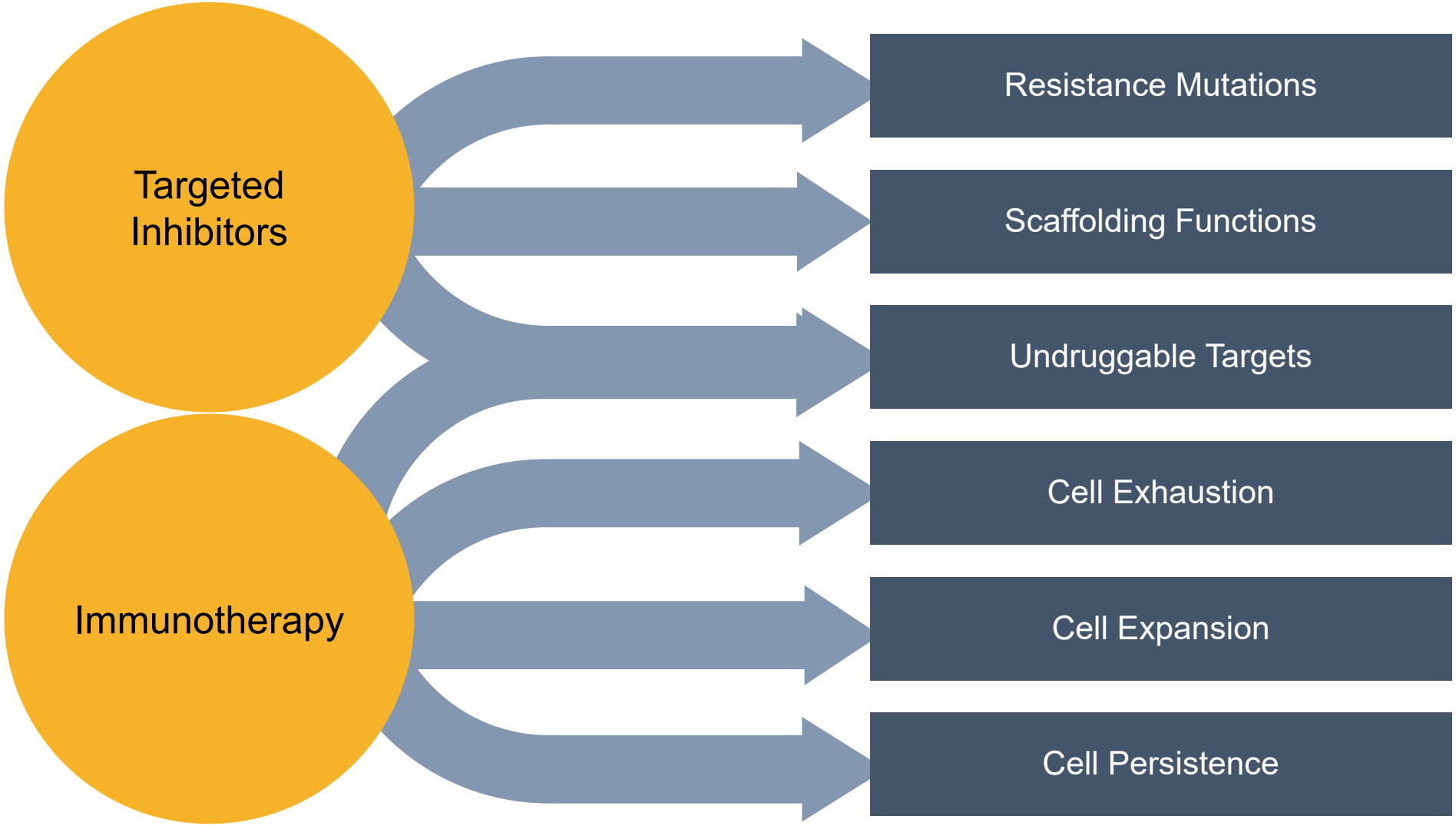


Ubiquitin is ligated to target proteins to tag them for degradation by the proteasome

Targeted Protein Elevation (TPE)

Inhibit ligases
to increase specific protein levels

Targeted Protein Modulation Addresses Key Limitations of Leading Cancer Therapy Modalities



The Evolution of Nurix Therapeutics

Breakthrough Science, Breakthrough Drugs

2009 – 2015
Groundbreaking Science

- Assembled initial scientific team
- Established biochemical proof-of-concept to drug a ligase

2015 – 2019
Building the Platform

- Innovated DNA encoded library collection and DELigase platform
- Built CBL and BTK programs
- Signed Celgene collaboration $150M upfront

2019 – 2022
Drive to the Clinic

- Signed Gilead collaboration: $45M upfront
- Signed Sanofi collaboration: $77M Upfront
- IPO, follow-on offering
- Initiated four Phase 1 programs
  - NX-2127 IND
  - NX-5948 CTA
  - NX-1607 IND
  - DeTIL-0255 IND

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	Pre-Clinical	Phase 1	Phase 2	Phase 3
TPD	**NX-2127** Degrader	BTK-IKZF *Oral*	B-Cell Malignancies				
	NX-5948 Degrader	BTK *Oral*	B-Cell Malignancies				
TPE	**NX-1607** Inhibitor	CBL-B *Oral*	Immuno-Oncology				
	DeTIL-0255 Cell Therapy	Adoptive Cell Therapy *Ex vivo CBL-B Inhibition*	Gynecologic Malignancies				

Today's Agenda

Part 1

Unmet Need in CLL

Anthony Mato, MD, MSCE
Director, CLL Program, Memorial Sloan Kettering Cancer Center

First Targeted Protein Degradation Drugs in Hematologic Malignancies: NX-2127 & NX-5948

NX-2127: BTK Degrader With Immunomodulatory Activity & Initial Phase 1a Clinical Findings

Robert J Brown, MD
EVP, Head of Clinical Development

NX-2127 & NX-5948: Multiple Market Opportunities

Stefani A Wolff
COO, EVP of Product Development

Q&A / Break

Today's Agenda

Part 2

First Targeted Protein Elevation Drugs in Immuno-Oncology: NX-1607 & NX-0255

CBL-B: Master of the Immune Response	Cristiana Guiducci, PhD *SVP, Immunology and Oncology Research*
NX-1607: Biomarkers that Light the Way	Robert J Brown, MD *EVP, Head of Clinical Development*
DeTIL-0255: Drug Enhanced Cell Therapy in the Clinic	Michael T Lotze, MD *Chief Cellular Therapy Officer*

Today's Agenda

Part 3

The Genesis: Powerful DELigase R&D Platform	Gwenn M Hansen, PhD *Chief Scientific Officer*	
Financial Snapshot	Hans van Houte *Chief Financial Officer*	
Conclusions **Q&A / Adjourn**	Arthur T Sands, MD, PhD *President, CEO and Board Director*	

The Team…

Conquering Cancer

Arthur T Sands, MD, PhD
President, Chief Executive Officer, and Board Director

Hans van Houte
Chief Financial Officer

Gwenn M Hansen, PhD
Chief Scientific Officer

Stefani A Wolff
Chief Operating Officer and Executive Vice President, Product Development

Cristiana Guiducci, PhD
Senior Vice President, Immunology and Oncology Research

Michael T Lotze, MD
Chief Cellular Therapy Officer

Christine Ring, PhD, JD
General Counsel and Secretary

Robert J Brown, MD
Executive Vice President, Head of Clinical Development

Jason Kantor, PhD
Executive Vice President, Finance and Business Strategy

Key Messages for Today

1

Resistance has met its match
with targeted protein modulation

2

We have positive and exciting findings
from the first trial of a TPD in a hematologic malignancy

3

We set the stage for the **next breakthrough in immune oncology**
with **more to come** from our powerful platform

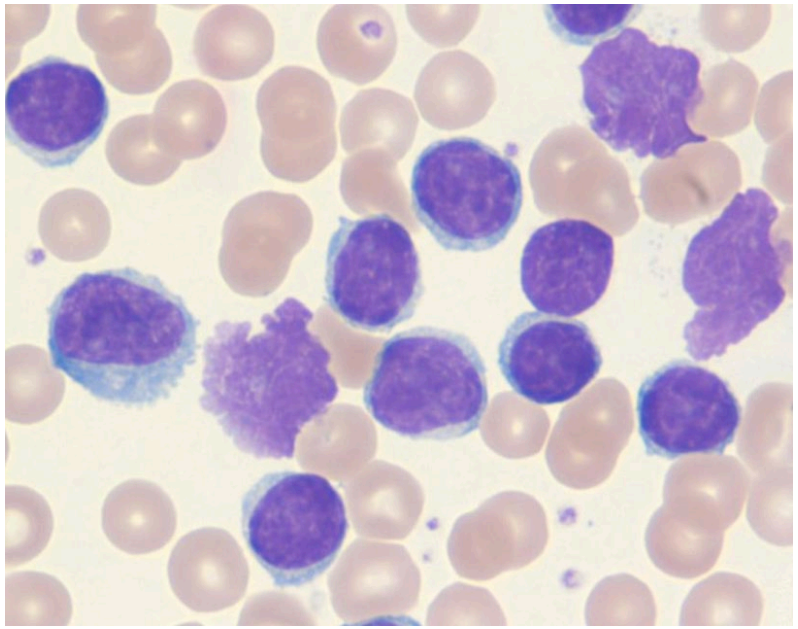
Memorial Sloan Kettering Cancer Center

Bench-to-Bedside and Back: Addressing the unmet needs in Chronic Lymphocytic Leukemia in 2022

Anthony R. Mato, MD, MSCE
Associate Attending
Director, Chronic Lymphocytic Leukemia Program
Memorial Sloan Kettering Cancer Center
New York, New York

Chronic Lymphocytic Leukemia

- CD5+ mature B-cell neoplasm
- Peripheral blood, lymph node and bone marrow compartments
- Median age at diagnosis: 72 years
- Most common leukemia in Western countries
- Heterogenous clinical presentation

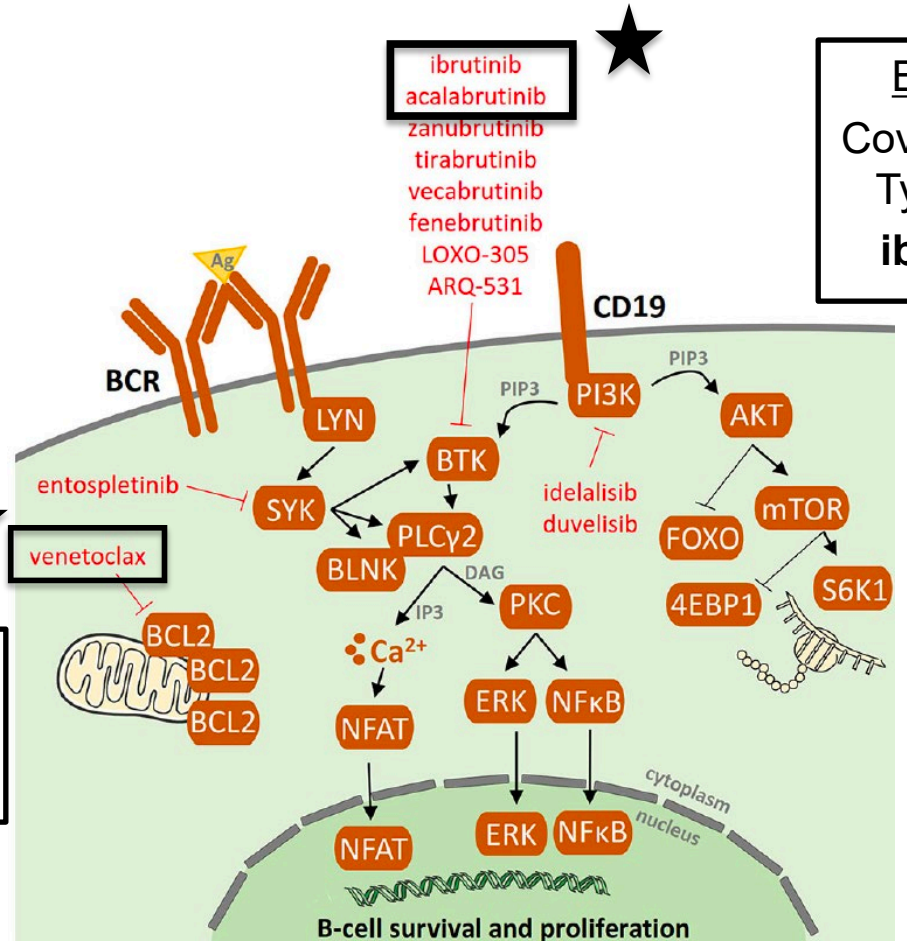


Remarkable Basic, Translational and Clinical Scientific Advances

An era of targeted therapy for treatment of CLL

Era of Targeted Therapies: Two Key Pathways

Targeted therapies are now standard of care options
in the front-line and relapsed/refractory settings



B-cell receptor signaling:
Covalent, irreversible Bruton's Tyrosine Kinase Inhibitors:
ibrutinib & acalabrutinib

Apoptotic Pathway:
Bcl2-inhibitor
venetoclax

Figure from Sedlarikova et al. Frontiers in Oncology 2020

Key Questions and Issues in Treating Relapsed CLL Patients

What are the unmet needs in the R/R setting?

Limitations of covalent BTK inhibitors and venetoclax

Limitations of noncovalent BTK inhibitors

No standard of care for double-refractory disease

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Covalent BTK inhibitors: Resistance and Intolerance Continue to be Major Reasons for Discontinuation

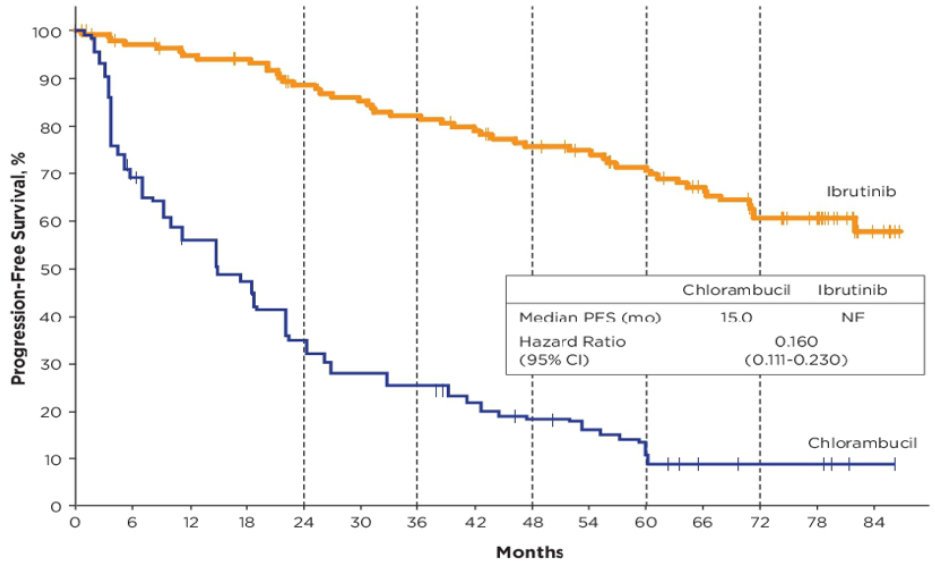
Even with Second Generation Agents!

Clinical Trials and Real-World Data

7 Years of Follow-Up in the RESONATE-2 Study

Overall discontinuation rate at 7 years = 53%

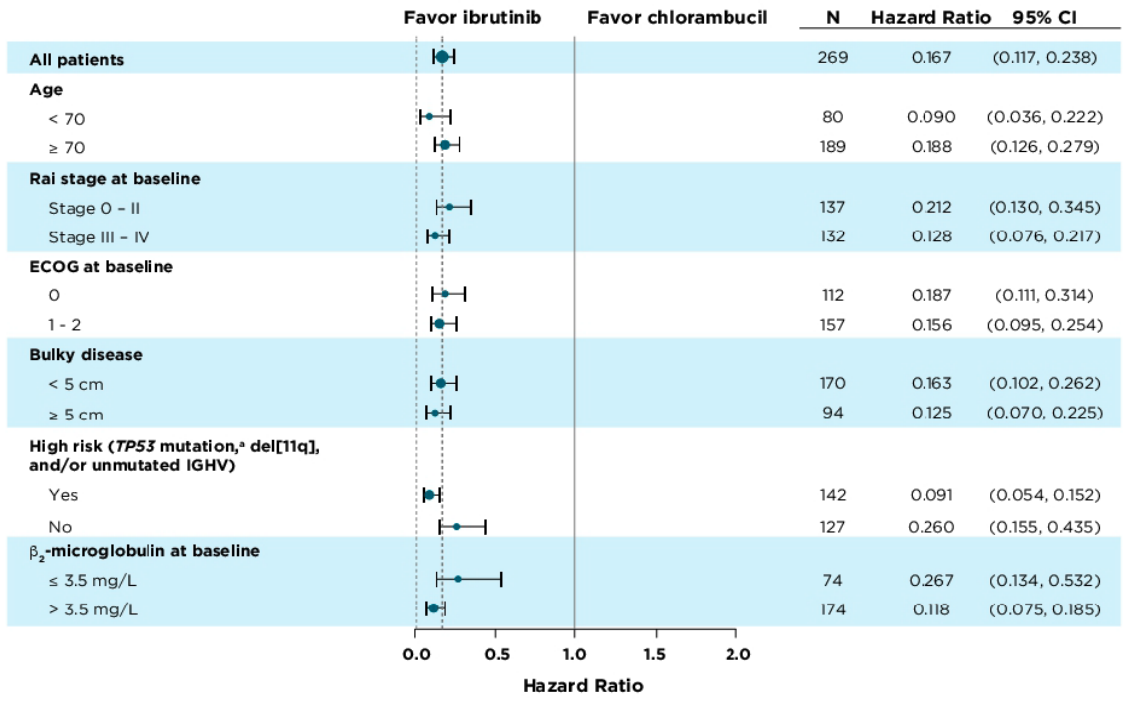
PFS: Ibrutinib vs Chlorambucil



Patients at Risk and PFS

Ibrutinib:	136	129	124	121	112	108	104	99	92	88	81	74	64	56	12
PFS, %:					89		82		76		71		61		
Chlorambucil:	133	88	69	57	41	33	30	25	19	16	12	6	5	5	1
PFS, %:					35		25		18		12		9		

PFS in Patient Subgroups of Interest



Efficacy

- Ibrutinib-treated patients had an 84% reduction in risk of progression or death
- Ibrutinib led to a 97% reduction in risk of PD or death in patients with del(11q) and 80% for those without del(11q) vs chlorambucil
- Ibrutinib led to an 89% and 80% reduction in risk of PD or death in patients with unmutated and mutated *IGHV*, respectively, vs chlorambucil

Barr PB, et al. ASCO 2020. Abstract 7523.

Ibrutinib Discontinuation For Intolerance in the "Real World Setting"

ARTICLES

Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis

41% of patients discontinued ibrutinib at a median follow-up of 17 months

Toxicity accounted for the **majority** of discontinuations (over half) in both F/L and R/R CLL patients

Most common toxicities in R/R population: **atrial fibrillation 12.3%, infection 10.7%, pneumonitis 9.9%, bleeding 9%, and diarrhea 6.6%**

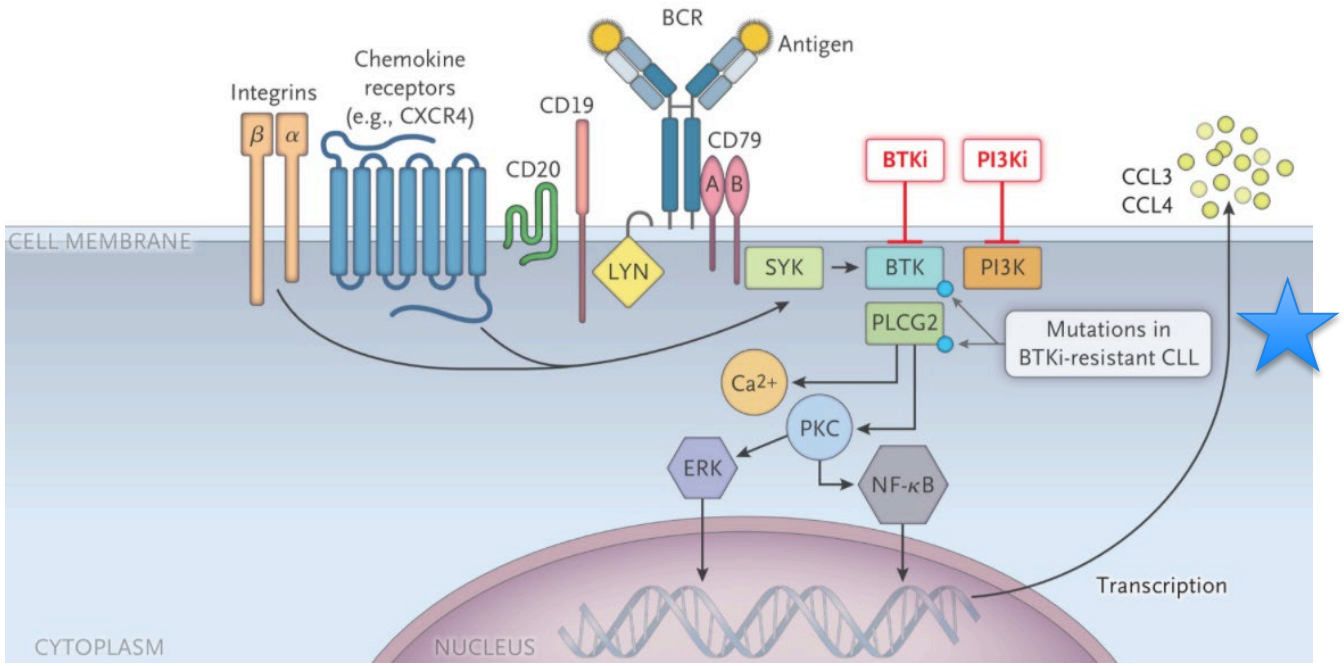
Reason for ibrutinib discontinuation	Ibrutinib in front-line (n=19)	Ibrutinib in relapse (n=231)
Toxicity	63.1% (n=12)	50.2% (n=116)
CLL progression	15.8% (n=3)	20.9% (n=49)
Other/unrelated death	5.3% (n=1)	12.1% (n=28)
Physician's or patient's preference	10.5% (n=2)	6.7% (n=15)
RT DLBCL	5.3% (n=1)	4.6% (n=10)
Stem cell transplantation/CAR T-cell	0	3.3% (n=8)
Financial concerns	0	0.8% (n=2)
Secondary malignancy	0	0.8% (n=2)
RT Hodgkin lymphoma	0	0.4% (n=1)

CLL: chronic lymphocytic leukemia; RT DLBCL: Richter transformation to diffuse large B-cell lymphoma; CAR T-cell: chimeric antigen receptor T-cell); RT: Richter transformation.

This study identified covalent BTK inhibitor **intolerance** as a major emerging issue in the field of CLL

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; F/L, first line; R/R, relapsed/refractory.
Mato et al *Haematologica* 2018;103:874-879.

Acquired Resistance to Covalent BTKi

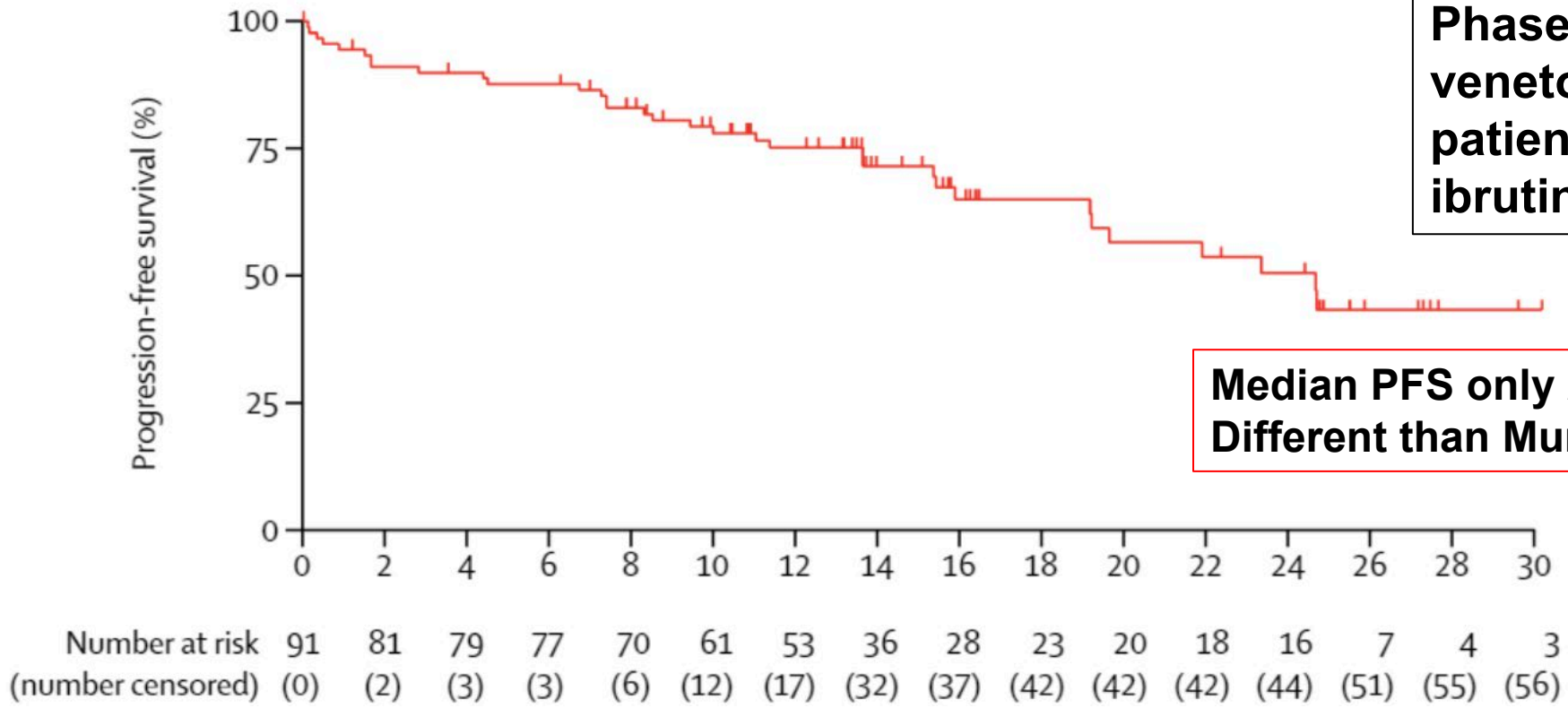


- Majority of patients have identified mutations in *BTK*C481 at the time of disease progression on ibrutinib; ~53-87% of patients
- Mutations also identified in PLCG2, immediately downstream of BTK
- *BTK*C481 mutations are also the main mechanism of resistance for acalabrutinib; 69% of patients

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

Treatment of CLL After Covalent BTKi

- **Venetoclax:** oral BCL2-inhibitor
- Front-line setting and relapsed setting including after cBTKi
- Approved as **fixed-duration** therapy (24 months in R/R setting)



Phase II study of venetoclax in CLL patients with prior ibrutinib

Median PFS only 24.7 months
Different than Murano PFS

Figure from Jones et al *Lancet Oncology* 2018;
Seymour et al *NEJM* 2020; Fischer et al *NEJM* 2020

Patients on Landmark R/R Studies Were Not Treated on Chemotherapy-Free Pathways or With Prior Novel Agents

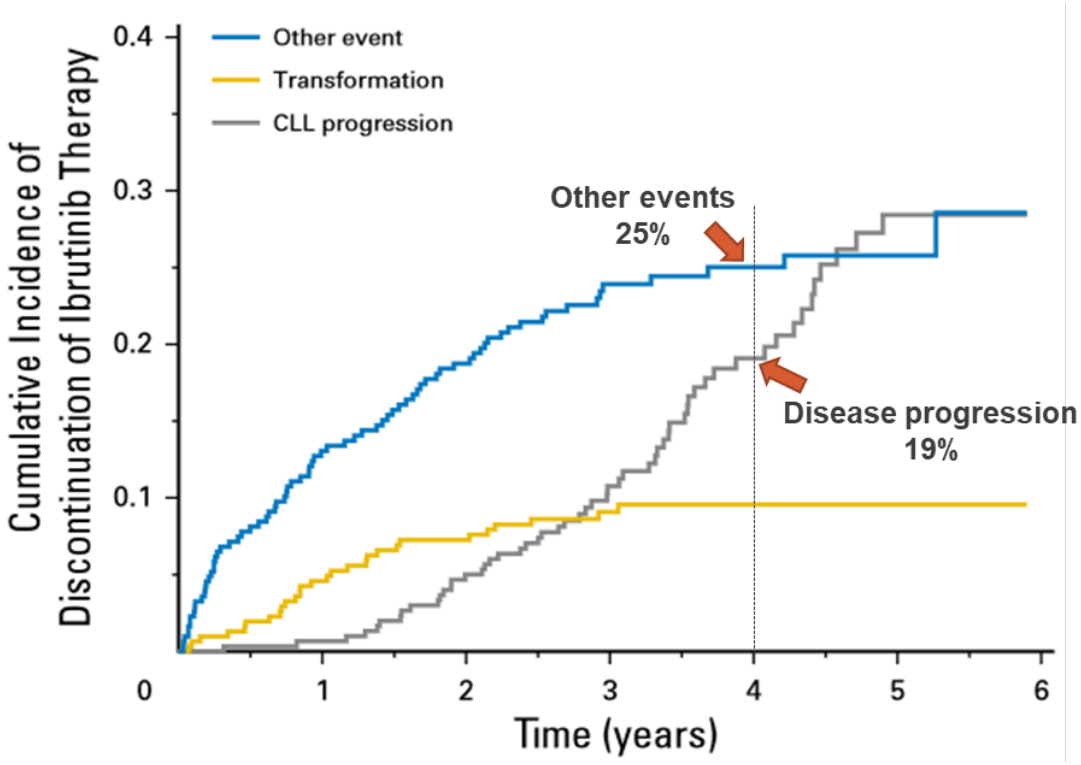
Agent	Study Name (Control Arm)	Number treated	Median (range) prior therapies	Percent on modern chemotherapy free pathways	Percent treated with ≥ 1 BTK, Ven or PI3K-i
Ibrutinib	RESONATE (ofatumumab)	195	3 (1 - 12)	0%	0%
Acalabrutinib	ASCEND (investigator's choice: BR or idela-ritux)	155	1 (1 - 8)	0%	0%
Venetoclax monotherapy	Del 17p study (single arm)	107	2 (0 - 10)	Unknown <3.7%	3.7% (n=4)
Venetoclax-rituximab	MURANO (BR)	194	1 (1 - >3)	Unknown <2.6%	2.6% (n=5)
Idelalisib-rituximab	STUDY 116 (placebo-ritux)	110	3 (1 – 12)	0%	0%
Duvelisib	DUO (ofatumumab)	160	2 (1 – 10)	0%	0%

Only 9 of 921 patients (~1%) from 6 landmark studies were previously treated with at least one BTKi, PI3Ki or venetoclax and likely none on a truly modern chemotherapy-free pathway

Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

- Options following covalent BTK inhibitor treatment are limited:
  - Covalent BTK inhibitor retreatment: Only effective in the context of covalent BTK intolerance, not progression
  - Venetoclax: Efficacious but complicated administration
  - PI3K Inhibitors: Limited benefit in this population and significant toxicity burden
  - Chemoimmunotherapy: Limited benefit in this population and most current patients have already received these regimens

Ibrutinib discontinuation from 4 prospective studies[1]



Ibrutinib discontinuation rates at 5 years
- Front line = 41%[1]
- Relapsed/refractory = 54%[2]

[1]Woyach et al. *J Clin Oncol*. 2017;35:1437-1443. [2]Burger. *Leukemia* 2020;34:787-7898.

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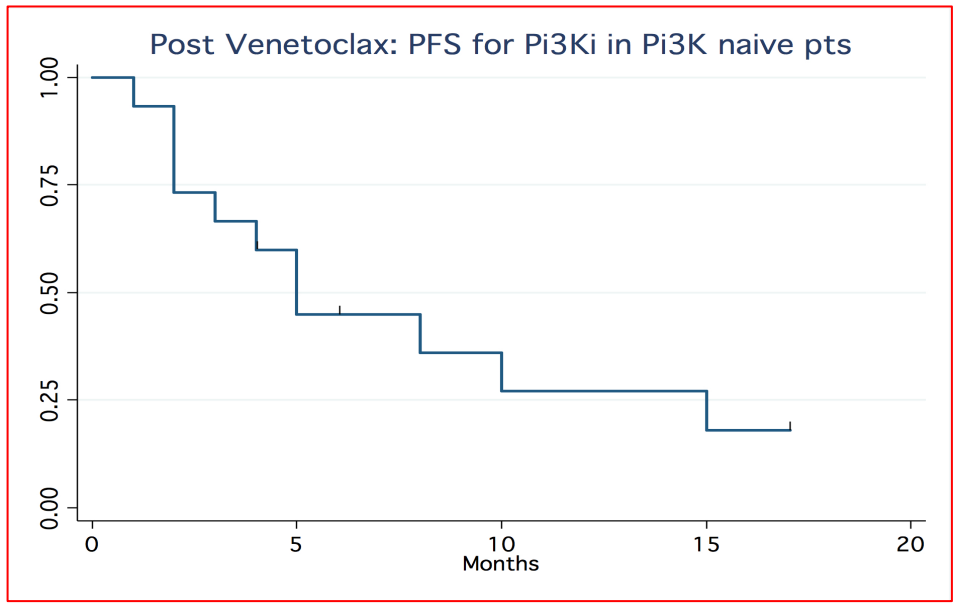
Double Exposed CLL Patients

The Cutting Edge of Unmet Needs in the Clinic Today

Management of the Double Refractory CLL Patient – Poor Survival Outcomes!

After BTKi → Venetoclax: PI3Ki did not result in durable remissions and therefore is not an acceptable SOC in the 3rd line setting in modern era

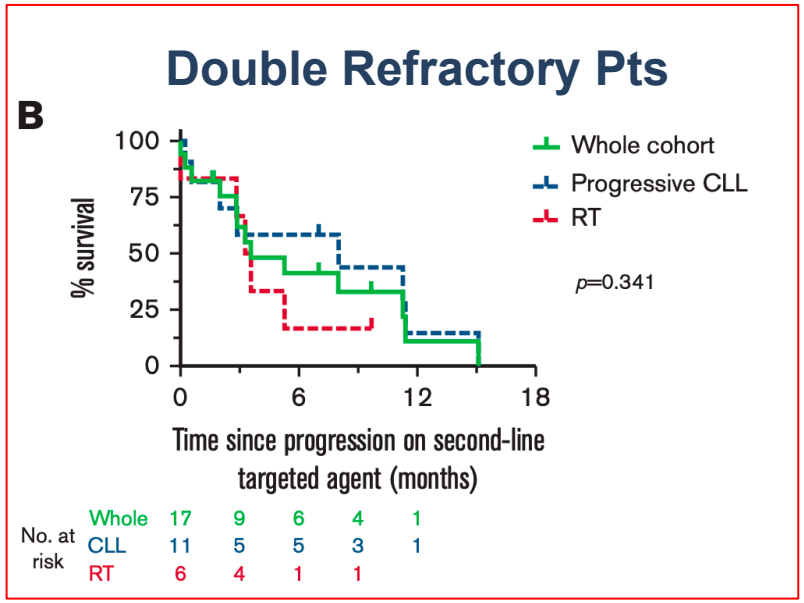


Median PFS = 4 months!

Outcomes of patients with CLL sequentially resistant to both BCL2 and BTK inhibition

Thomas E. Lew,[1,2,*] Victor S. Lin,[1-3,*] Edward R. Cliff,[1] Piers Blombery,[1,3,4] Ella R. Thompson,[4] Sasanka M. Handunnetti,[1] David A. Westerman,[1,3,4] Bryone J. Kuss,[5] Constantine S. Tam,[1,3,6] David C. S. Huang,[2,3] John F. Seymour,[1,3] Andrew W. Roberts,[1-3] and Mary Ann Anderson[1,2]

[1]Department of Clinical Haematology, The Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Blood Cells and Blood Cancer Division, Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia; [3]Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, VIC, Australia; [4]Department of Pathology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [5]College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia; and [6]Department of Haematology, St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia



Median OS = 3.6 months

Mato et al, CCR 2020, Lew, et al Blood Advances 2022

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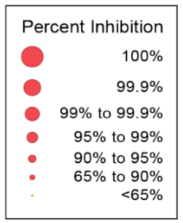
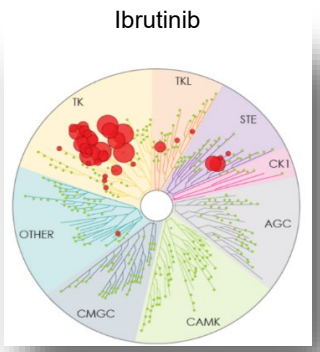
Noncovalent BTK Inhibitors

Several BTKi Options to Consider with Differences in BTKi Specificity, MOA, and Potential for Off-target Effects

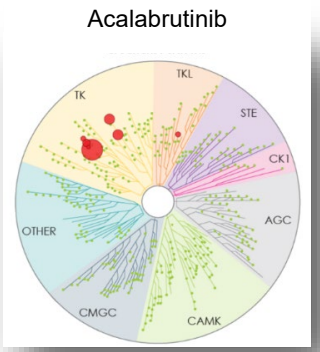
Irreversible



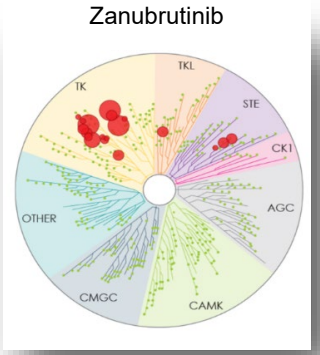
Ibrutinib



Acalabrutinib

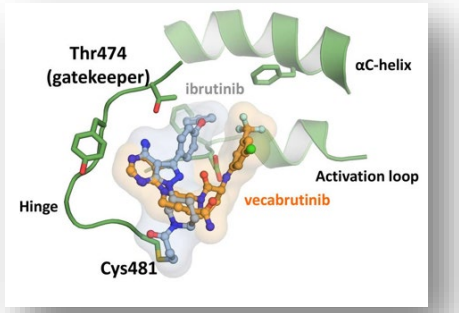


Zanubrutinib

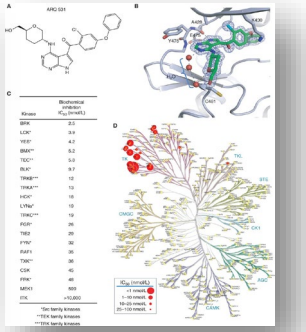


Reversible

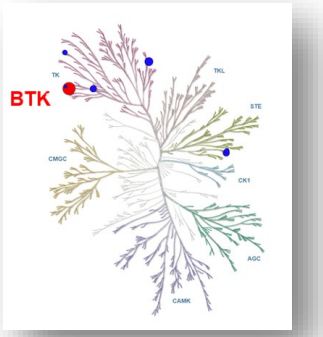
Vecabrutinib



Nemtabrutinib/ARQ-531



Pirtobrutinib/LOXO-305



Kaptein et al. Blood 2018;132(suppl 1):1871.

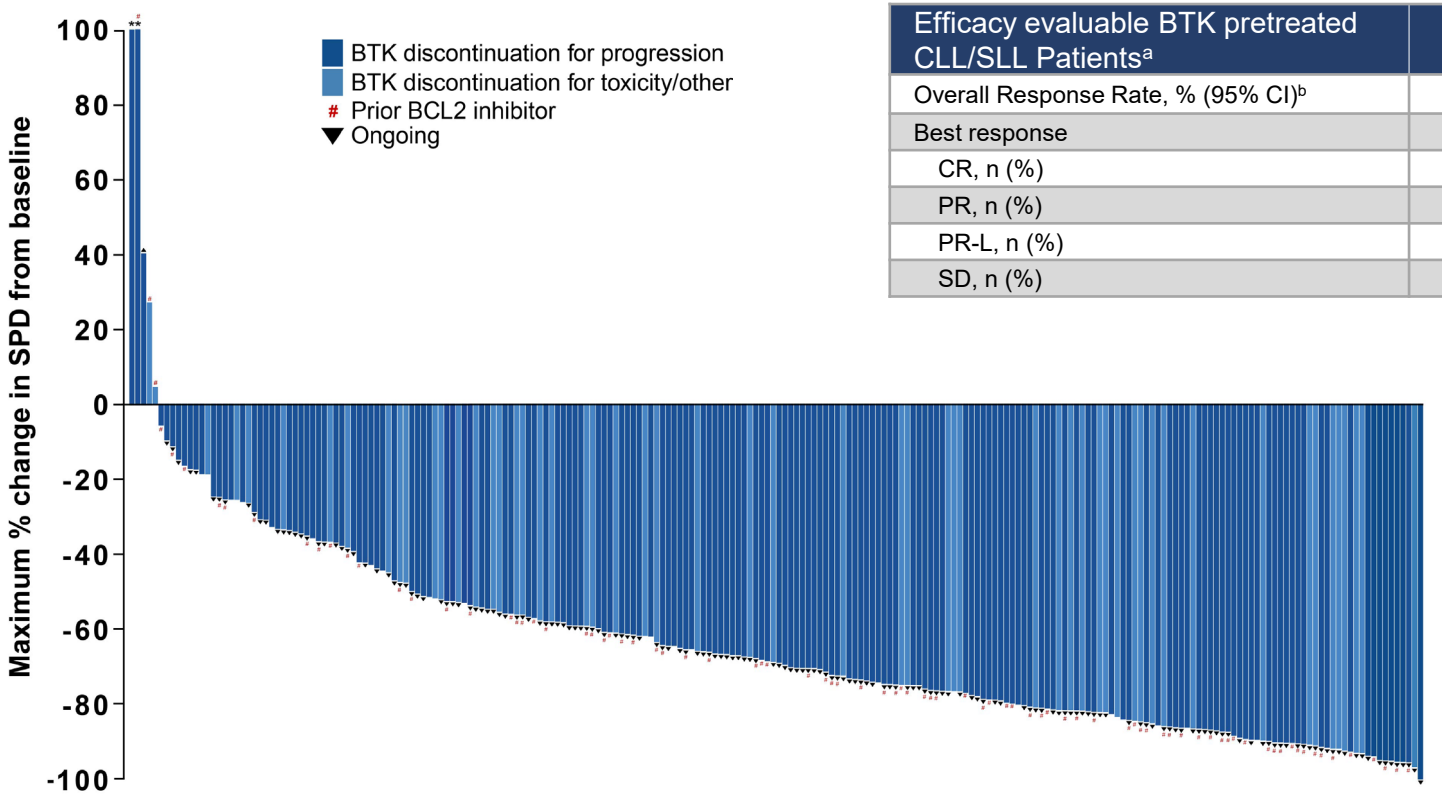
BTK Pretreated CLL/SLL Patient Characteristics

Characteristics	N = 261
Median age, y (range)	69 (36-88)
Female, n (%)	84 (32)
Male, n (%)	177 (68)
ECOG PS[a], n (%)	
0	138 (53)
1	104 (40)
2	19 (7)
Median number of prior lines of systemic therapy (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	261 (100)
Anti-CD20 antibody	230 (88)
Chemotherapy	207 (79)
BCL2 inhibitor	108 (41)
PI3K inhibitor	51 (20)
CAR-T	15 (6)
Stem cell transplant	6 (2)
Allogeneic stem cell transplant	5 (2)
Autologous stem cell transplant	1 (<1)
Reason discontinued prior BTKi, n (%)	
Progressive disease	196 (75)
Toxicity/Other	65 (25)

Baseline Molecular Characteristics[a]	
Mutation status, n (%)	
BTK C481-mutant	89 (43)
BTK C481-wildtype	118 (57)
PLCG2-mutant	33 (16)
High Risk Molecular Features, n (%)	
17p deletion	51 (28)
TP53 mutation	64 (37)
17p deletion or TP53 mutation	77 (36)
Both 17p deletion and TP53	38 (27)
mutation	168 (84)
IGHV unmutated	45 (25)
11q deletion	

Data cutoff date July 16, 2021.
BTK, Bruton tyrosine kinase; ECOG, Eastern Cooperative Oncology group performance status;
Total % may be different than the sum of the individual components due to rounding. [a]Molecular characteristics were determined centrally, in those patients with sufficient sample to pass assay quality control. 207 patients were tested for BTK and PLCG2, 180 patients for 17p deletion, 175 patients for TP53, 143 patients for 17p deletion + TP53, 200 patients for IGHV and 180 patients for 11q deletion.
Mato et al. Abstract 391. ASH 2021. https://ash.confex.com/ash/2021/webprogram/Paper147599.html

Pirtobrutinib Efficacy in BTK Pretreated CLL/SLL Patients



Efficacy evaluable BTK pretreated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	68 (62-74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Data cutoff date July 16, 2021.
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; PR, partial response; SD, stable disease; SLL, small lymphocytic leukemia.
*Patients with >100% increase in SPD. Data for 30 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total % may be different than the sum of the individual components due to rounding.
Mato et al. Abstract 391. ASH 2021. https://ash.confex.com/ash/2021/webprogram/Paper147599.html

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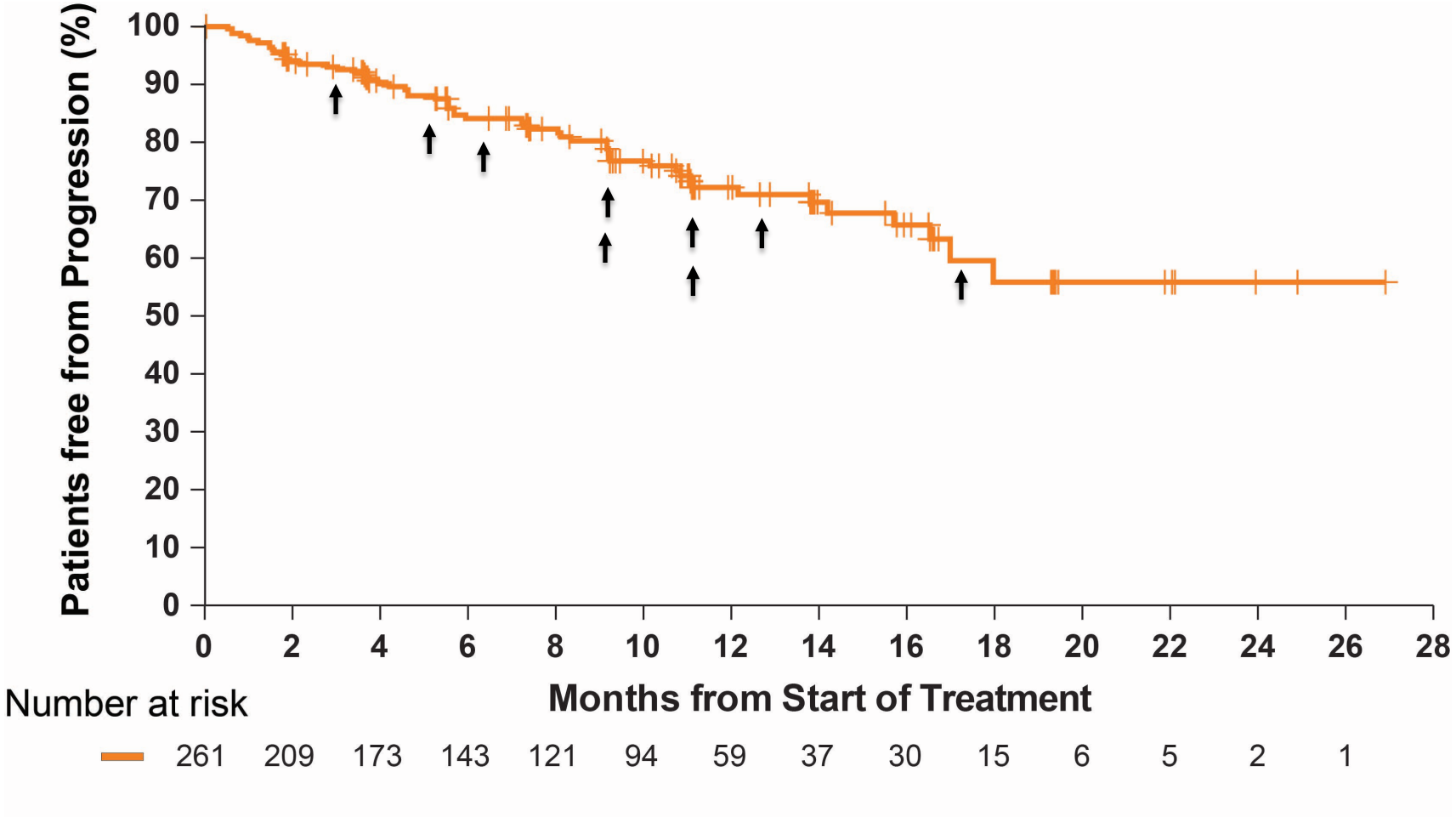
From the Clinic to the Lab

Mechanisms of Resistance to ncBTKi

Progression on Pirtobrutinib: MSK Cohort



Mato et al. Abstract 391. ASH 2021. https://ash.confex.com/ash/2021/webprogram/Paper147599.html

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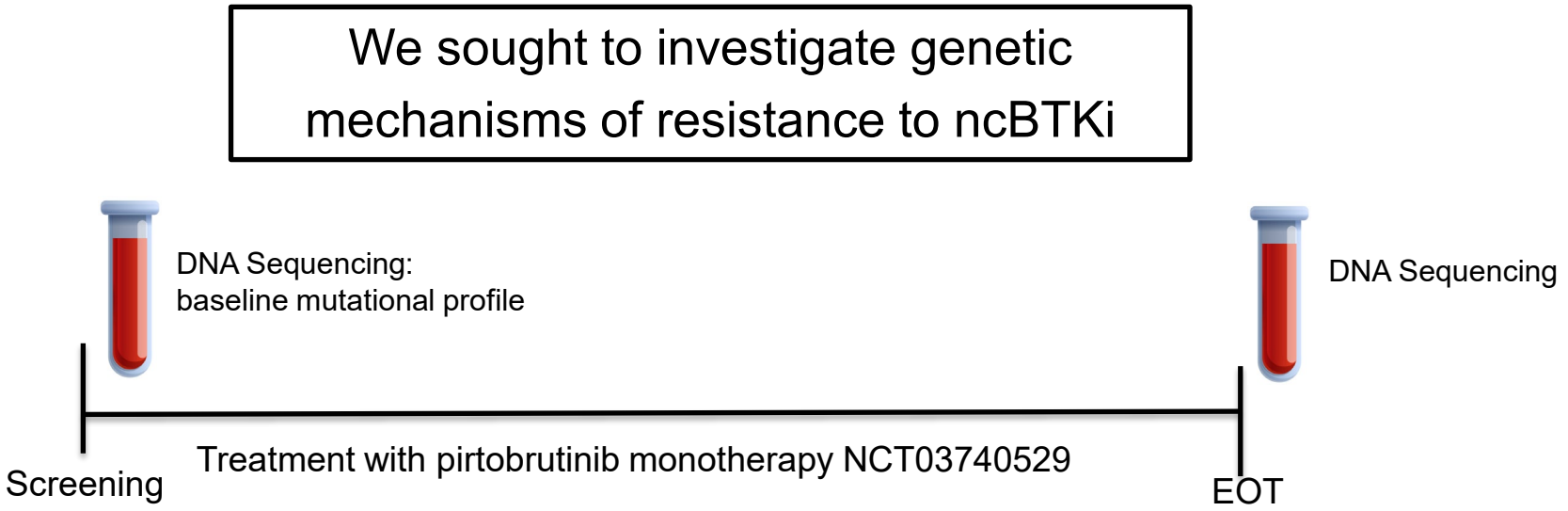
Mechanisms of Resistance to Noncovalent BTKi

ORIGINAL ARTICLE FREE PREVIEW

Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors

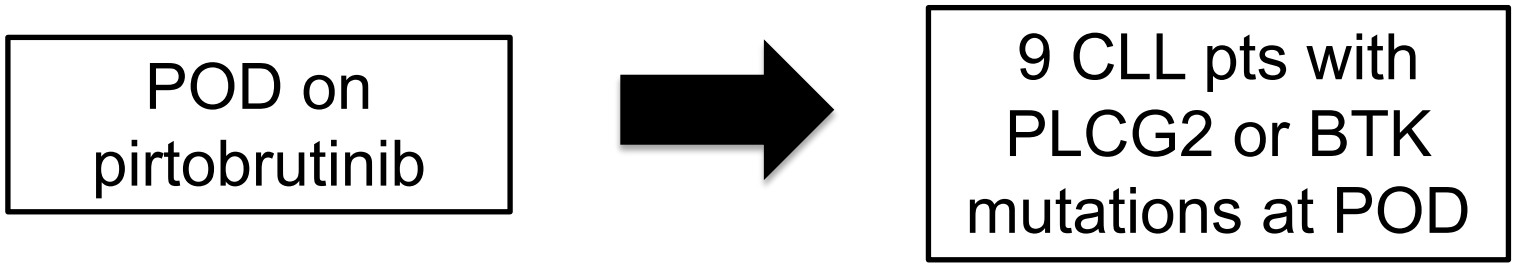
Eric Wang, Ph.D., Xiaoli Mi, M.D., Meghan C. Thompson, M.D., Skye Montoya, B.Sc., Ryan Q. Notti, M.D., Ph.D., Jumana Afaghani, B.Sc., Benjamin H. Durham, M.D., Alex Penson, Ph.D., Matthew T. Witkowski, Ph.D., Sydney X. Lu, M.D., Ph.D., Jessie Bourcier, M.D., Simon J. Hogg, Ph.D., Caroline Erickson, B.Sc., Dan Cui, B.Sc., Hana Cho, B.Sc., Michael Singer, B.Sc., Tulasigeri M. Totiger, Ph.D., Sana Chaudhry, B.Sc., Mark Geyer, M.D., Alvaro Alencar, M.D., Adam J. Linley, Ph.D., M. Lia Palomba, M.D., Catherine C. Coombs, M.D., Jae H. Park, M.D., Andrew Zelenetz, M.D., Ph.D., Lindsey Roeker, M.D., Mary Rosendahl, Ph.D., Donald E. Tsai, M.D., Ph.D., Kevin Ebata, Ph.D., Barbara Brandhuber, Ph.D., David M. Hyman, M.D., Iannis Aifantis, Ph.D., Anthony Mato, M.D., M.S.C.E., Justin Taylor, M.D., and Omar Abdel-Wahab, M.D.

Investigating Mechanisms of Resistance



- Collected patient samples at screening and at the time of disease progression for CLL/SLL patients treated with pirtobrutinib.
  - Peripheral blood and bone marrow and lymph node samples if clinically indicated.
- Performed **DNA sequencing** with **MSK IMPACT Heme** at baseline and at the time of disease progression for CLL/SLL patients treated with pirtobrutinib monotherapy.

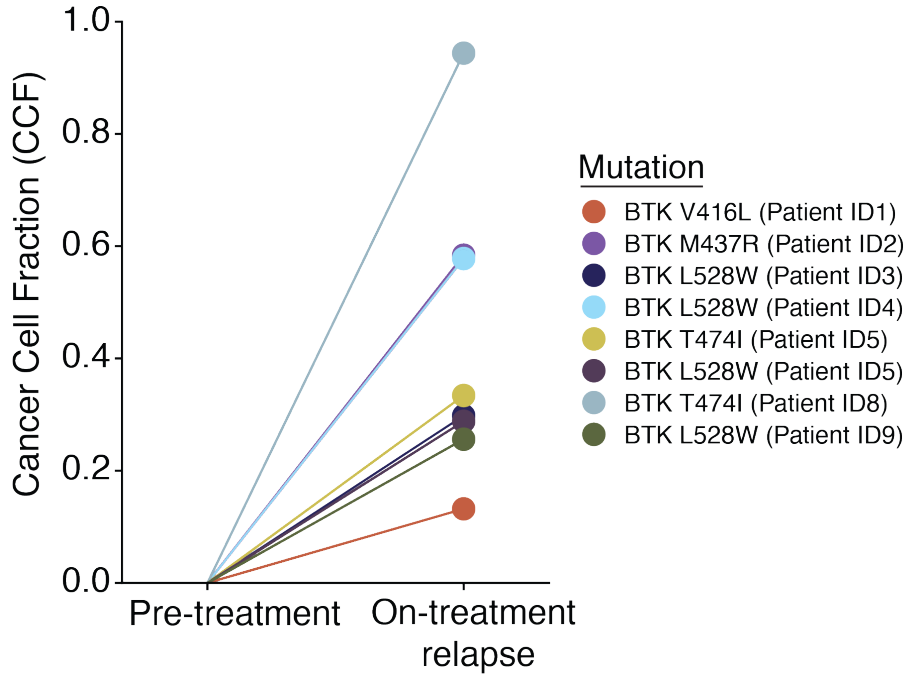
CLL Patients with POD on Pirtobrutinib

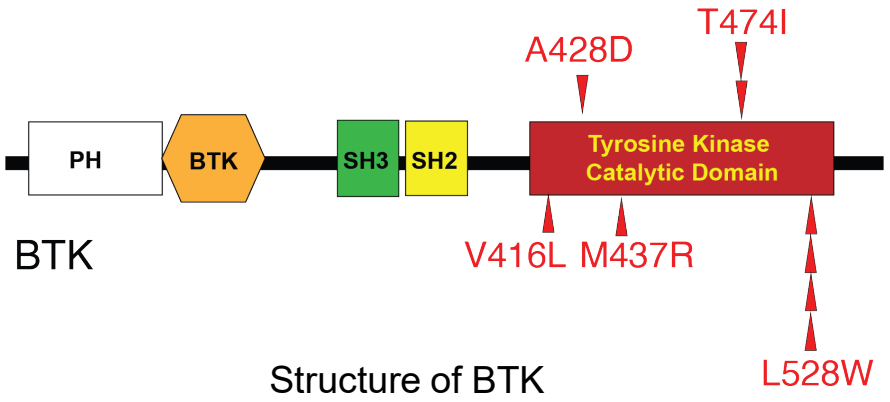


- 100% with prior covalent BTKi (100% ibrutinib)
- Prior lines of therapy: range 2-10
- Baseline BTK C481 mutation: 44.4%
- Baseline PLCG2 mutation 33.3%
- Treated with pirtobrutinib for 3-17 months
- Overall response rate to pirtobrutinib 44.4%

Wang E*, Mi X*, Thompson MC*… Mato, AR*, Taylor J*, Abdel-Wahab O*, NEJM 2022

Acquired *BTK* Mutations on Pirtobrutinib





Structure of BTK

We identified novel acquired mutations in BTK at the time of disease progression including:

- *BTK* L528W
- *BTK* V416L
- *BTK* M437R
- *BTK* T474I
- *BTK* A428D

These mutations cluster around the tyrosine kinase catalytic domain of BTK

Additionally, several patients with progressive disease had pre-existing PLCG2 mutations

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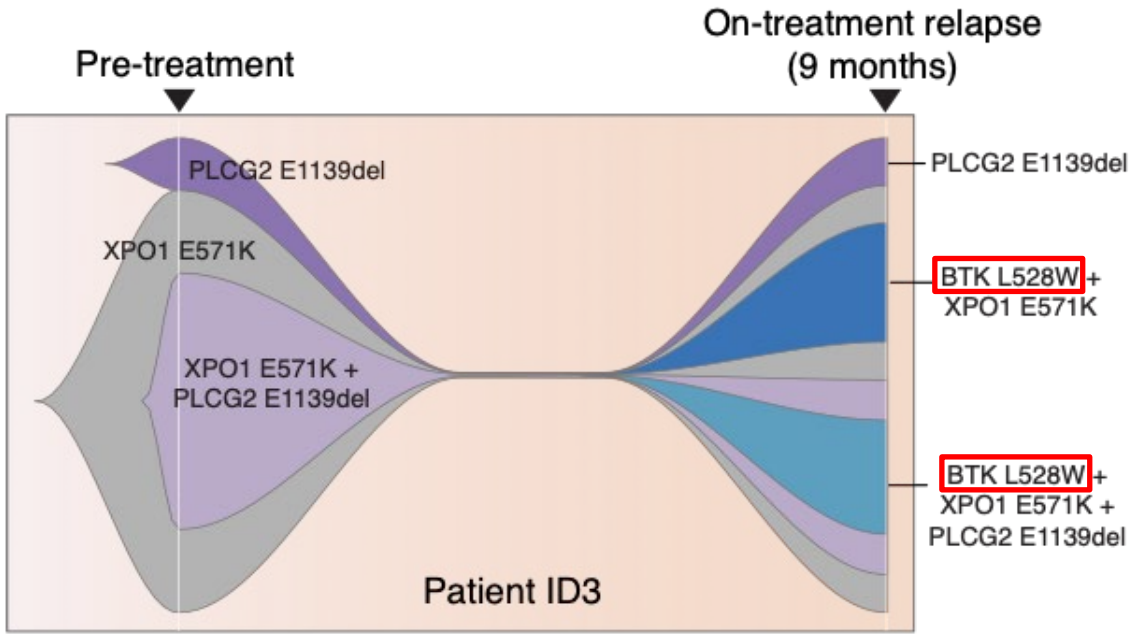
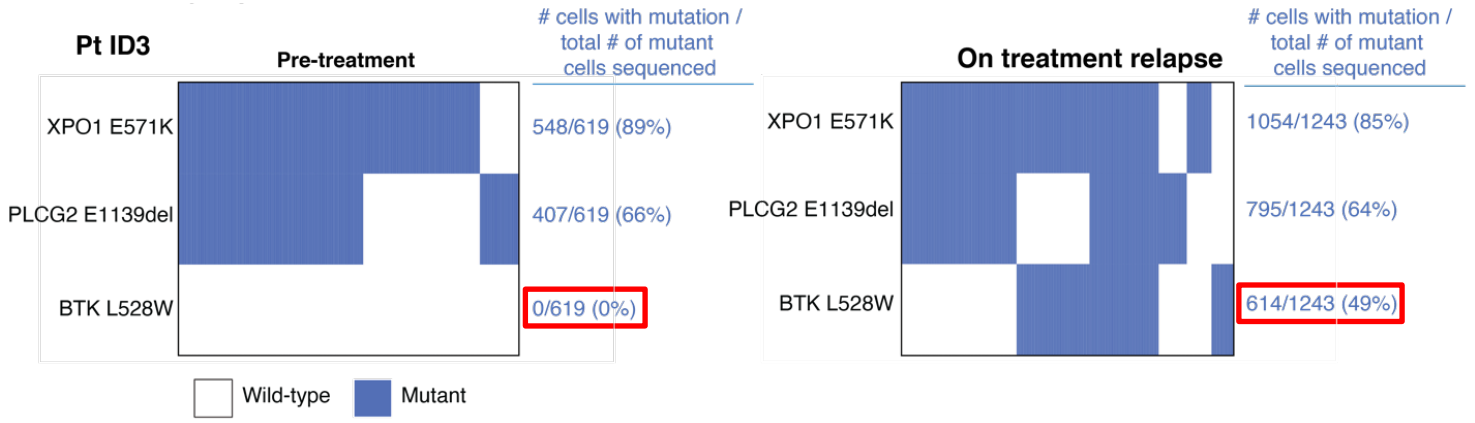
Acquired BTK L528W in Multiple Subclones at the Time of Relapse





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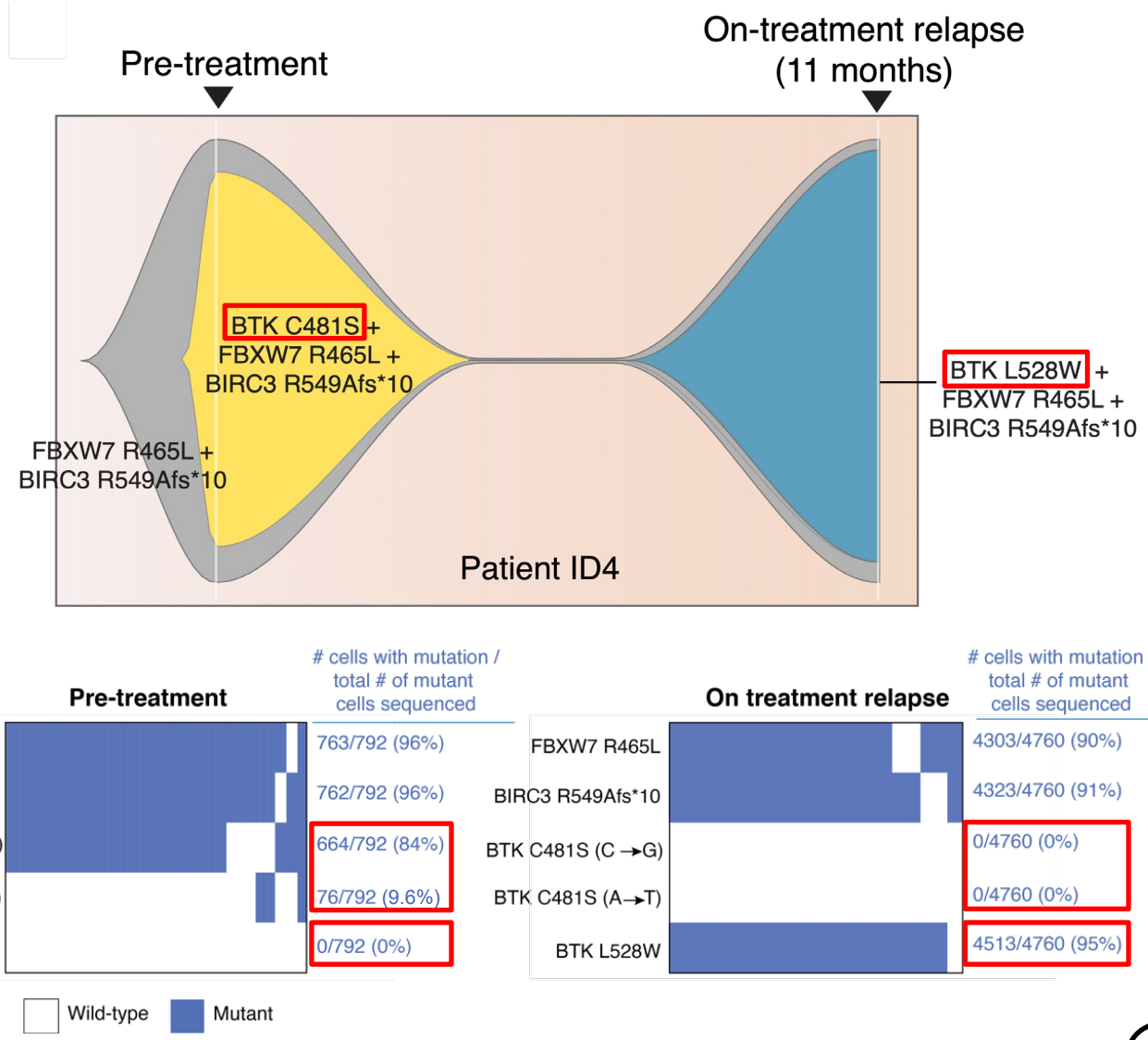
Suppressed BTK C481S but Acquired L528W at the Time of Relapse



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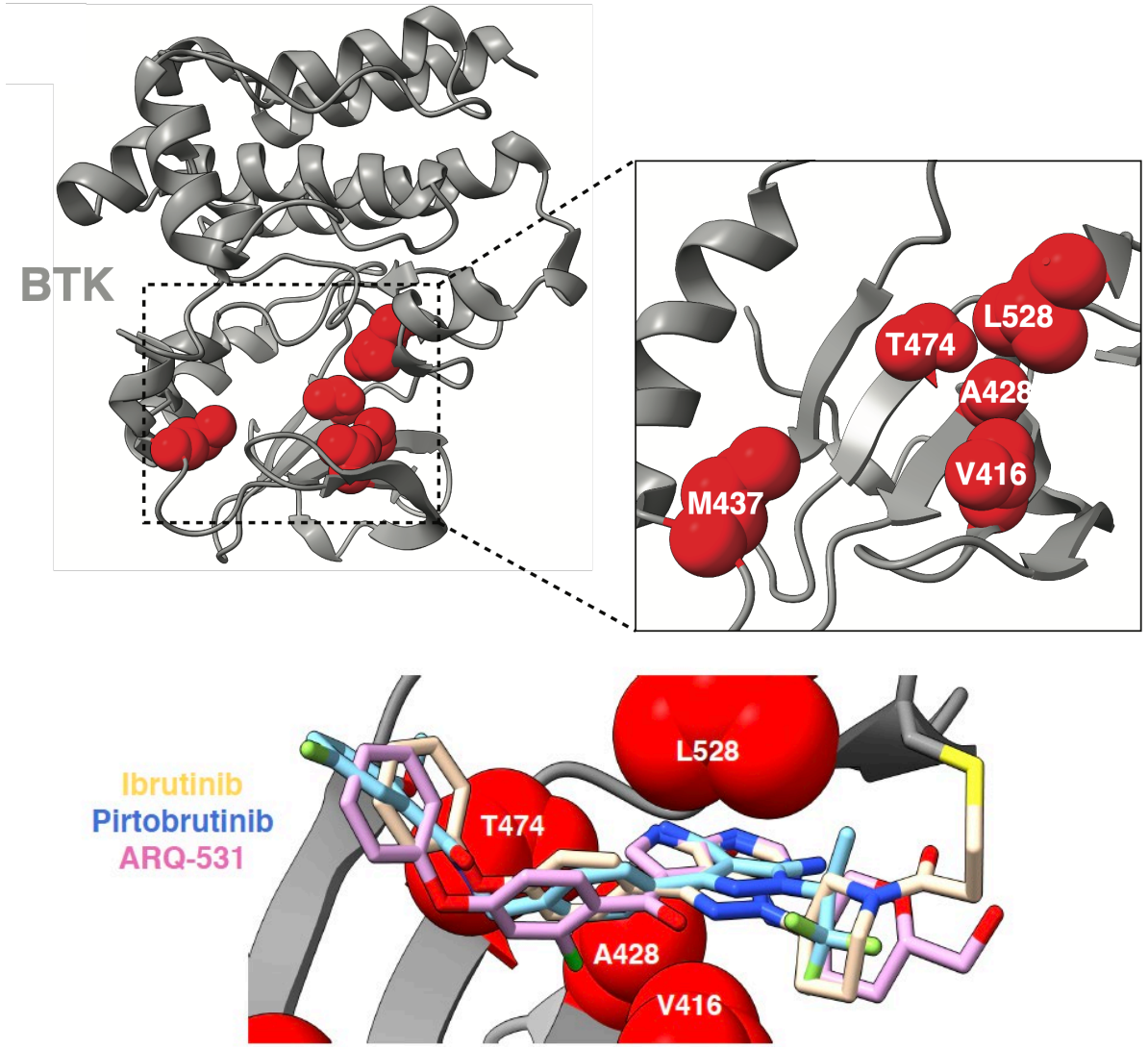
Novel BTK Mutations Identified in Pirtobrutinib-Resistant Patients Clustered Within the BTK Kinase Domain



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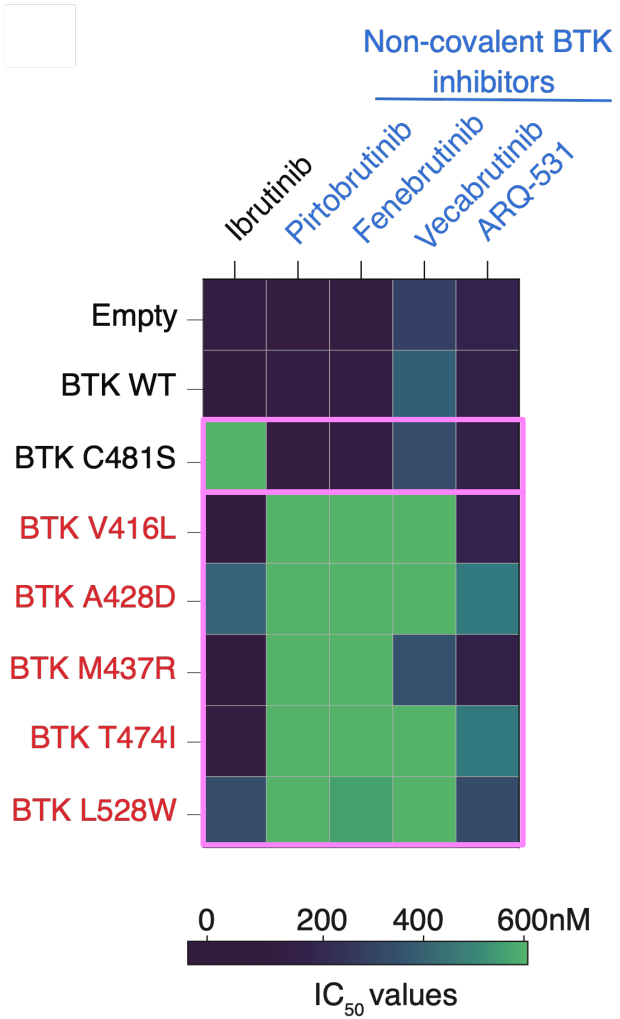
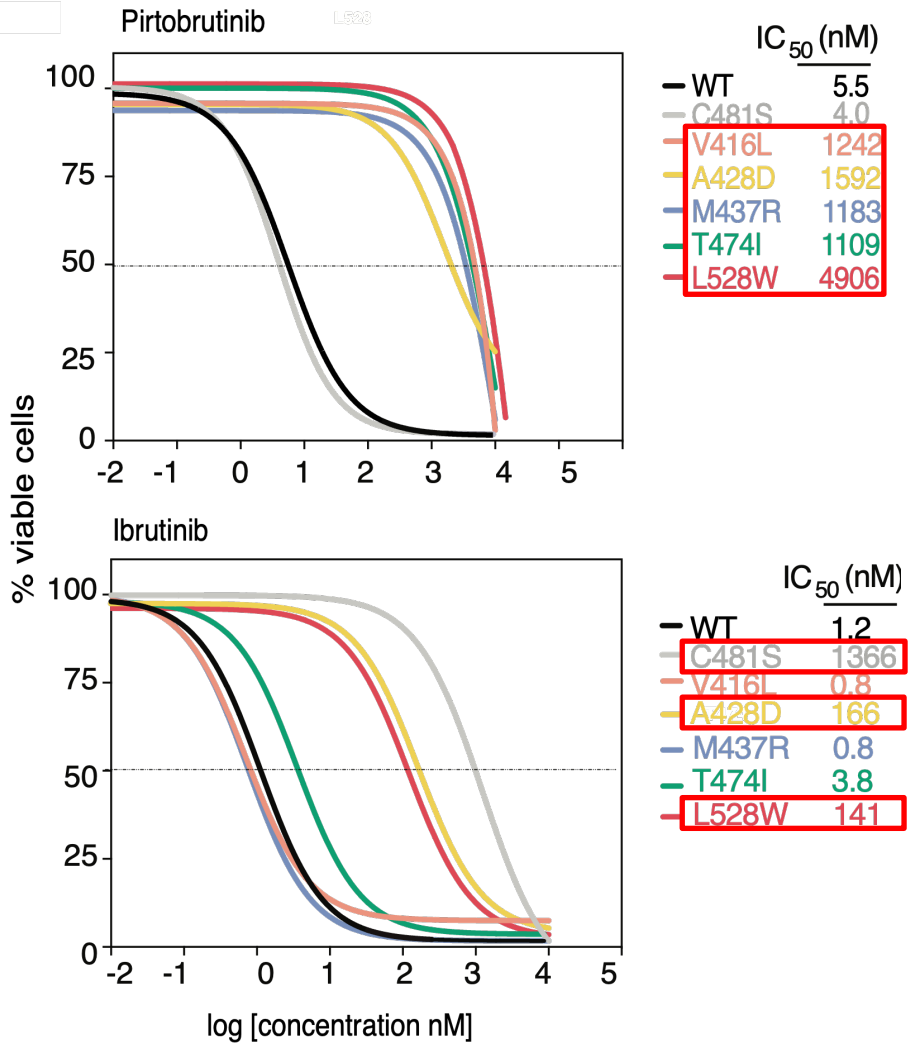
Novel BTK Mutations Confer Broad Resistance to Noncovalent BTK Inhibitors





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Novel BTK Mutations Impaired Binding of Both Noncovalent and Covalent Inhibitors

	Noncovalent inhibitors (K_D in nM)				Covalent inhibitors (Kinact/KI, in μM^{-1} sec^{-1}; except where indicated)		
BTK Protein	Pirtobrutinib	ARQ531	Vecabrutinib	Fenebrutinib	Ibrutinib	Acalabrutinib	Zanubrutinib
WT BTK	0.9	87	0.8	0.2	0.044	0.005	0.052
A428D	No binding detected	2300	No binding detected	No binding detected	No binding detected	No binding detected	No binding detected
M437R	71	29	1.2	159	0.088	<0.001	0.050
T474I	14	8000	14	2.1	0.015	<0.001	<0.001
L528W	No binding detected	No binding detected	24	1.5	No binding detected	<0.001	No binding detected
C481S	2.6	79	2.5	5.1	29 nM	358 nM	69 nM

*Red values indicate mutants which decrease drug binding affinity by at least 10-fold

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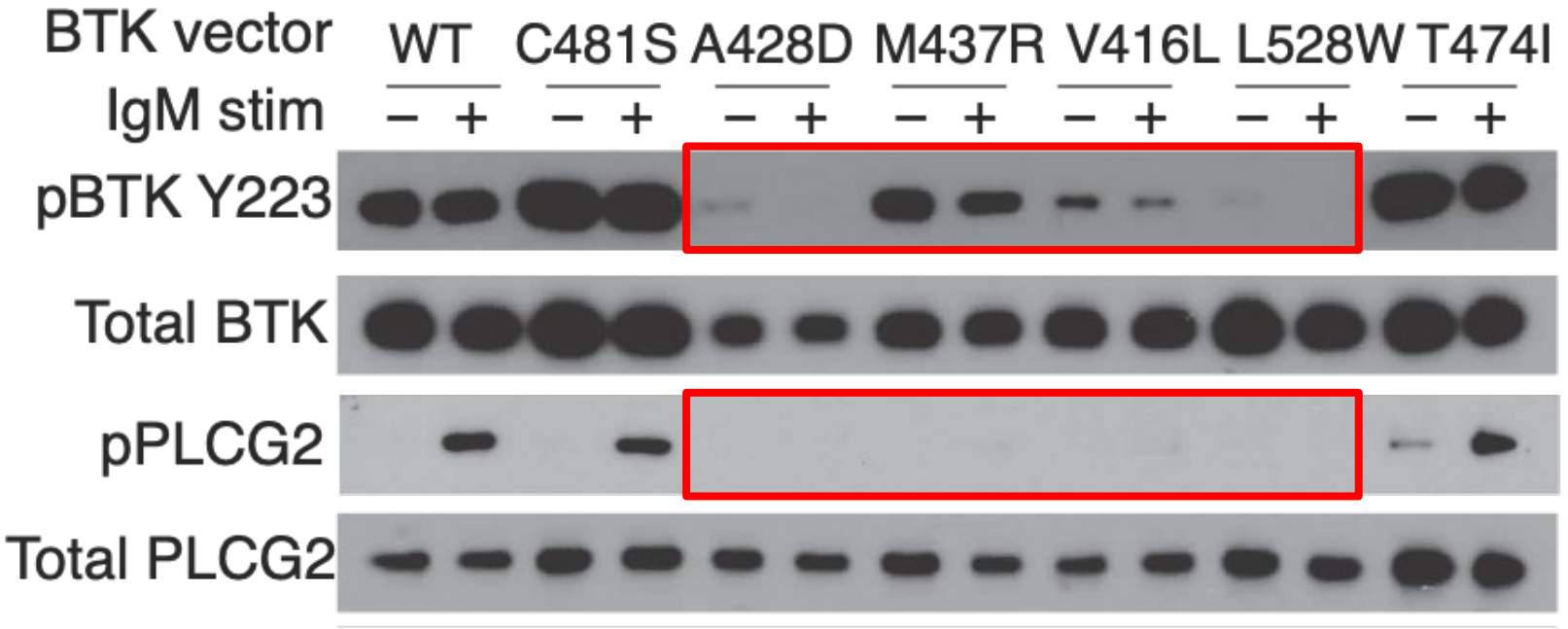
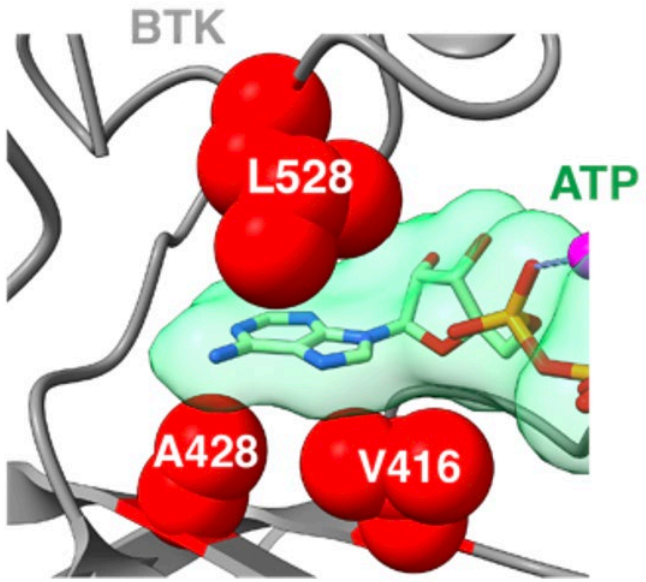
Many of the Novel Acquired BTK Mutations Reduced Phosphorylation of BTK and Downstream PLCγ2





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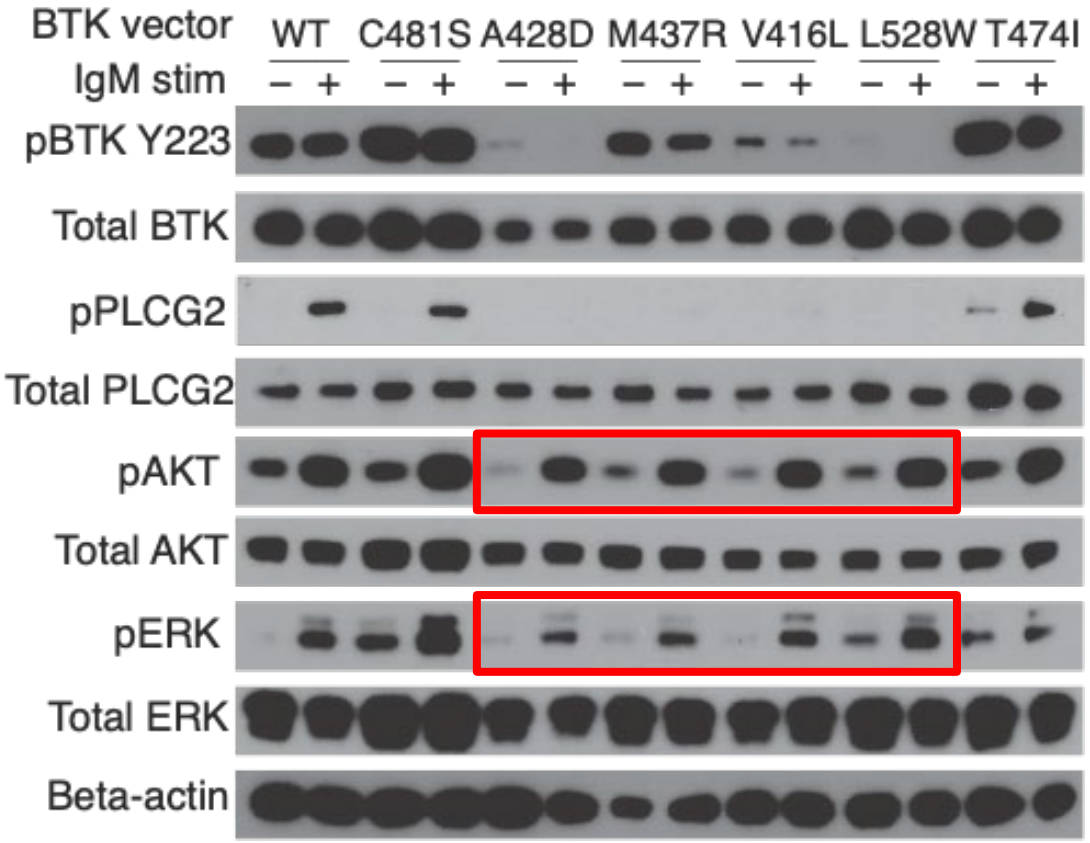
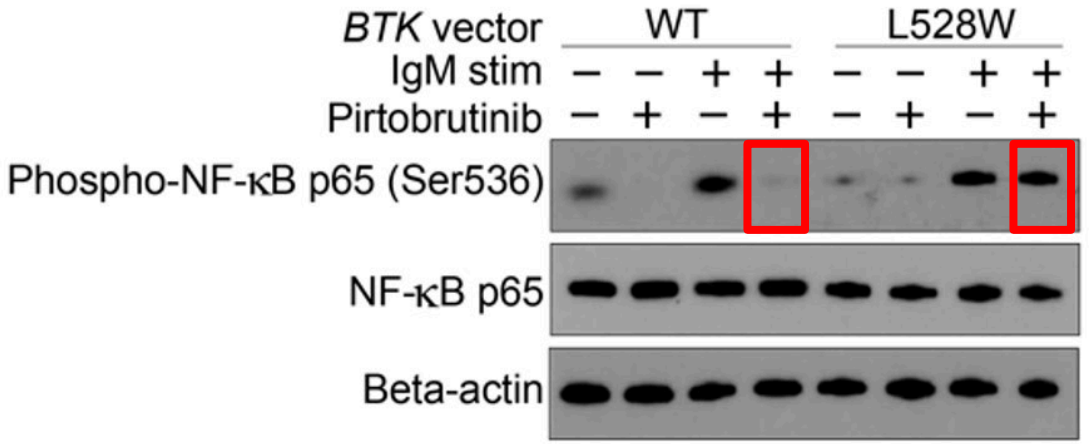
Upon IgM Stimulation, “Kinase Dead” BTK Mutants Still Enabled AKT, ERK, and NF-κB Activation





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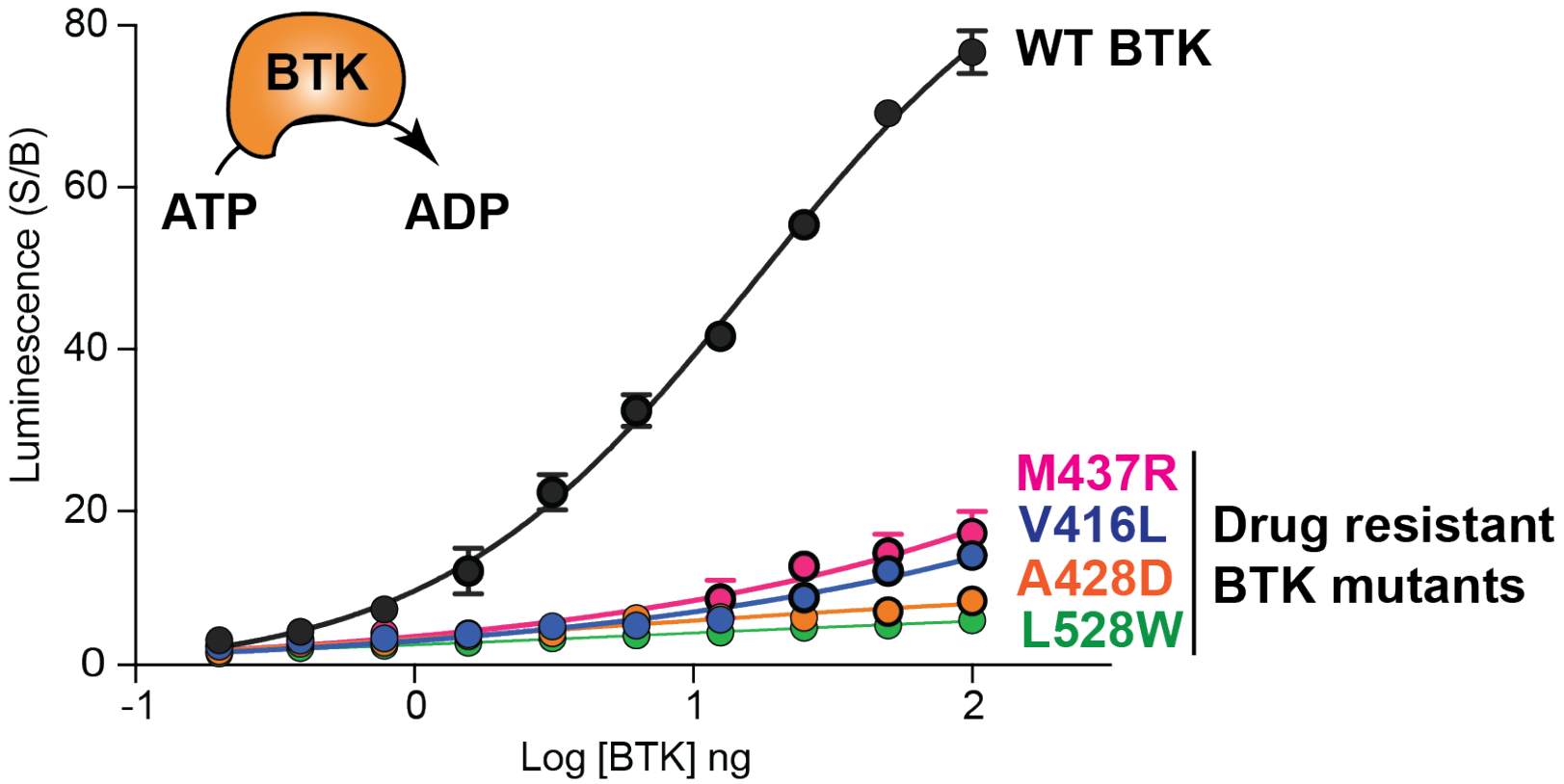
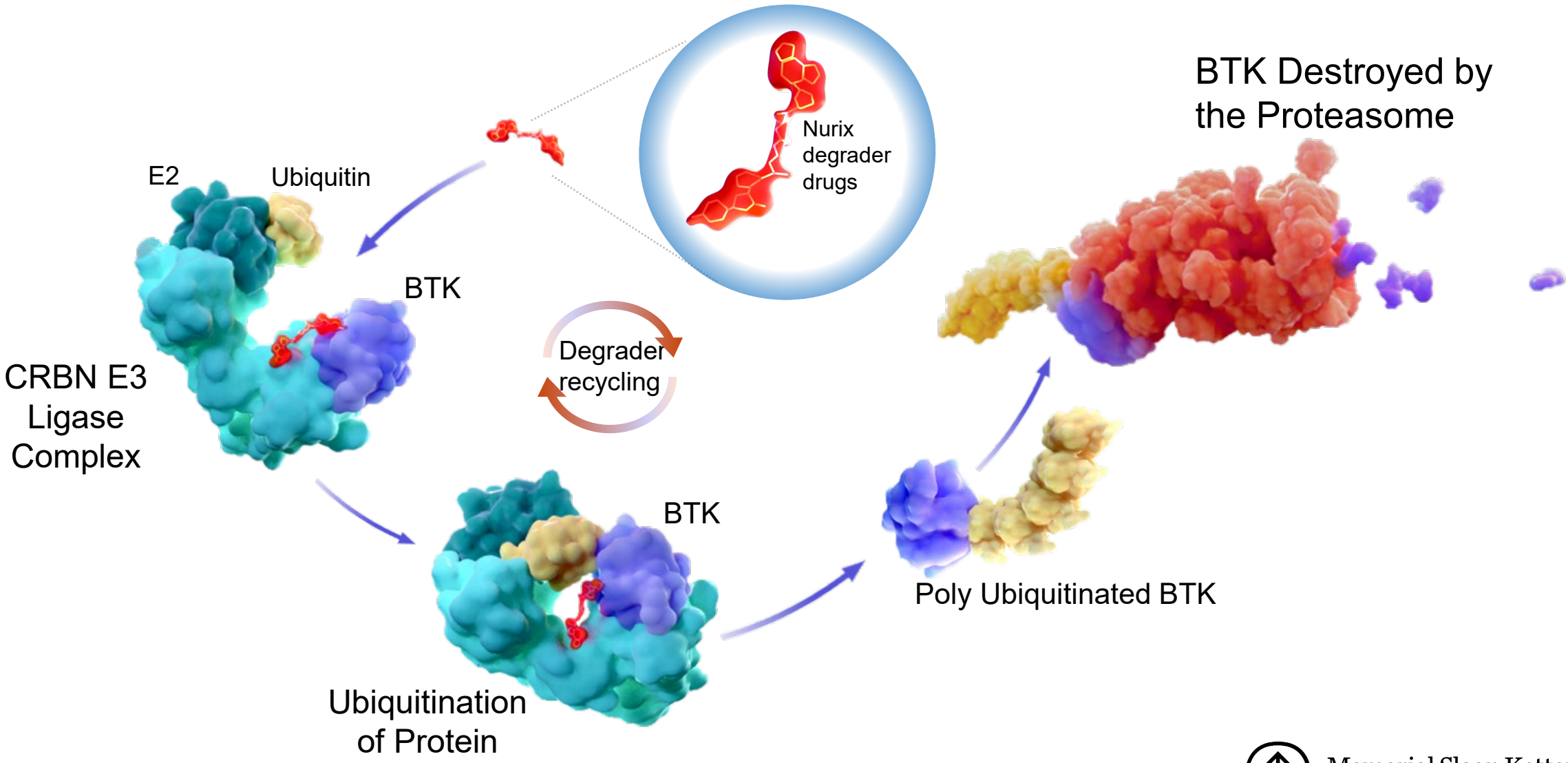
Next Steps & New Means to Inhibit BTK

Discovery of Kinase Dead BTK Mutants



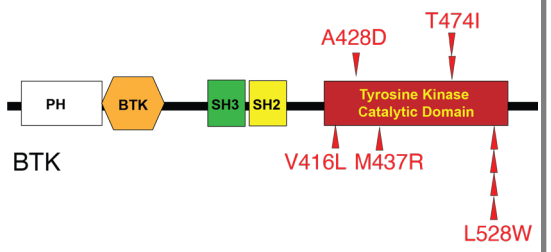
How do kinase dead BTK mutant activate B-cell receptor signaling?
Are cells dependent on mutant BTK?
Can we target these BTK mutants?

Targeted Protein Degradation of BTK

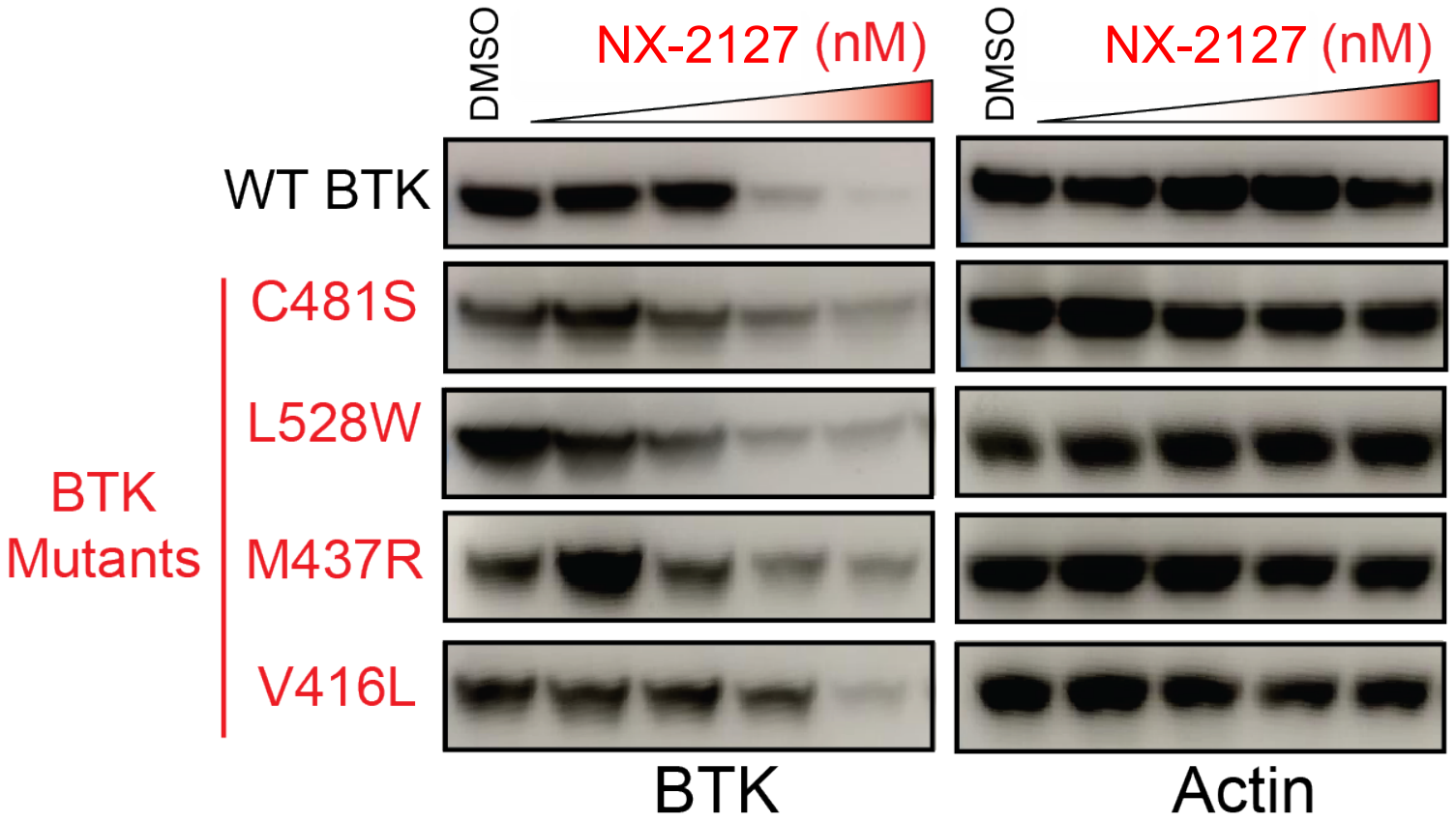


Effective Degradation of Wild-type and Mutant BTK Protein with Nurix Compounds

BTKi resistance mutations



Wang, Mi, Thompson, et al. NEJM 2022



Both NX-2127 and NX-5948 degrade wild-type & drug resistant mutant forms of BTK

nurix

Leader in Targeted Protein Modulation

First Targeted Protein Degradation Drugs in Hematologic Malignancies

NX-2127 & NX-5948

R&D Day
New York, NY
May 26, 2022

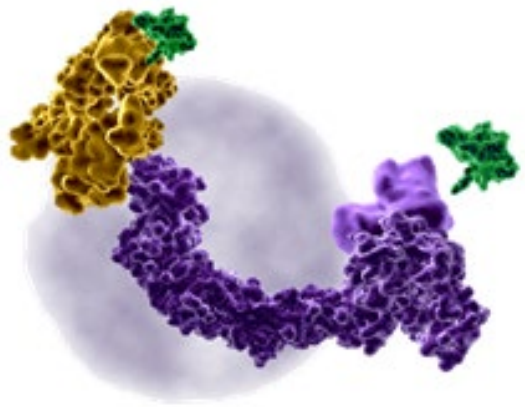
NX-2127: BTK Degrader With Immunomodulatory Activity

Robert J Brown, MD
EVP, Head of Clinical Development
Nurix Therapeutics

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

BTK DEGRADATION & IMMUNOMODULATION NX-2127 (Oncology)

- Robust BTK degradation and immunomodulatory activity observed across all dose levels to date
- Positive clinical activity in all CLL patients, including responses in double-refractory patients with BTK or BCL2 mutations
- Initiated cohort expansion for CLL patients
- Dose exploration is ongoing for patients with NHL

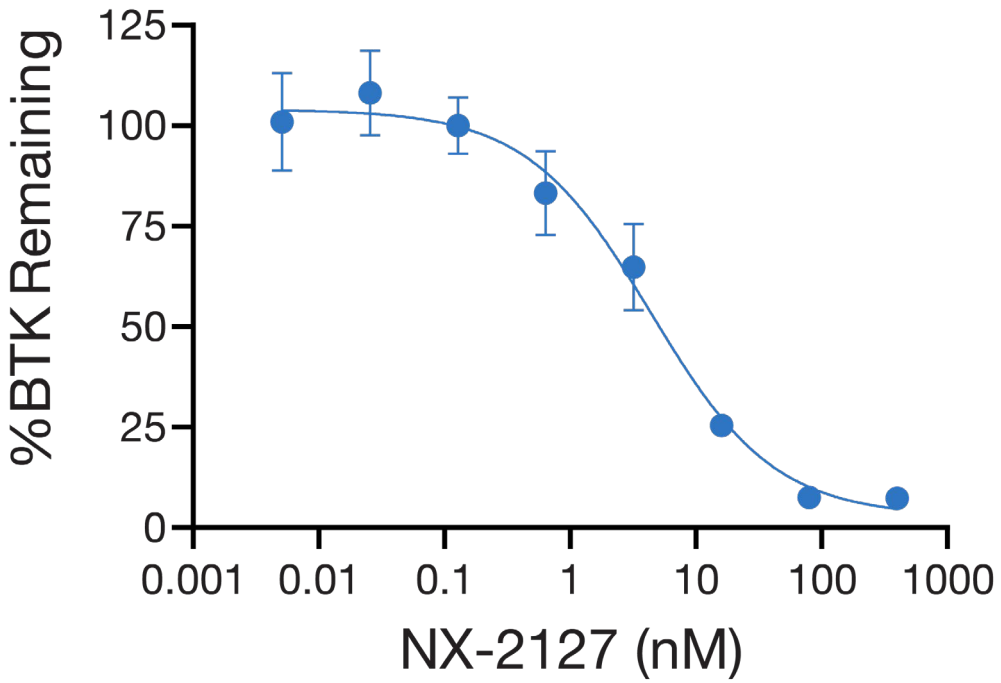


BTK DEGRADATION NX-5948 (Oncology & Autoimmune)

- Active against multiple BTK inhibitor-resistant mutations
- Crosses blood brain barrier and degrades BTK in brain-resident lymphoma cells and microglia in animal models
- Activity in multiple models of autoimmune disease
- First patient dosed in Phase 1a dose escalation trial

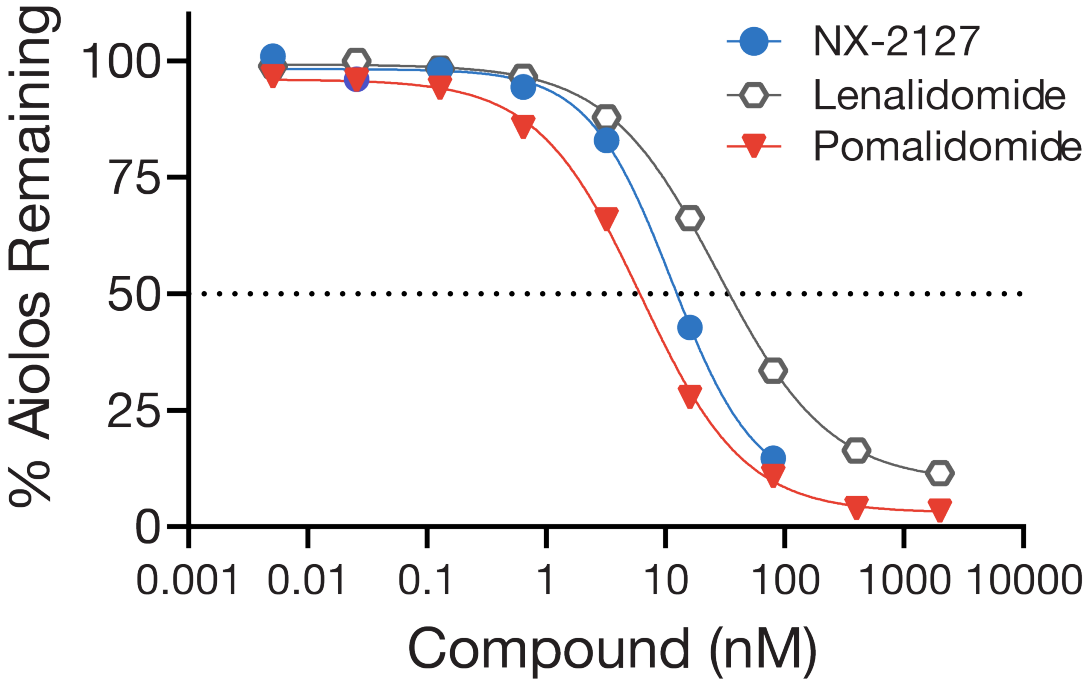
NX-2127 Degrades Both BTK and Immunomodulatory Cereblon Neosubstrate Aiolos

BTK Degradation in TMD8 Cells



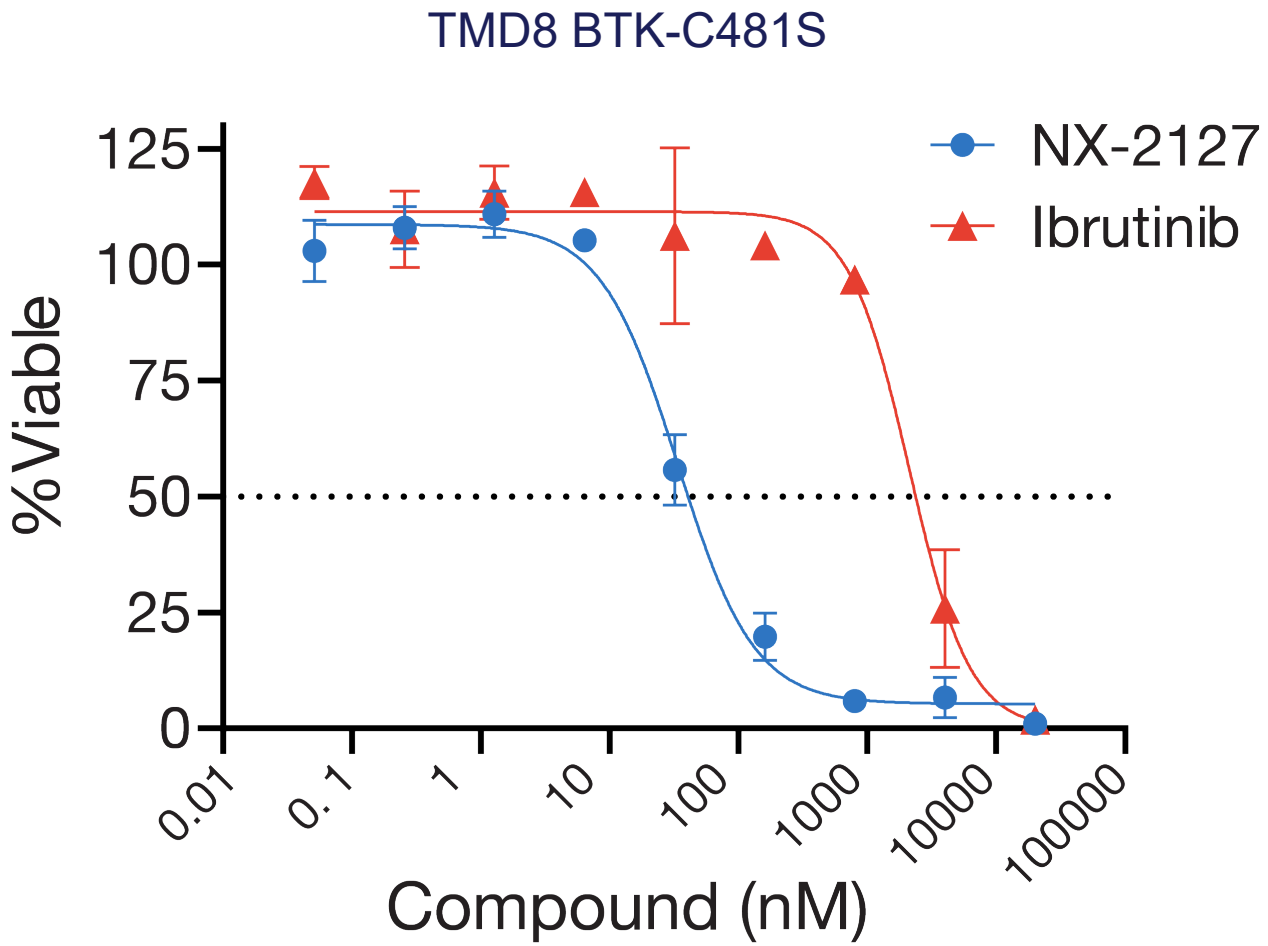
NX-2127 shows potent BTK degradation in TMD8 cells (human DLBCL cell line)

Aiolos Degradation in T Cells



NX-2127 degradation of Aiolos in human T cells occurs at a similar potency to lenalidomide and pomalidomide

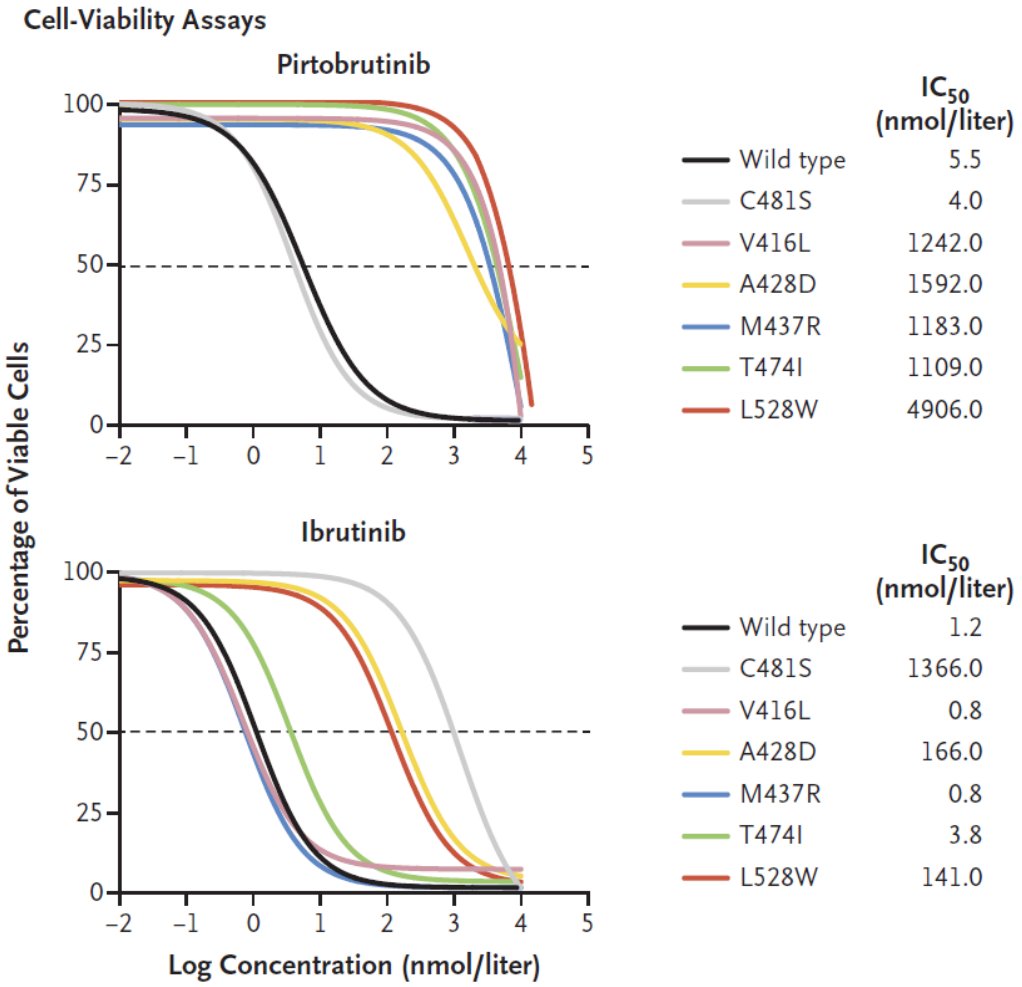
NX-2127 Is Active Against Ibrutinib-Resistant Tumor Cell Lines



BTK-C481 mutations are the most common resistance mutations to ibrutinib and other covalent BTK inhibitors

NX-2127 may offer a therapeutic option for patients with resistance to BTK inhibitors

Resistance to Noncovalent BTK Inhibitors Presents a New and Growing Challenge to Treatment



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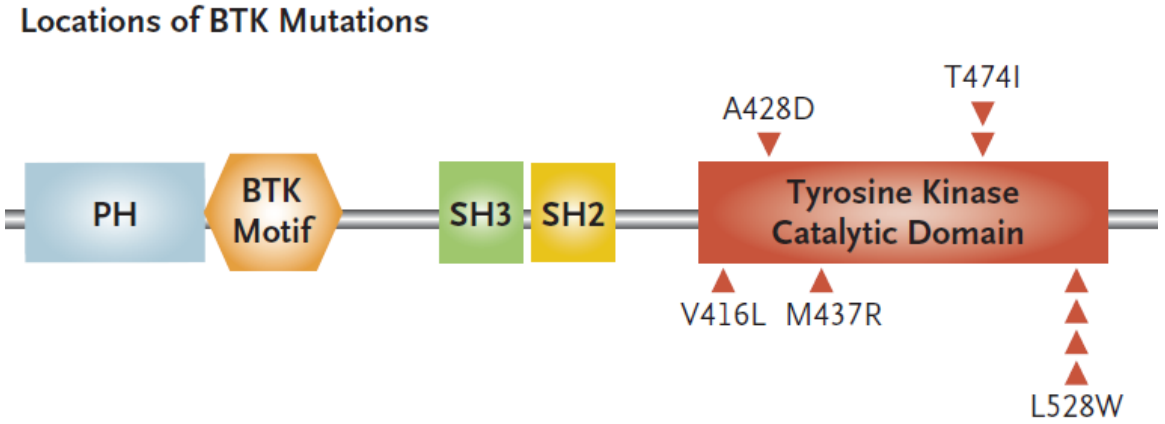
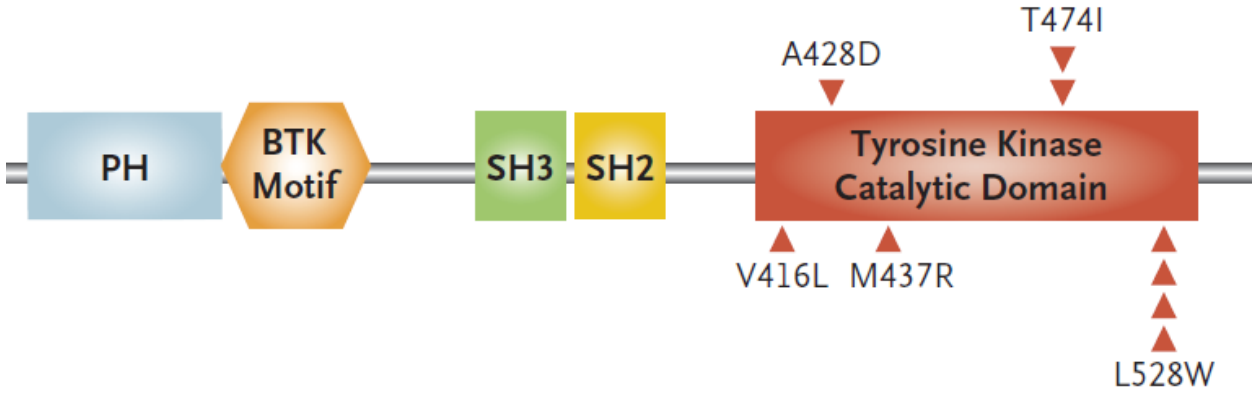
"Our data suggest potential new therapeutic approaches to overcome the newly described BTK inhibitor resistance mechanisms. For example, these data provide a rationale for therapies aimed at addressing the potential scaffold function of BTK rather than inhibiting BTK kinase activity."



Source: Wang et al, N Engl J Med 2022;386:735-43

Degraders Directly Address Emerging Resistance Mutations and BTK Scaffolding Activity

BTK mutations identified from patients progressing on the noncovalent inhibitor pirtobrutinib

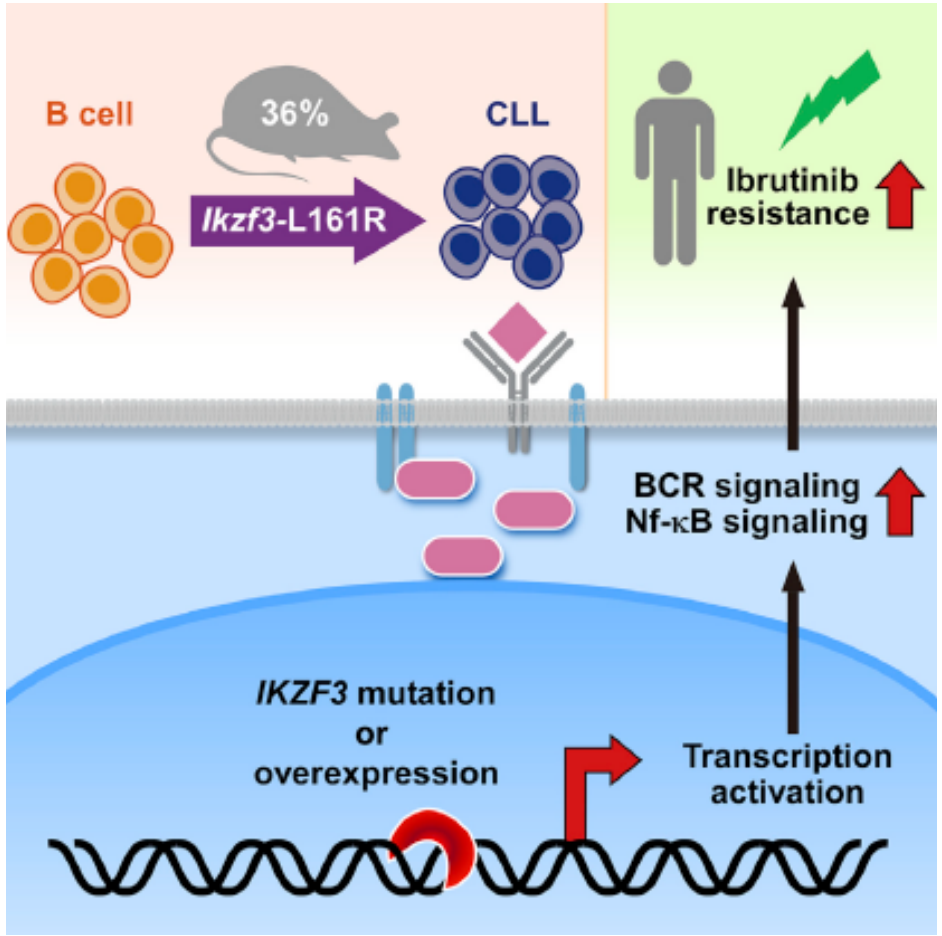


NX-2127 has demonstrated clinical activity in patients harboring a variety of BTK mutations

Nurix has confirmed the activity of NX-2127 and NX-5948 in multiple BTKi-resistant engineered cell lines

Source: Wang et al, N Engl J Med 2022;386:735-43

Aiolos (IKZF3) Overexpression Drives BTK Inhibitor Resistance in CLL, a Rationale for a Combination Strategy



Article

Cancer Cell

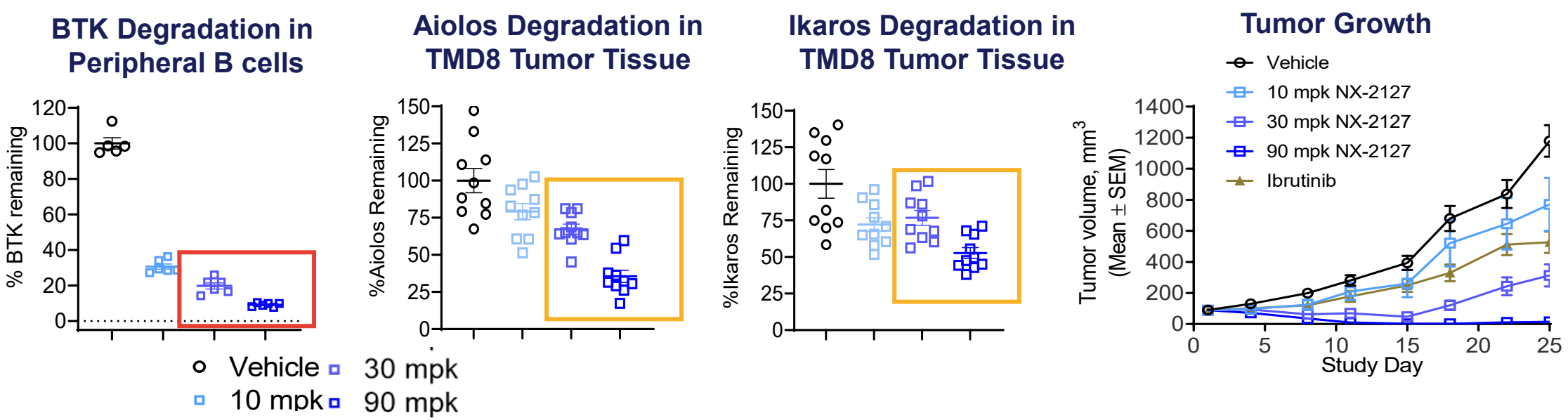
A hotspot mutation in transcription factor *IKZF3* drives B cell neoplasia via transcriptional dysregulation

"Our results thus highlight IKZF3 oncogenic function in CLL via transcriptional dysregulation and demonstrate that this pro-survival function can be achieved by either somatic mutation or overexpression of this CLL driver. This emphasizes the need for combinatorial approaches to overcome IKZF3-mediated BCR inhibitor resistance."

Source: Lazarian et al; Cancer Cell 39, 380–393, March 8, 2021

BTK Degradation of 80%+ Drives Potent Anti-tumor Activity in Preclinical Models

Ikaros and Aiolos degradation also achieve target range at therapeutic doses



Oral dose of NX-2127 (mg/kg)	10	30	90
% BTK degradation in peripheral B cells	69%	80%	91%
% Aiolos degradation in tumor tissue	21%	33%	64%
% Ikaros degradation in tumor tissue	28%	23%	47%
% Tumor growth inhibition vs Vehicle(Day 24)	58%	74%	100%

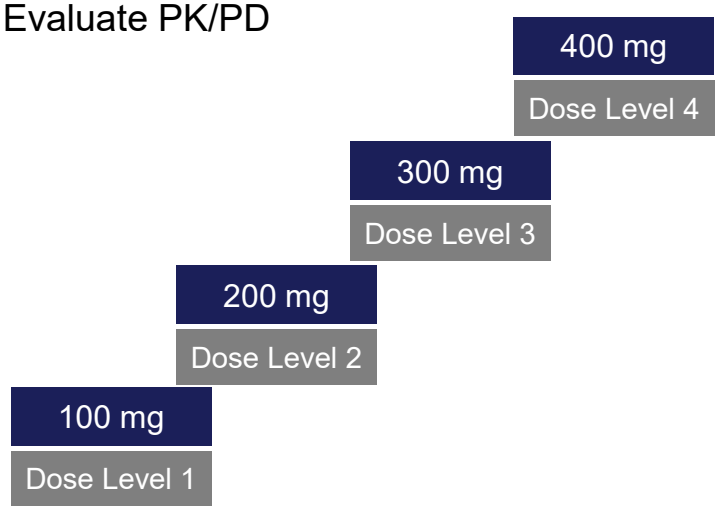
NX-2127-001: Initial Phase 1a Clinical Findings

Meeting the Need in CLL

NX-2127-001
Trial Design and Active Sites

Dose Escalation

Objectives:
- Assess safety and tolerability
- Identify maximum tolerated dose
- Evaluate PK/PD



Oral daily dosing

Potential Dose Expansion

- CLL with BTK C481 mutation (n≈20)
- CLL without BTK C481 mutation (n≈20)
- MCL, MZL, WM (n≈20)
- FL (n≈20)
- DLBCL (n≈20)

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenstrom's macroglobulinemia.

- Memorial Sloan Kettering Cancer Center
- MD Anderson Cancer Center
- City of Hope: Duarte, California
- National Institutes of Health Clinical Center
- Sarah Cannon Research Institute
  - Colorado Blood Cancer Institute
  - Florida Cancer Specialists
  - Tennessee Oncology
- University of California, San Francisco
- University of California, Irvine
- OSU Wexner Medical Center
- Swedish Cancer Institute, Seattle

Heavily Pretreated Patient Population, Including Double-Refractory CLL Patients

NX-2127-001

Characteristics	Overall Population (N = 21)**	CLL (N = 13)	Non-CLL (N=7)
Median Age, years (range)	76.0 (61 - 92)	76 (65 – 86)	77 (67 - 92)
Female, n(%) Male, n(%)	7 (33.3%) 14 (66.7%)	7 (53.8%) 6 (46.2%)	0 7 (100%)
Prior Therapy*, median (range) - BTK inhibitor, n(%) - BCL2 inhibitor, n(%)	4.5 (1 – 8) 16 (76.2%) 7 (33.3%)	6.0 (2 – 8) 12 (92.3%) 7 (53.8%)	2.0 (1 - 5) 4 (57.1%) 0

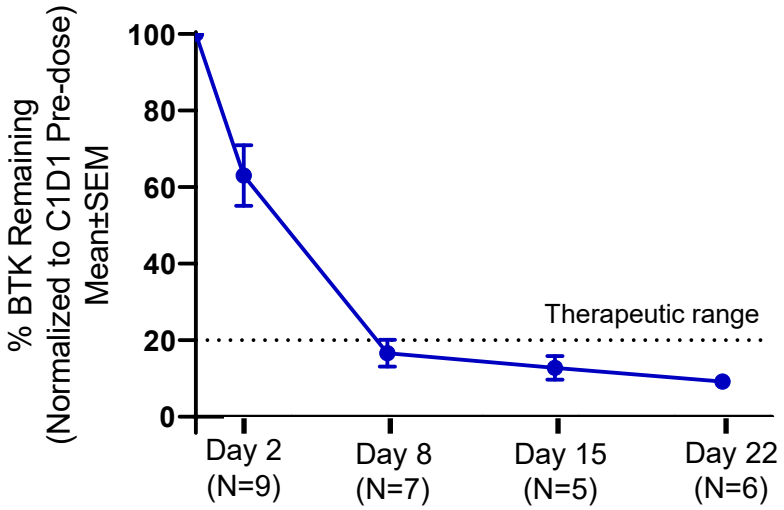
Type of Disease	Cohort 1 (100mg) (N = 12)	Cohort 2 (200mg) (N = 6)	Cohort 3 (300mg) (N = 3)	Total (N = 21)
Chronic Lymphocytic Leukemia (CLL)	8 (66.7%)	3 (50%)	2 (66.7%)	13 (61.9%)
Mantle Cell Lymphoma (MCL)	1 (8.3%)	1 (16.7%)	1 (33.3%)	3 (14.3%)
Diffuse Large B-Cell Lymphoma (DLBCL)	2 (16.7%)	1 (16.7%)	0 (0%)	3 (14.3%)
Waldenstrom's Macroglobulinemia (WM)	0 (0%)	1 (16.7%)	0 (0%)	1 (4.8%)
TBD***	1 (8.3%)	0 (0%)	0 (0%)	1 (4.8%)

* Prior therapies were not entered into the database for all enrolled patients at the time of Data Cut. Some data pending/ongoing.
** One patient's disease type wasn't identified in the EDC at the time of extract, but disease type was coded based on source data
*** One subject was screened into the study, but the indication and cohort weren't entered in the EDC at the time of data extract

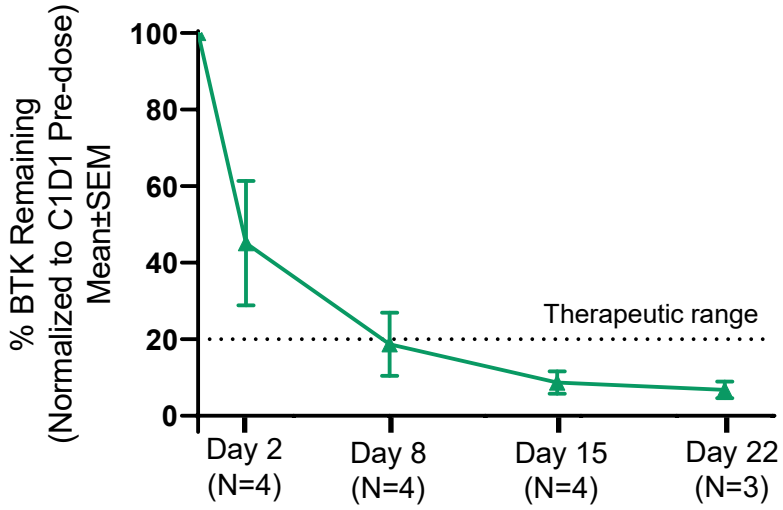
Robust BTK Degradation Observed with NX-2127 Across All Dose Levels and Malignancies

NX-2127-001

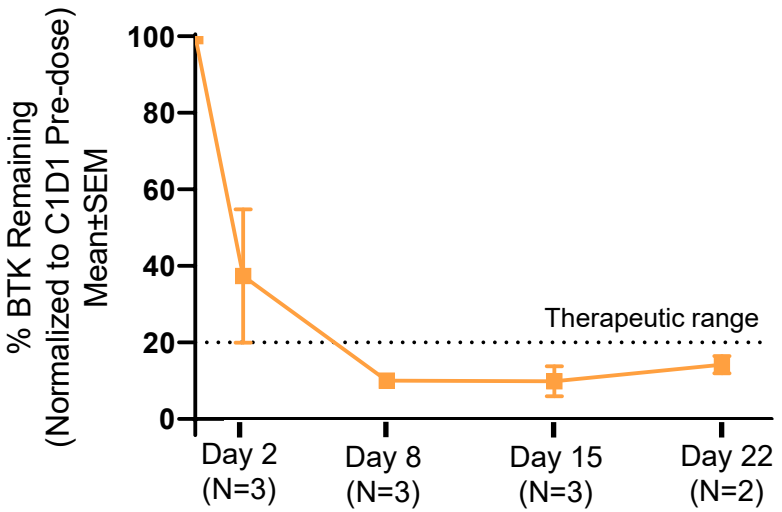
Cohort 1-100 mg
% BTK remaining in CD19+ B cells



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



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

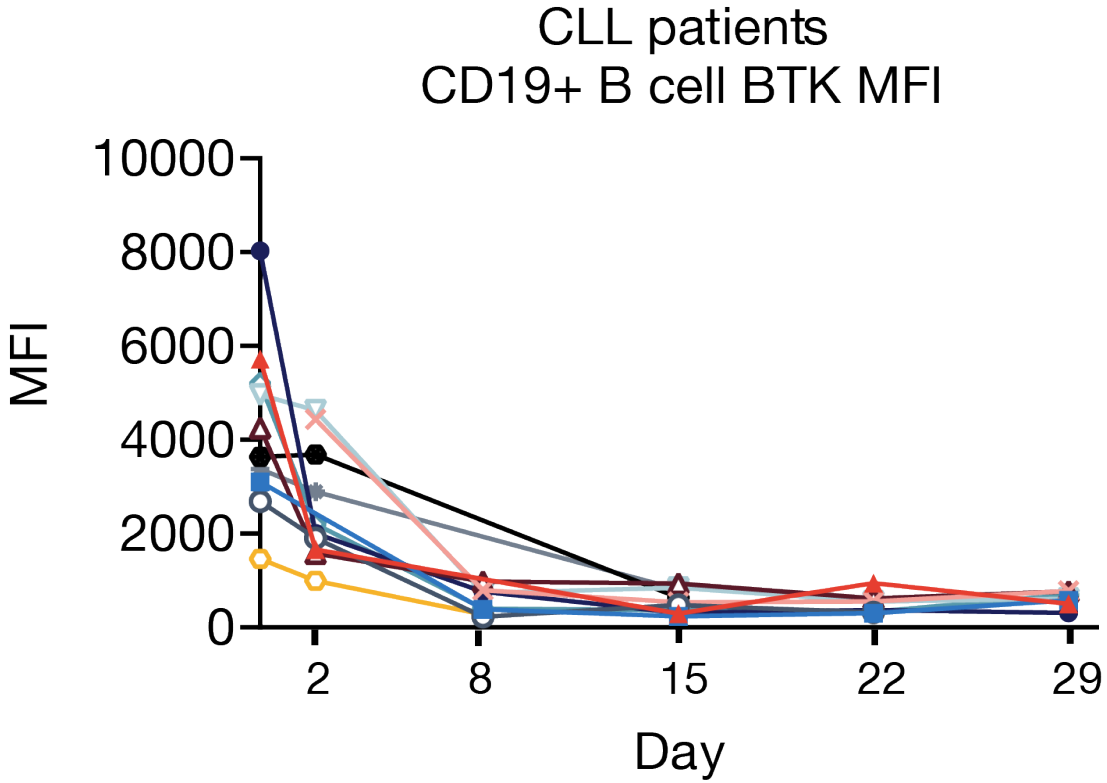


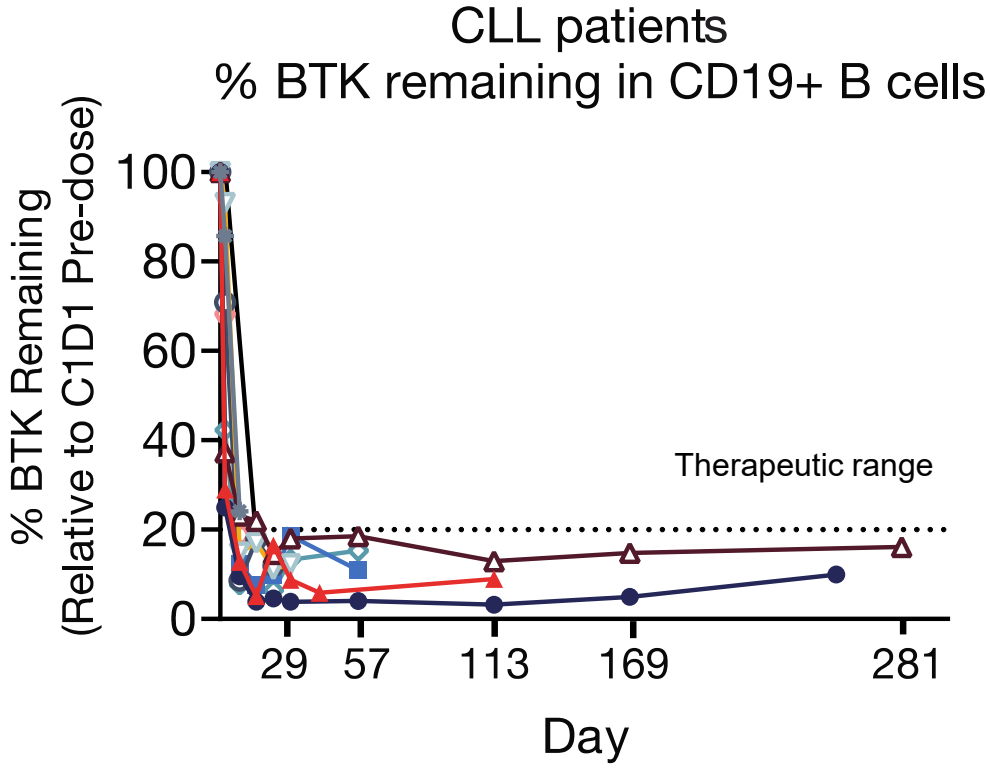
Dose	% BTK Degraded (Average trough)				
	Baseline	Day 2	Day 8	Day 15	Day 22
100 mg	0	37	83	87	90
200 mg	0	55	81	91	93
300 mg	0	63	90	90	86¥

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

Rapid and Sustained Degradation of BTK in Patients with CLL

NX-2127-001





Target BTK degradation achieved by Day 15 (steady state) for all starting BTK levels

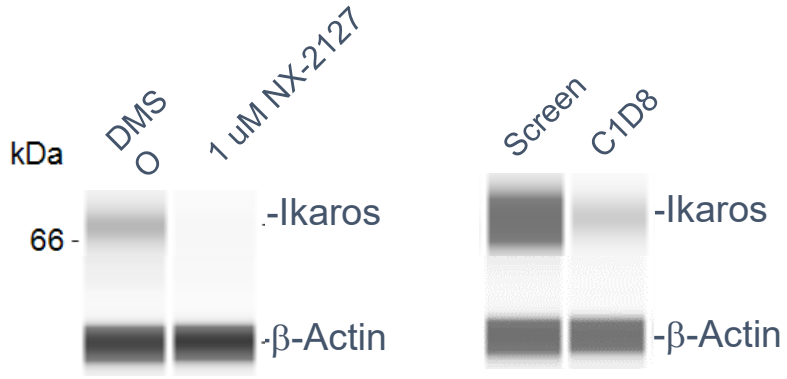
BTK degradation is sustained

NX-2127 Demonstrates Greater Ikaros Degradation, Consistent with Cereblon Immunomodulatory Activity

NX-2127-001

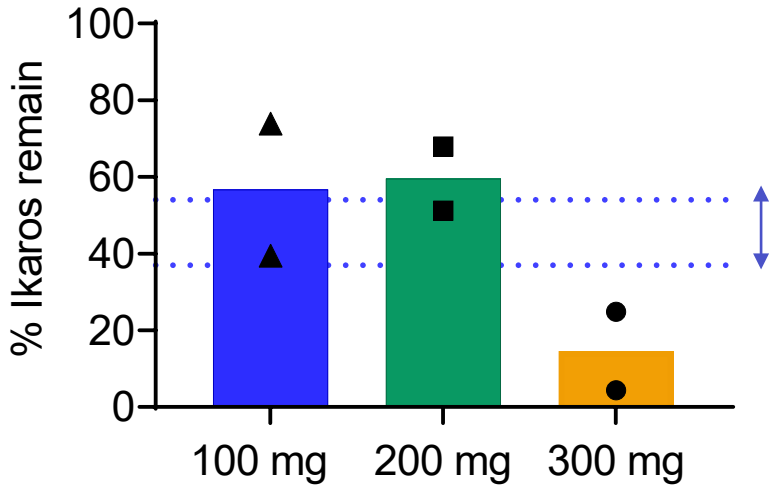
Healthy Donor
(ex vivo positive control)

Example 100 mg
CLL Patient



Ikaros protein was detected from PBMC cell lysate from healthy donor or patient in NX-2127-001 trial

% Ikaros Remaining
at C1D8



Range of Ikaros decrease seen with lenalidomide

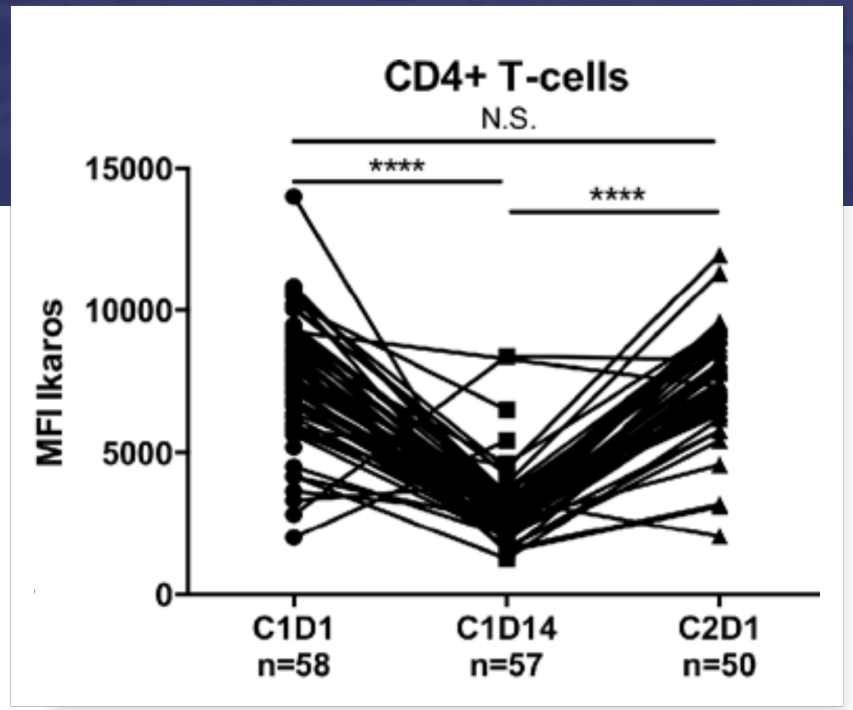
Franssen et al; 2018

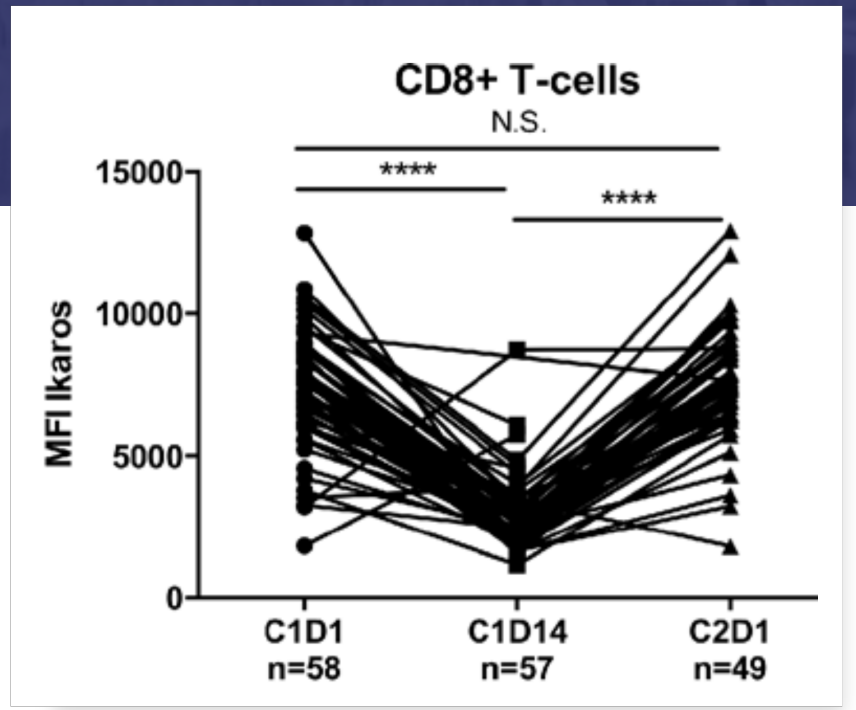
- Degradation of cereblon neo-substrate Ikaros confirmed by Western Blot
- Ikaros degradation is sustained on treatment
- Ikaros degradation consistent with published reports for immunomodulatory drugs

Lenalidomide Treatment Achieves 46-63% Ikaros Degradation in Immune Cells

Ikaros decreases:

- 63% median decrease in both CD4+ and CD8+ T cells
- 59% median decrease in NK cells
- 46% median decrease in B cells

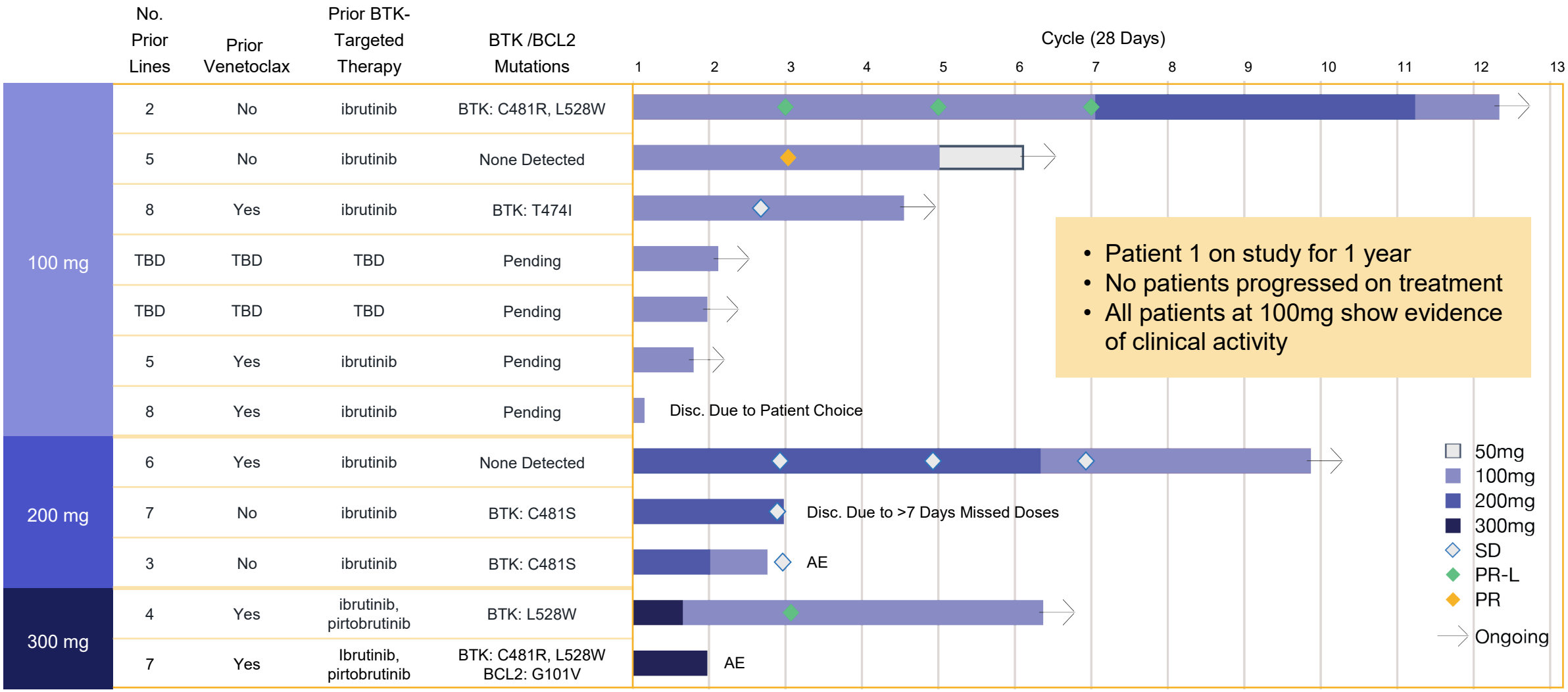




Ikaros levels in patients with MM treated with lenalidomide +low-dose cyclophosphamide and prednisone, shown in CD4+ and CD8+ T cells

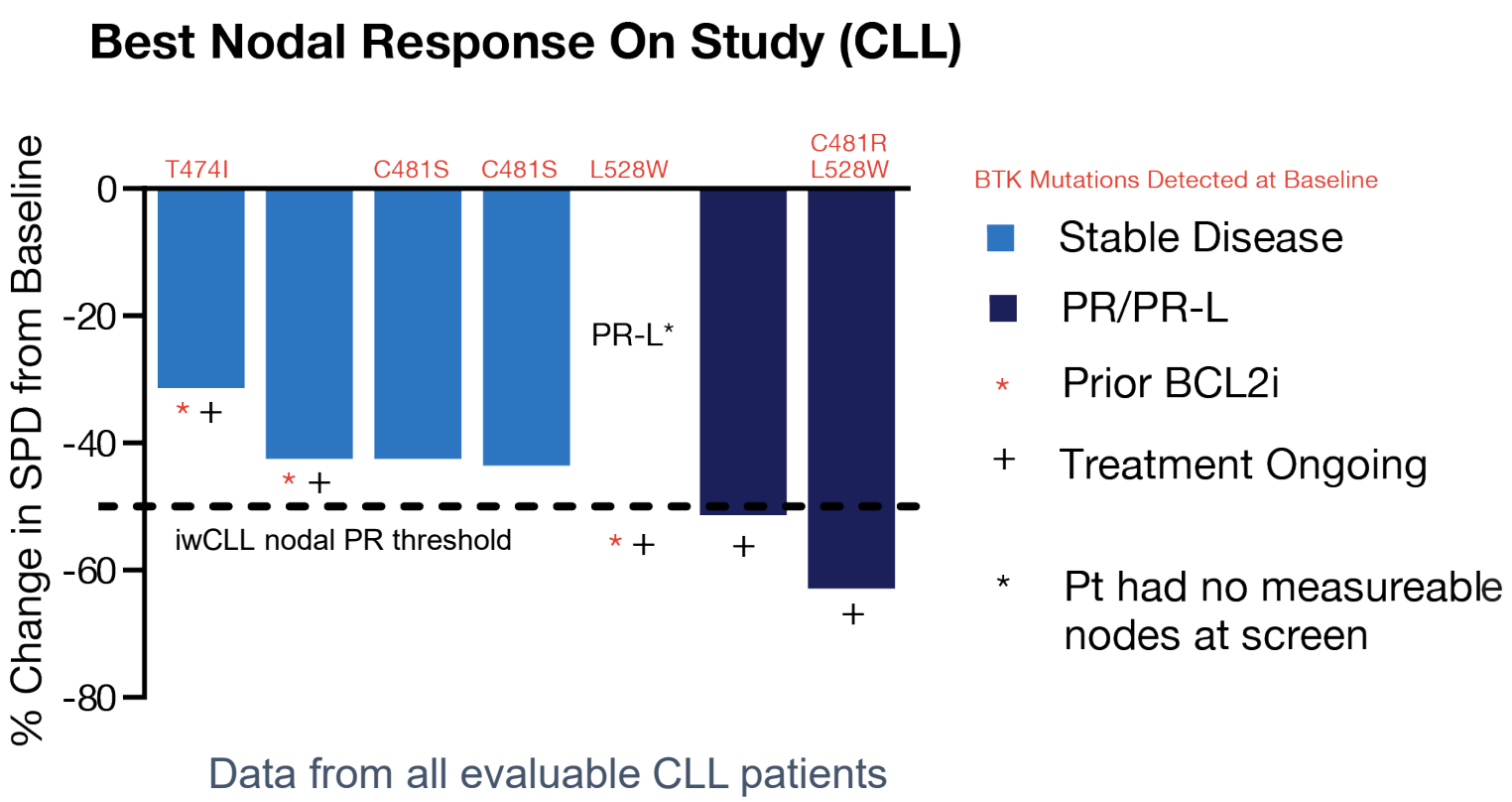
Source: Franssen et al; Oncotarget,Vol. 9 (No. 74), 2018

NX-2127-001: Durable Benefit In CLL Patients With A Median of 6 Prior Treatments



TBD: Data not available at time of database cut
Note: Table excludes 1 patient included in overall population as dosing not available at time of database cut

NX-2127-001 Phase 1a: Positive Initial Findings in CLL Support Expansion at 100 mg



Data from all evaluable CLL patients

SPD, sum of the product of diameters; iwCLL, international Workshop on CLL

- Meaningful clinical benefit in CLL patients with a median of 6 prior lines of therapy
- Biologic activity including nodal reductions and/or lymphocytosis observed in all patients treated
- Responses in patients with resistance mutations to covalent and non-covalent BTK inhibitors
- Responses include a double-refractory patient who had prior BCL2 inhibitor therapy

Safety Observations By Dose: All Patients, Grade ≥ 3

NX-2127-001

Adverse Event Preferred Term, Grade ≥3	100mg (N=10) n (%)	200mg (N=6) n (%)	300mg (N=3) n (%)
Neutropenia	1 (10%)	3 (50%)	2 (66.7%)
Hypertension	0 (0%)	1 (16.7%)	0 (0%)
Dyspnea	0 (0%)	1 (16.7%)	0 (0%)
Anemia	1 (10%)	1 (16.7%)	0 (0%)
Pain in extremity	0 (0%)	0 (0%)	1 (33.3%)
Clostridium difficile colitis	0 (0%)	1 (16.7%)	0 (0%)
Clostridium difficile infection	0 (0%)	1 (16.7%)	0 (0%)
Cognitive disorder	0 (0%)	0 (0%)	1 (33.3%)
Upper resp. tract infection	0 (0%)	1 (16.7%)	0 (0%)

Safety population included 19 subjects. Two subjects were assigned to the 100mg cohort but treatment was not entered in the EDC at time of extract.

Additional safety observations:

- Dose limiting toxicity observed at 300 mg in a CLL patient; cognitive AE believed to be related to immunomodulatory activity
- Two AEs of lower grade atrial fibrillation were observed at 100 mg in a patient with MCL, and at 200 mg in a patient with CLL

Preliminary Positive Clinical Findings Support Expansion of CLL Cohorts at the 100mg Dose

- Robust BTK degradation achieved in all patients
- Immunomodulatory activity achieved in all patients
- Favorable safety profile at dose selected for expansion cohorts
- Meaningful clinical benefit observed in multiple CLL patients with a median of 6 prior treatments
- Responses seen in the setting of resistance mutations to both covalent and non-covalent BTK inhibitor

Expansion dose declared in CLL at 100mg

NX-2127-001: Phase 1 First-in-Human Clinical Trial Design

Phase 1a continues in NHL and Phase 1b CLL cohort initiated at 100mg

	Dose Escalation (Phase 1a)
Indications	CLL, MCL, MZL, WM, FL, DLBCL
Line of Therapy	Third line or later (Waldenstrom patients second line or later)
Dose Range*	50mg – 300mg oral once daily
Status	CLL: 100mg expansion dose selected MCL, MZL, WM, DLBCL: Current dose 200mg; dose escalation ongoing

	Cohort Expansion (Phase 1b)
Initiated	**CLL (n≈40)** Failed 2 or more prior treatments including a BTK inhibitor and regardless of baseline BTK mutation status
Potential	**MCL, MZL, WM (n≈20)** **FL (n≈20)** **DLBCL (n≈20)**

*50mg dose added as per project Optimus guidance

NX-2127 & NX-5948 Multiple Market Opportunities

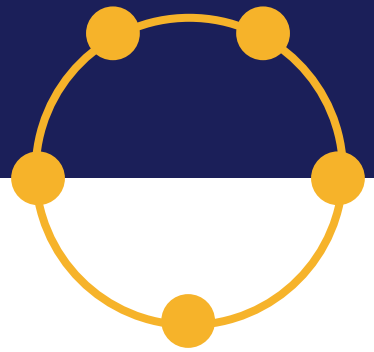
Stefani A Wolff
COO, EVP of Product Development
Nurix Therapeutics

Nurix Portfolio of Degraders Poised To Take a Leadership Position

NX-2127

BTK degrader + immunomodulatory activity in B-cell malignancies

- Beachhead in CLL
- Near term commercial rationale
- Expansion into NHL



NX-5948

BTK degrader in B-cell diseases (malignancies and autoimmune)

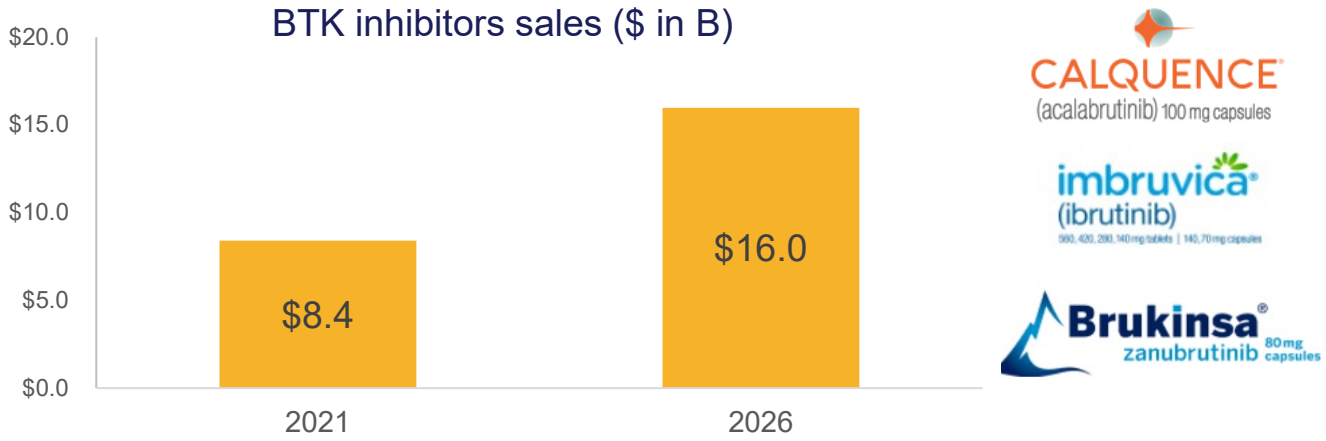
- Potential across lines of therapy
- Opportunity in autoimmune indications (CNS penetrating immunology)

Expands market potential

Opens more clinical and commercial opportunities

Ability to capture more share

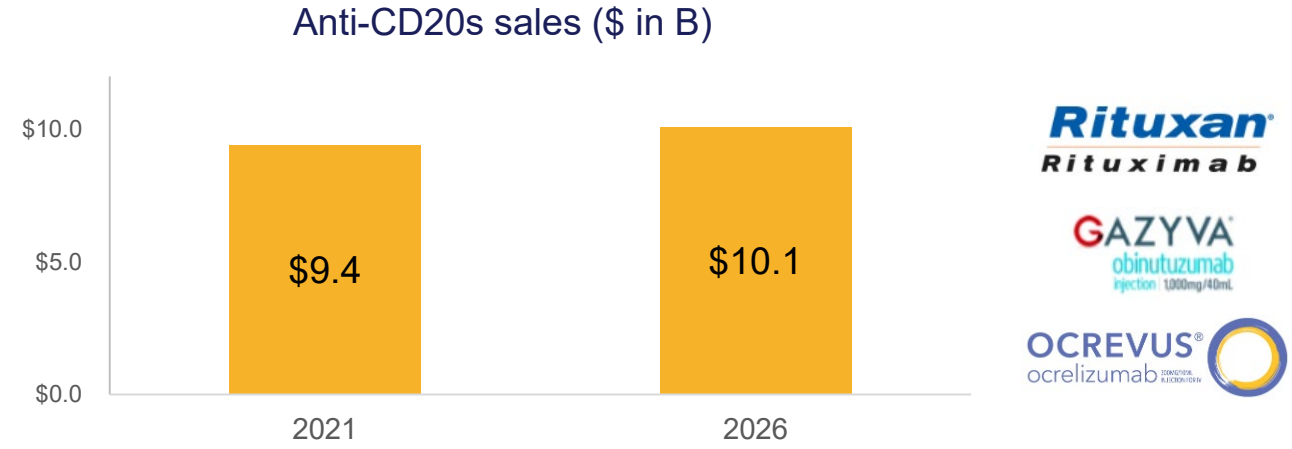
Multi-Billion-Dollar Revenue Opportunity Within the B-cell Therapy Universe for NX-2127 and NX-5948



CALQUENCE (acalabrutinib) 100 mg capsules

imbruvica (ibrutinib)

Brukinsa 80mg zanubrutinib capsules



Rituxan Rituximab

GAZYVA obinutuzumab injection 1,000mg/40mL

OCREVUS ocrelizumab

- B-cell directed therapies represent almost $18B in revenue in 2021
- BTK inhibitors worth $8.4B in 2021 and expected to grow 90% to $16B by 2026
- Anti-CD20s remain cornerstone of therapy in B-cell diseases with sales of $9.4B in 2021
- Three branded anti-CD20 antibodies developed by Genentech expanded market opportunity and allowed them to capture majority of share
- NX-2127 and NX-5948 has potential to compete in multiple B-cell mediated diseases

2021 BTK inhibitor sales exclude double counting of profit shares on ibrutinib.

2026 estimate from Cortellis:
1. Sales data is global-based (US and ex-US)
2. Generic and biosimilar entry included in sales projections

GlobalData: Imbruvica LOE is 2026 (EU), 2027 (US)

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B-Cell Malignancies Opportunity

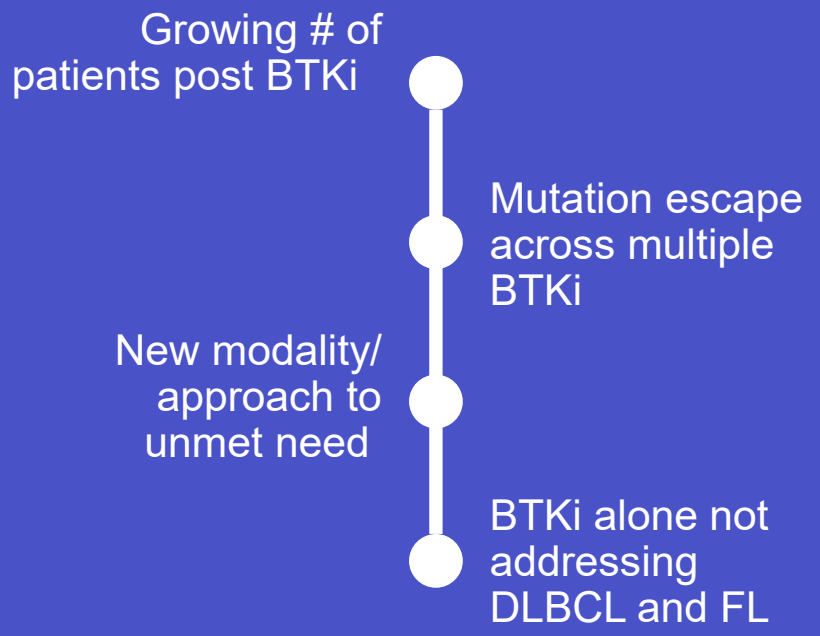
BTK inhibitors are a standard of care in certain hematologic malignancies (e.g., CLL, WM, MCL, MZL)

BTK degraders address key unmet needs arising from mutational escape

BTK degraders have potential to grow beyond traditional BTK-sensitive indications

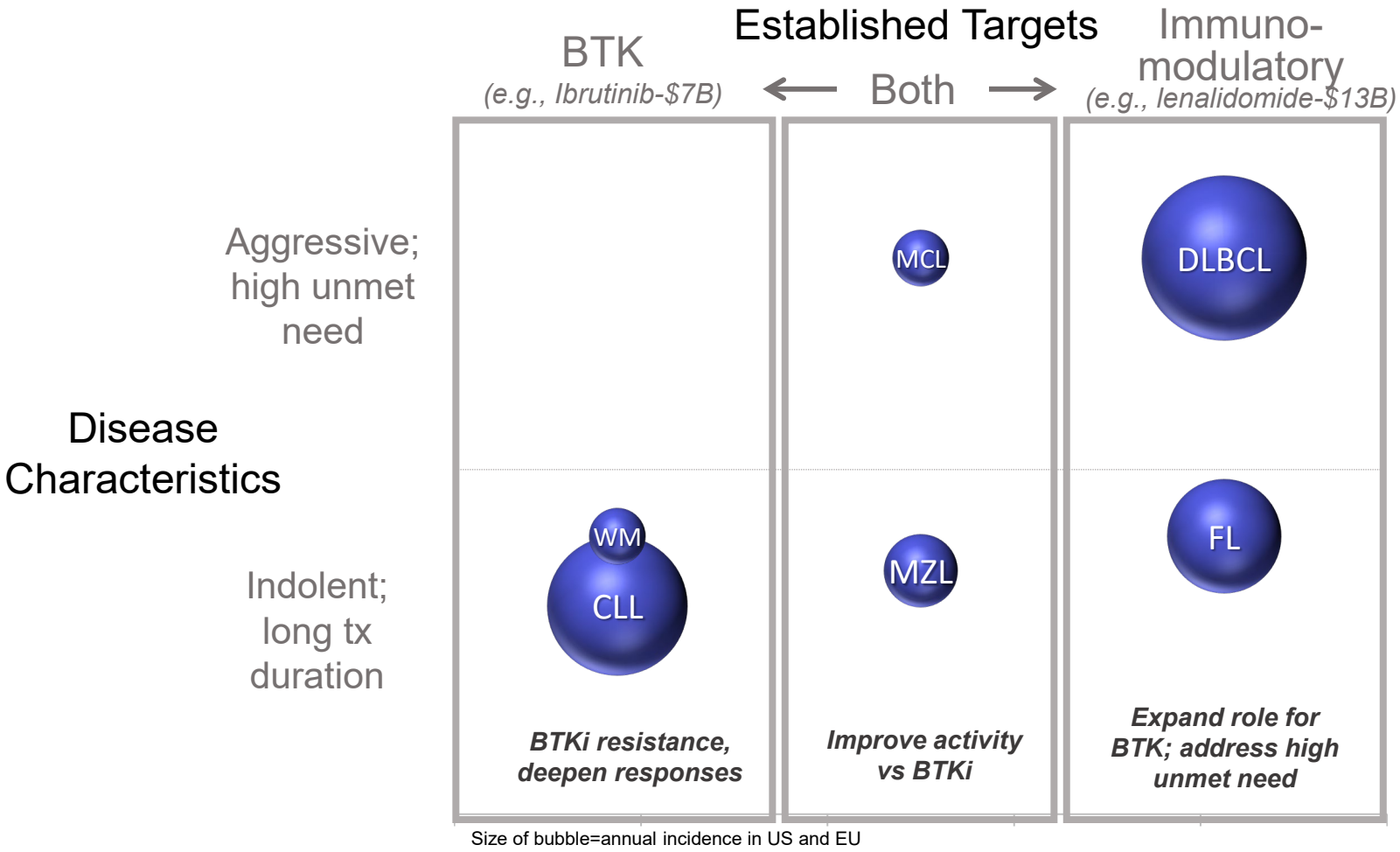
BTK Degrader

OPPORTUNITIES



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

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

The dual activity of NX-2127 has potential to meet a breadth of needs, capture share from existing markets and expand beyond BTK sensitive tumor types

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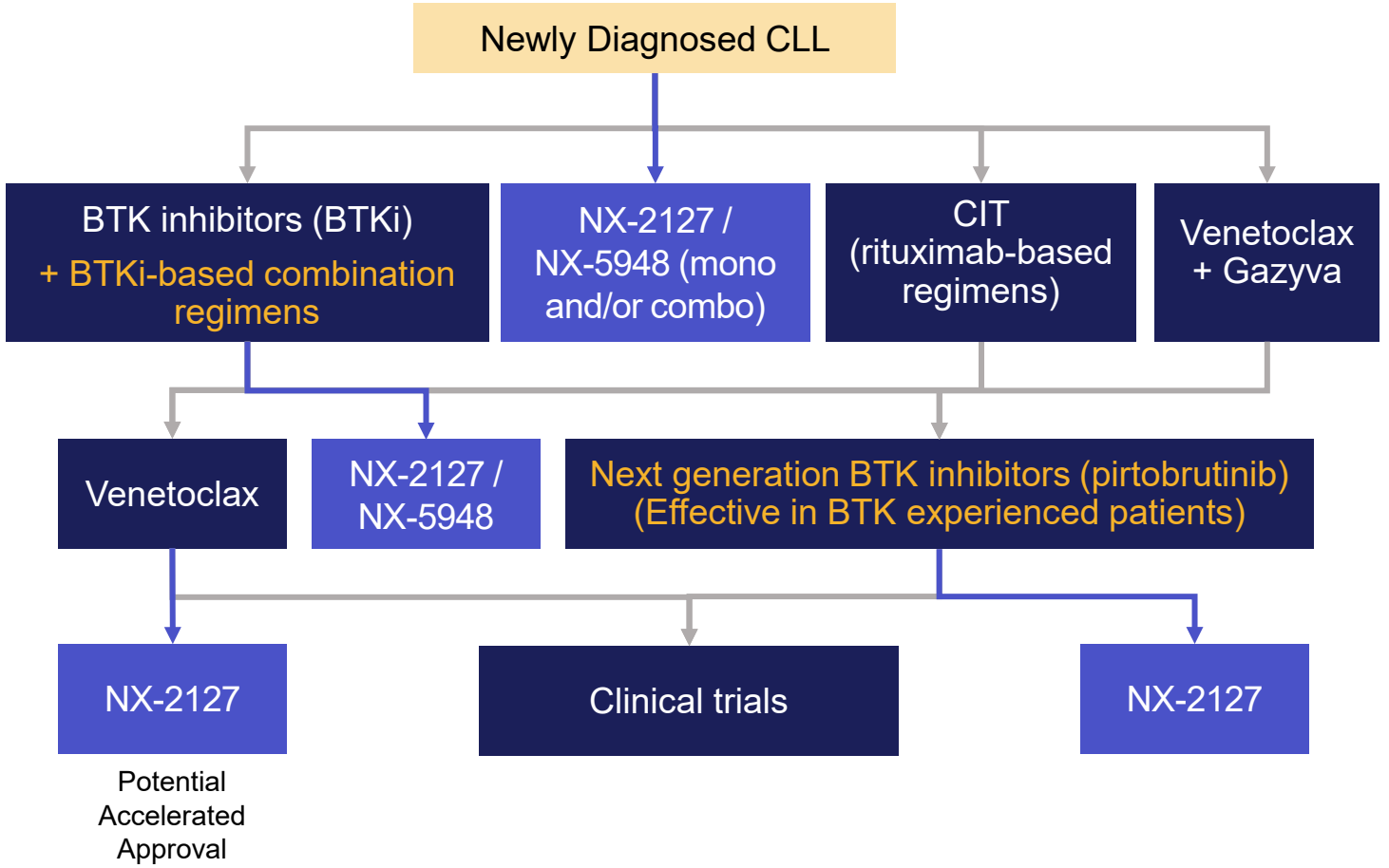
BTK, Bruton tyrosine kinase; DLBCL, Diffuse large B cell lymphoma; CLL, Chronic lymphocytic leukemia, SLL, small lymphocytic lymphoma; MCL, Mantle cell lymphoma; WM, Waldenstrom's macroglobulinemia; MZL, Marginal zone lymphoma; FL, Follicular lymphoma; NHL, non-Hodgkin lymphoma

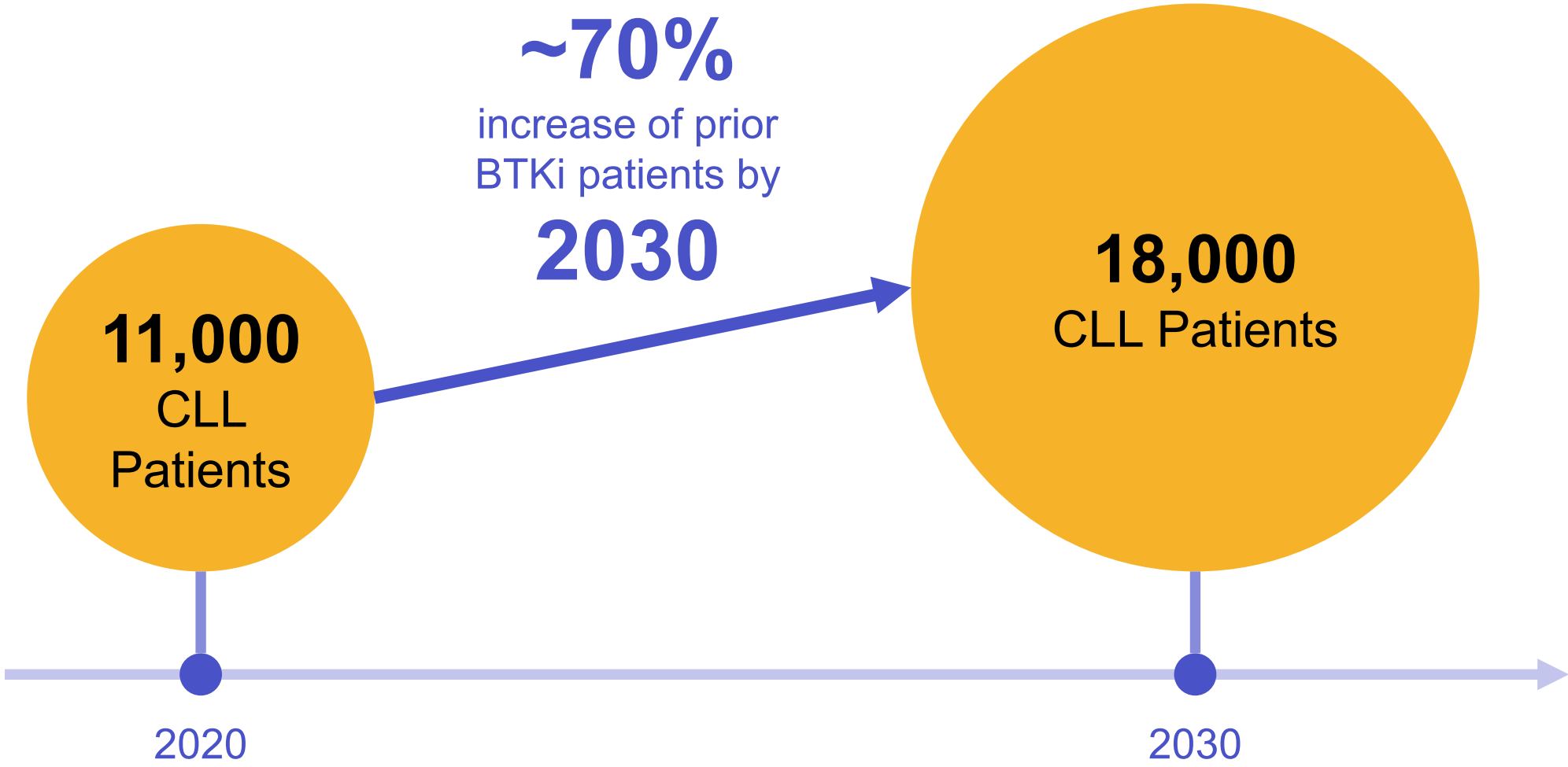
Potential Positioning of Nurix BTK Degrader Franchise Across All Lines of Therapy in CLL

Diagnosis
Treatment
Future
Positioning



CIT = chemoimmunotherapy

Considerable Growth in CLL Patients Previously Treated with BTK Inhibitors



NX-2127 Path to Market and Expansion

Initial Opportunity

- Clear unmet need in later lines of CLL per FDA at recent ODAC meeting
- Third-line double-exposed CLL (post-BTKi and post-venetoclax)
- Potential accelerated approval path for single study
- Growth in earlier lines as BTKi-resistance mutations grow in prevalence

Expansion

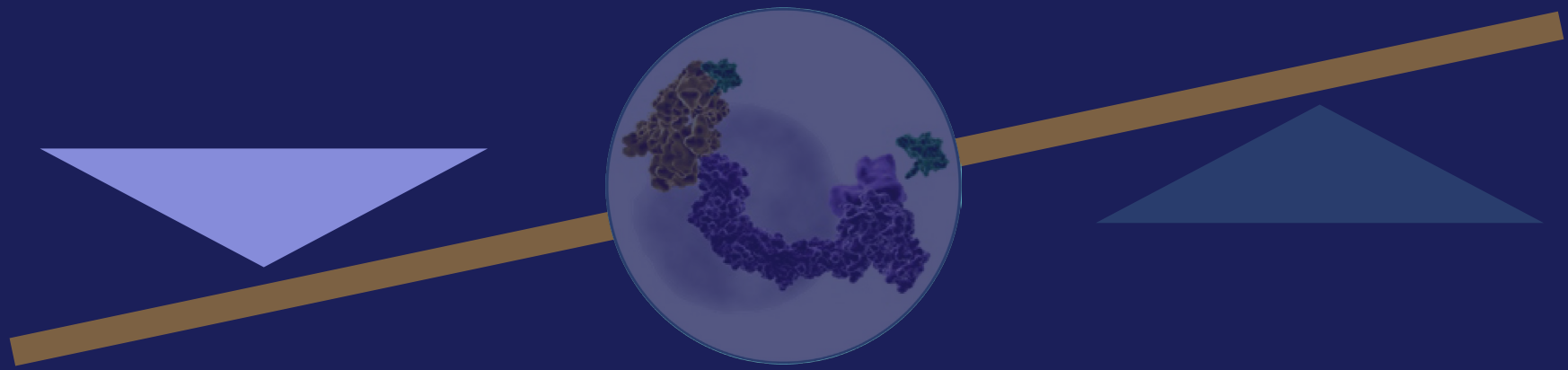
- Earlier line CLL if degradation and dual activity drive superior responses
- MCL for high unmet need where current therapies have limited efficacy
- Treatment resistant tumors
- DLBCL and FL if proof of concept for dual degrader can expand beyond typical BTK-sensitive tumor types

Nurix Is Creating a BTK Degrader Franchise: NX-2127 and NX-5948

- Potential for BTK degraders to take share from established, blockbuster markets (BTK inhibitors and anti-CD20s)
- Nurix is the leader in this new modality – BTK degradation
- Multiple pathways for success in hematology/oncology
- Autoimmune indications remain wide open for novel B-cell targeted modalities
- Franchise of multiple BTK degraders
  - ⇢ Address multiple markets and needs
  - ⇢ Maximize share with differentiated product profiles
  - ⇢ Establish beachheads in unmet need and expand

Q&A

BTK Portfolio and CLL



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Leader in Targeted Protein Modulation

First Targeted Protein Elevation Drugs in Immuno-Oncology

NX-1607 & DeTIL-0255

R&D Day
New York, NY
May 26, 2022

CBL-B: Master of the Immune Response

Cristiana Guiducci, PhD
SVP, Immunology and Oncology Research
Nurix Therapeutics

First-in-Class Targeted Protein Elevation Drugs

CBL-B Inhibitors

Rationale for targeting CBL-B in oncology

Highlight the properties and mechanism of action of Nurix's CBL-B inhibitors

Development of highly optimized proximal biomarkers and their use in the clinic

NX-1607-101 initial clinical experience

A Better Immuno-Oncology Target:
A CBL-B Inhibitor Can Revolutionize Cancer Treatment

- The ultimate goal of cancer immunotherapy is to generate a coordinated immune system response against cancer associated antigens
- Immune checkpoint agents such as anti-PD-1/PD-L1 have demonstrated impressive long-lasting responses in only a subset of patients
- Resistance mechanisms prevent most patients from responding:
  - ⇢ Low antigen presenting cells and NK cells within the tumor
  - ⇢ Tumor microenvironment not permissive to T cell trafficking in the tumor
  - ⇢ Excessive T cell exhaustion from chronic antigen stimulation
  - ⇢ Downregulation of MHC Class I
- CBL-B inhibitors are optimal next generation IO agents: act on multiple immune cells, addressing multiple resistance mechanisms

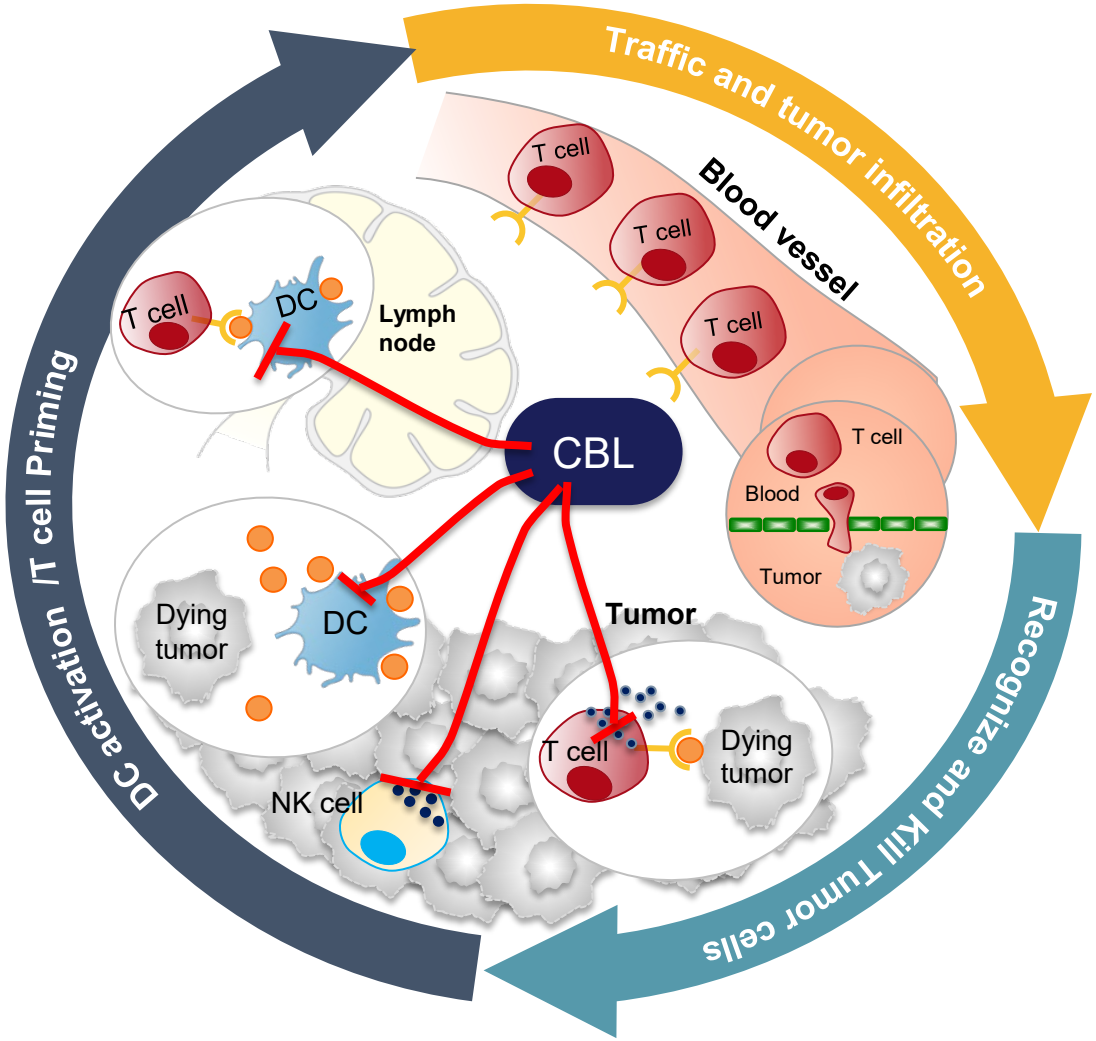
Targeting CBL-B Enhances Antitumor Response

A Master Orchestrator of the Immune System

CBL-B mediated mechanisms strongly restrains a productive anti-tumor response

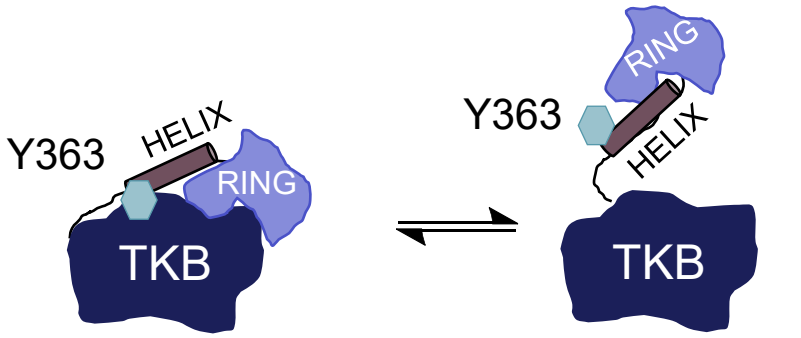
CBL-B inhibition increases:

- DC and NK infiltration and function
- T cell priming
- Cytotoxic T cells function
- Ability of T cells to resist tumor immunosuppressive mechanisms: Treg, MDSC, and TGF-β



NX-1607 Mechanism of Action: Intramolecular Glue

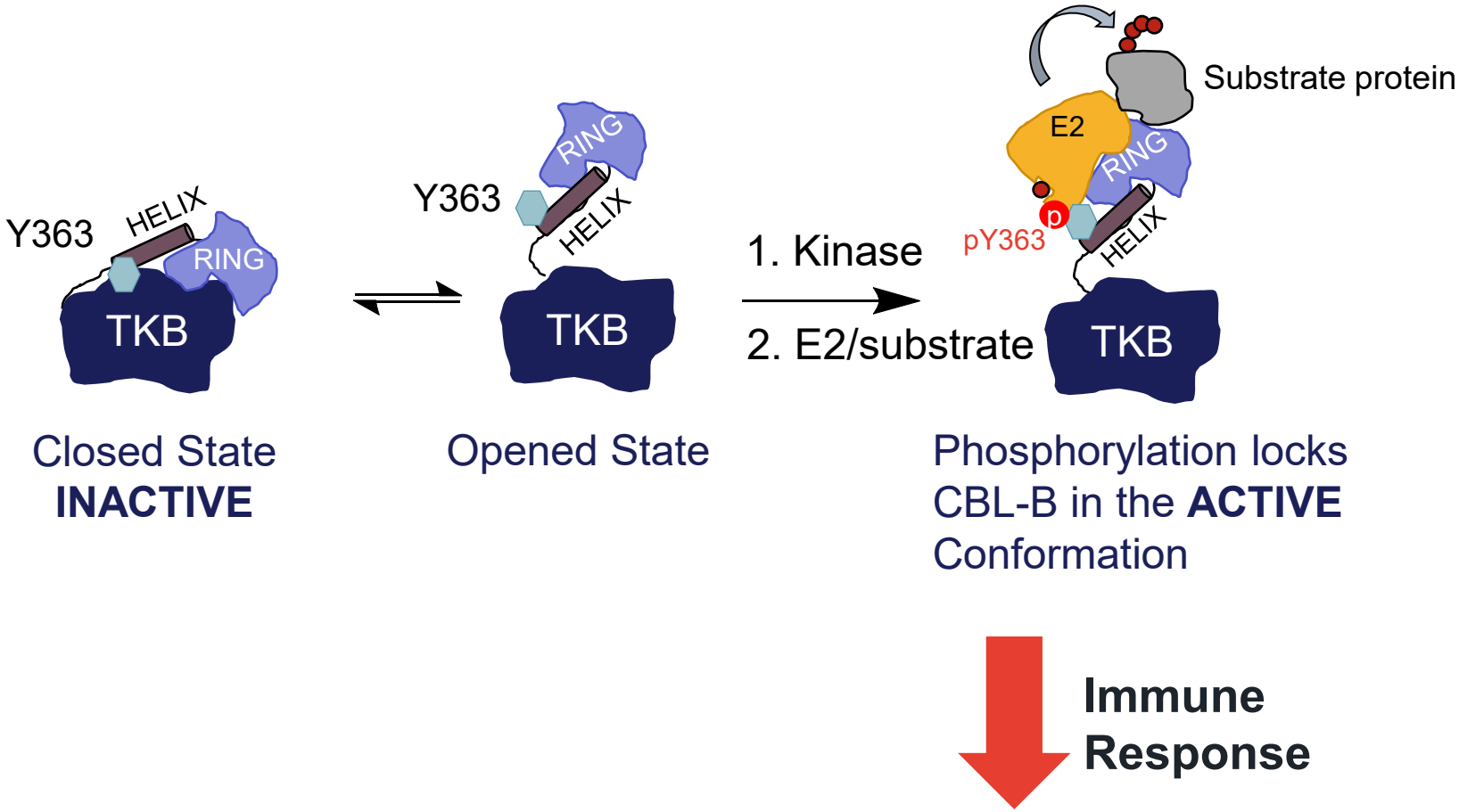
CBL-B is in Equilibrium Between Closed and Opened State



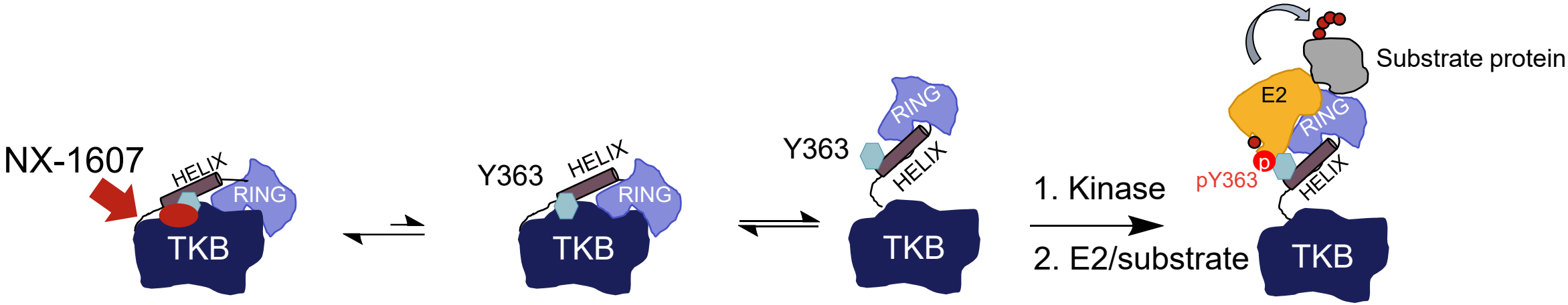
Closed State
INACTIVE

Opened State

NX-1607 Mechanism of Action: Intramolecular Glue



NX-1607 Mechanism of Action: Intramolecular Glue



NX-1607 acts as an intramolecular glue forcing CBL-B in its folded **INACTIVE** state

Closed State **INACTIVE**

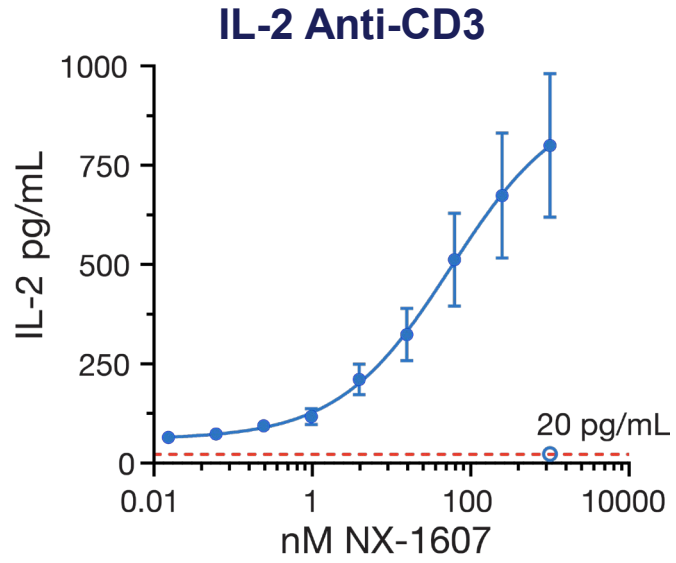
Opened State

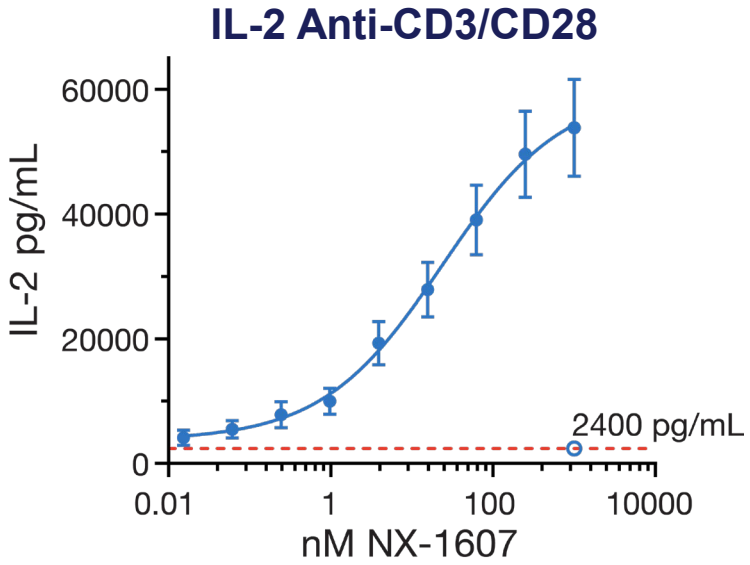
Phosphorylation locks CBL-B in the **ACTIVE** Conformation

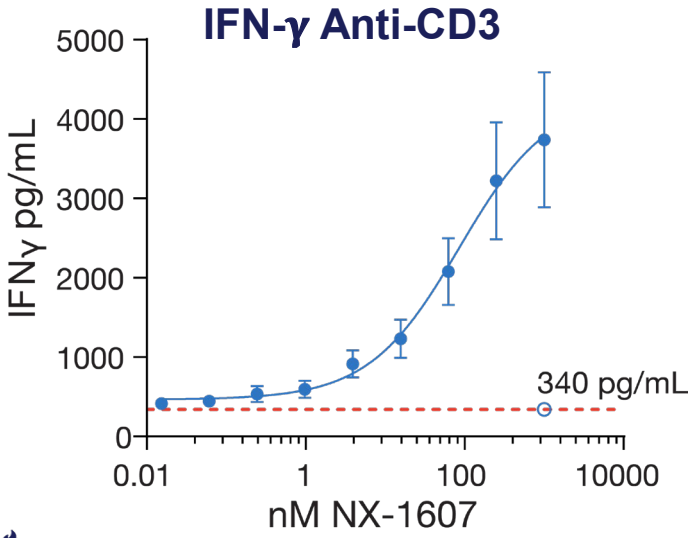
Immune Response

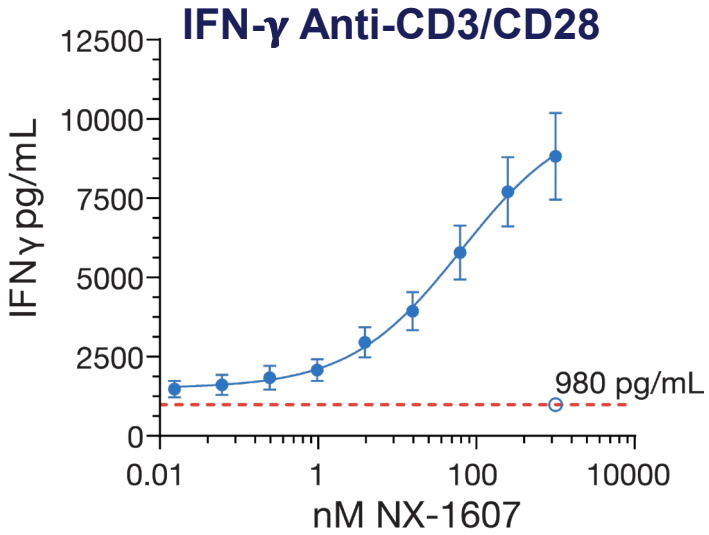
Immune Response

NX-1607 Increases IL-2 and IFN-γ Secretion in TCR Stimulated Primary Human T cells









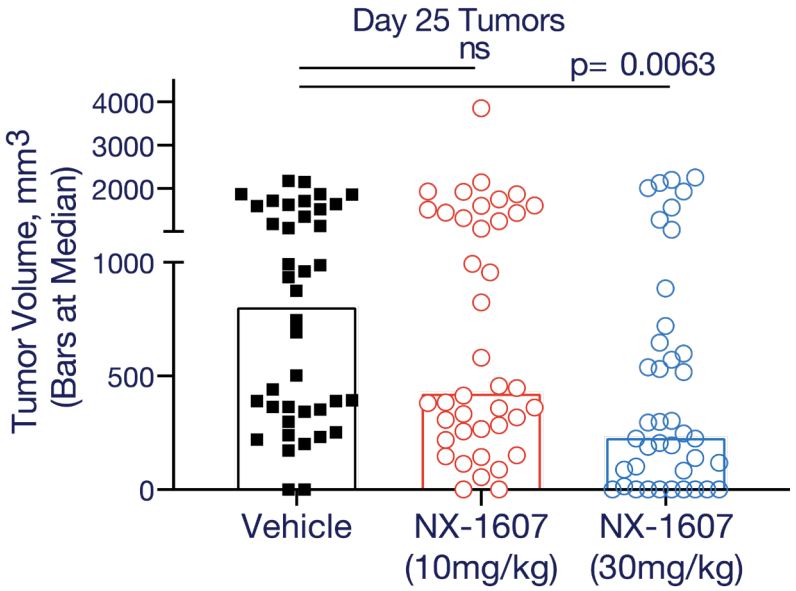
NX-1607 increases TCR stimulation-dependent production of IL-2 and IFN-γ in primary human T cells

NX-1607 has no impact in the absence of T cell stimulation as measured by proliferation, activation, or cytokine release

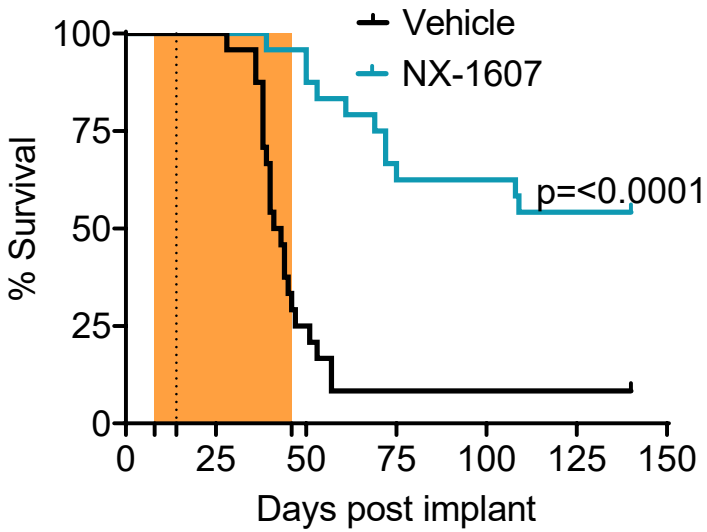
Cytokine Response
Baseline Response

Single-Agent NX-1607 Induces Antitumor Response in Multiple Models

NX-1607 Reduced Tumor Volume
Colorectal

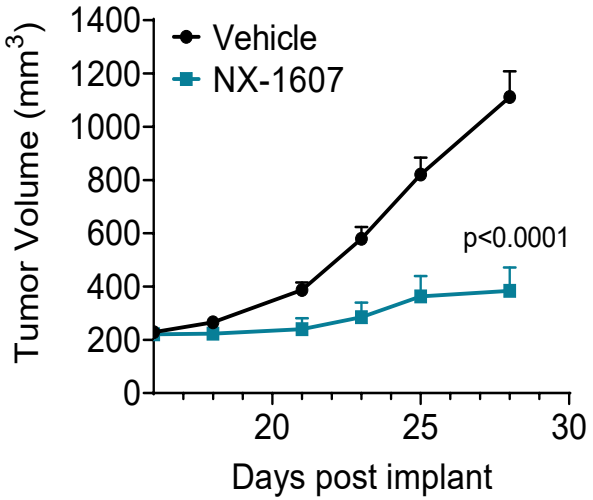


NX-1607 Prolonged Survival
Triple-Negative Breast



NX-1607 30 mg/kg day 7 to 46

NX-1607 Reduced Tumor Volume
B Cell Lymphoma

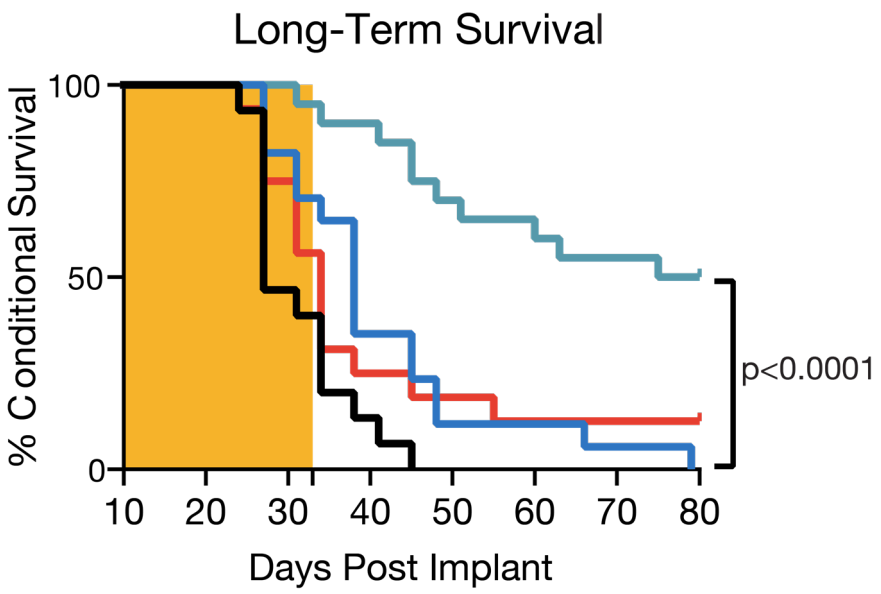


NX-1607 30 mg/kg day 16 to 28

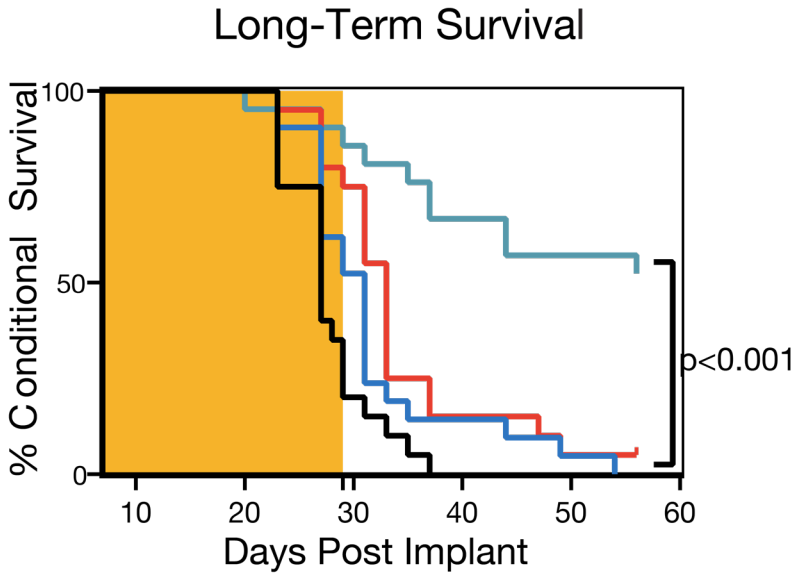
Shaded area indicates dosing period

NX-1607 and Anti-PD-1 Synergize to Enhance Anti-tumor Effects and Survival of Mice in Multiple Tumor Models

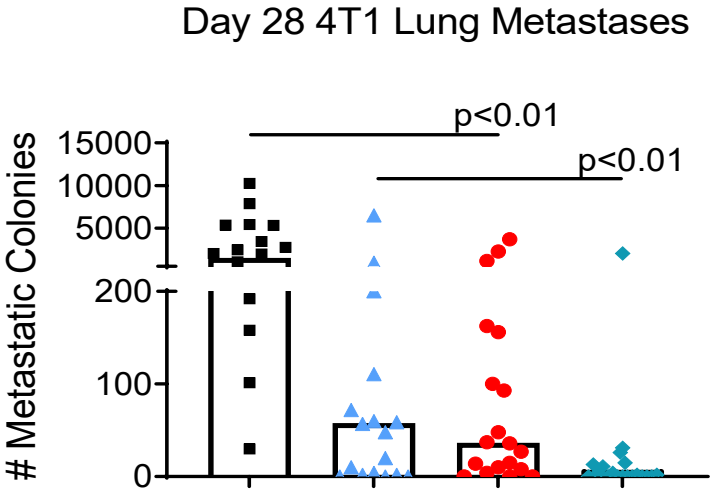
Colorectal (CT26)



Colorectal (MC38)

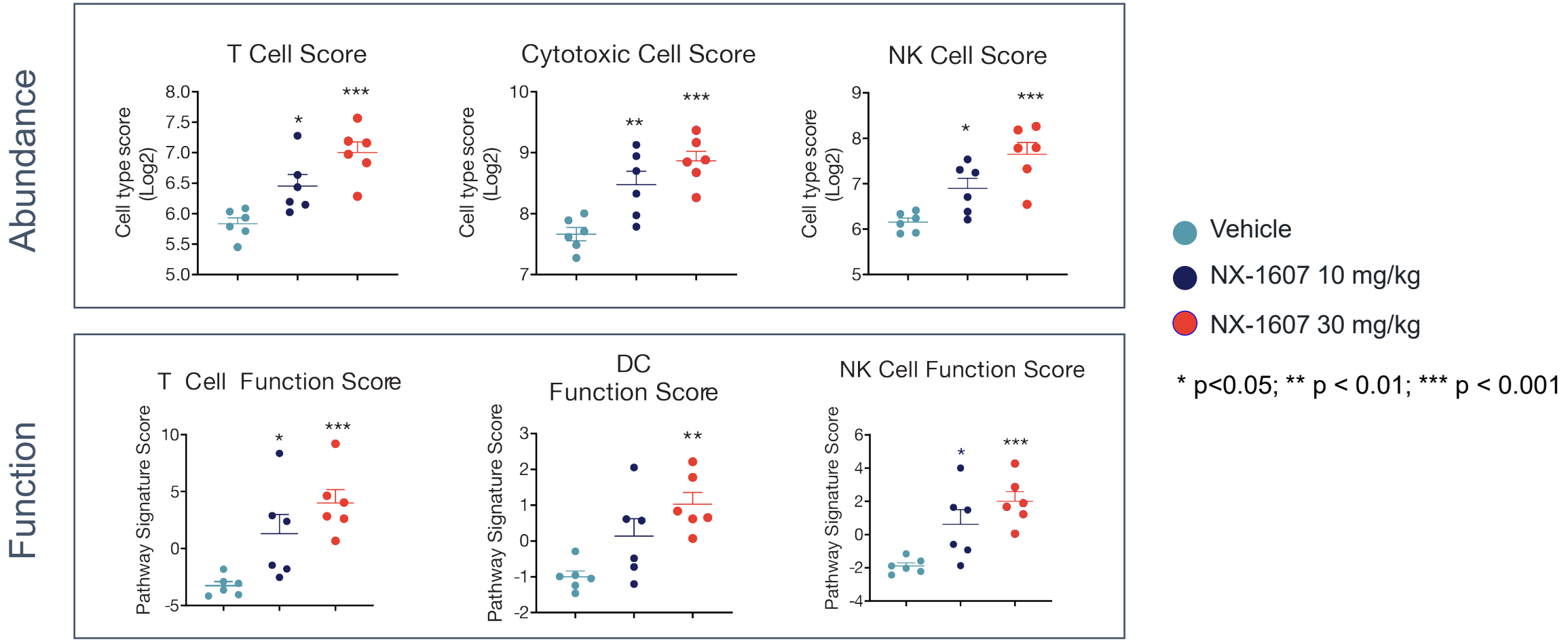


Triple-Negative Breast (4T1)



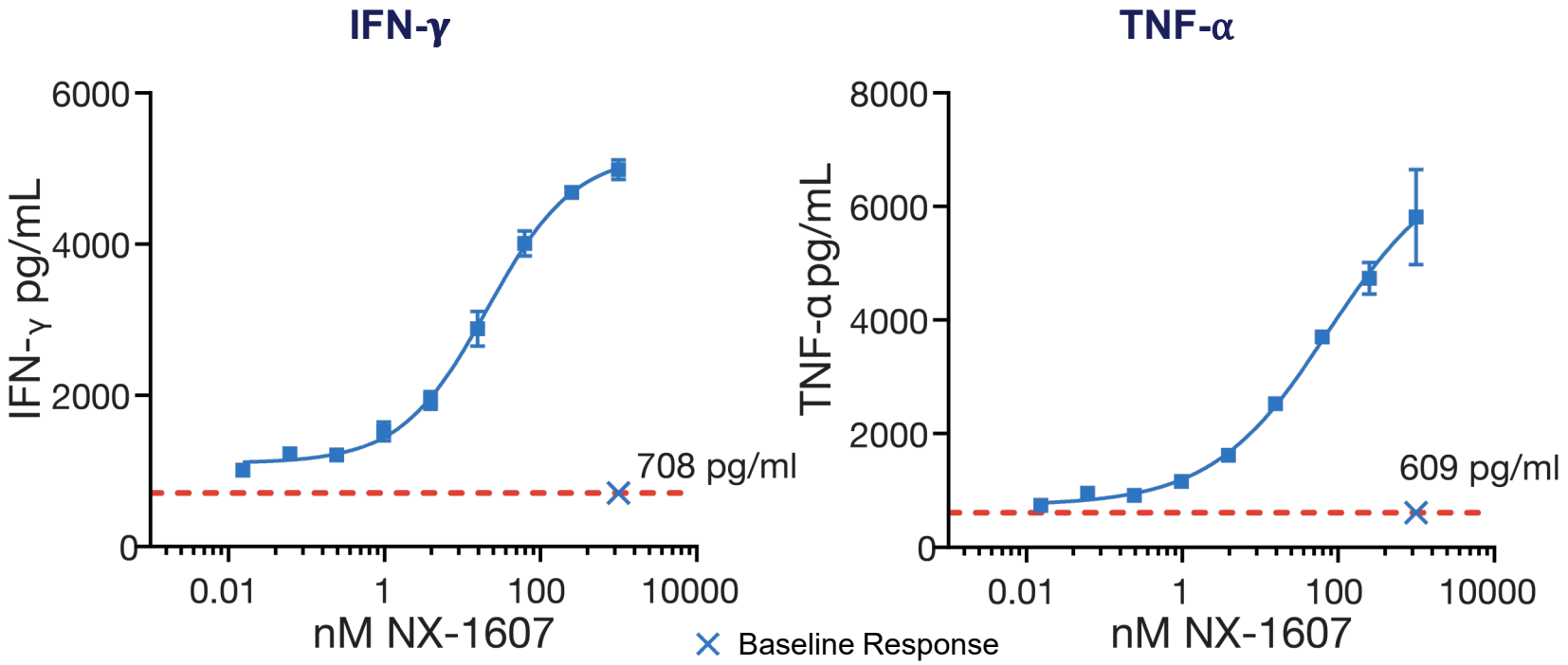
Shaded area indicates dosing period: NX-1607 (30 mg/kg, PO daily) and anti-PD-1 twice a week at 10 mg/kg dosing period

NX-1607 Treatment Induces Dose Dependent T and NK Cell Intratumoral Infiltration and Enhanced Function



Tumor-bearing mice treated for 18 days with NX-1607 at 10 or 30 mg/kg. Tumor microenvironment profiled using NanoString technology.

NX-1607 Increases Secretion of Pro-Inflammatory Cytokines in Human NK cells



NX-1607 increases stimulation-dependent production of IFN-γ and TNF-α in primary human NK cells

NX-1607 has no impact in the absence of NK cell stimulation, as measured by cytokine release

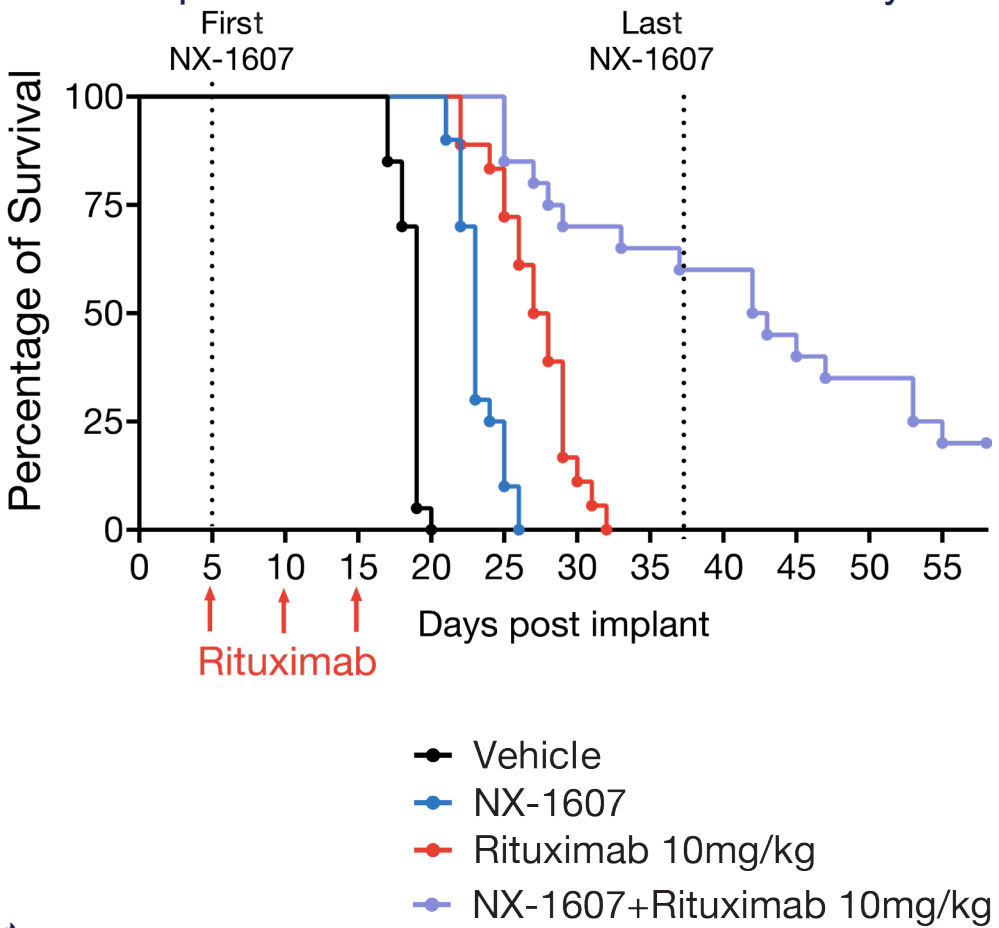
NK K562 Killing Assay

- 1 hour compound pre-treatment prior to addition of K562s target cells
- 6 hour NK/K562 coculture

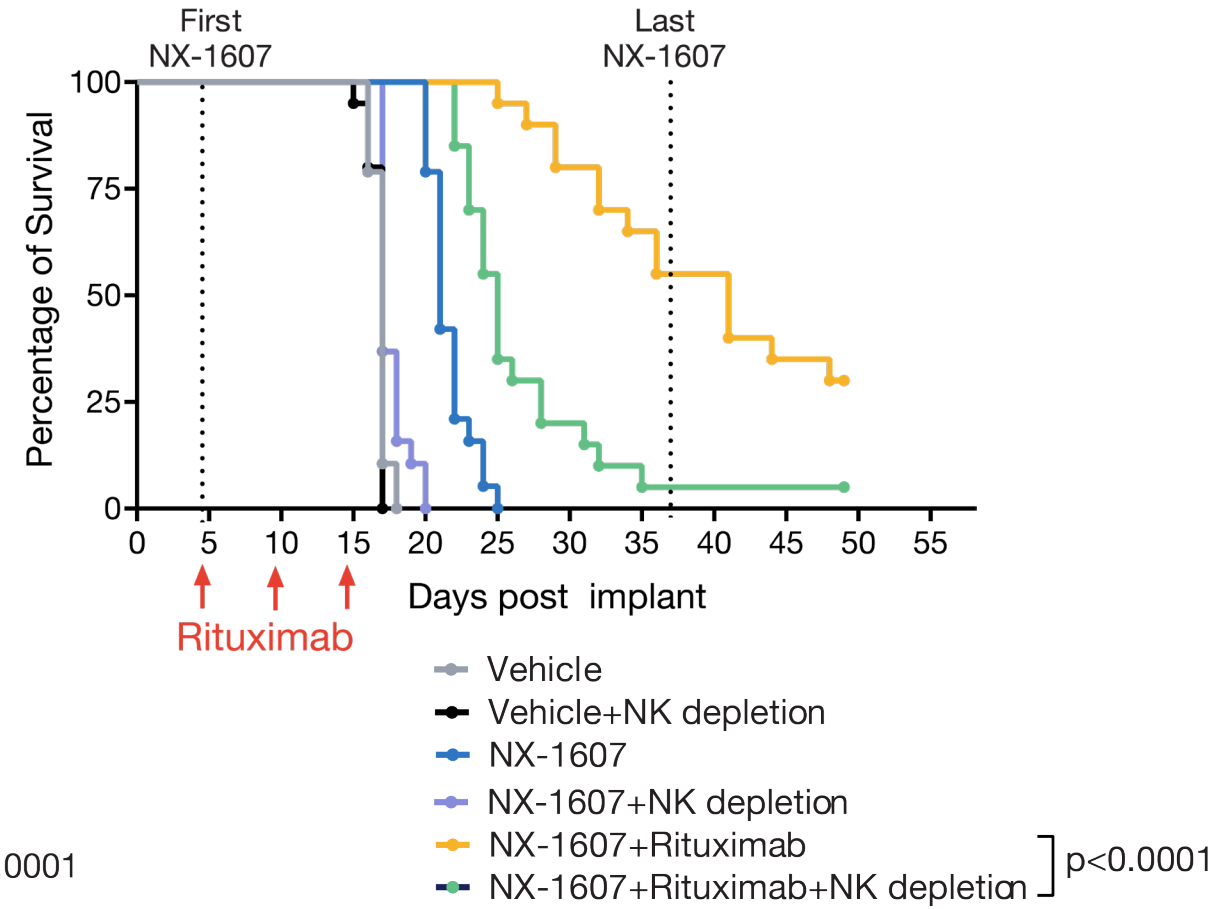
Combination of NX-1607 and Rituximab Enhances Anti-tumor Activity in a Human NHL Animal Model

NX-1607 Strongly Potentiate Rituximab-Directed NK Cell ADCC Against Tumor Cells

NX-1607-mediated NK activation potentiates rituximab antitumor activity



NK depletion abrogates NX-1607 and NX-1607 + Rituximab antitumor activity



NX-1607: Biomarkers that Light the Way

Robert J Brown, MD
EVP, Head of Clinical Development
Nurix Therapeutics

What Makes a Good Clinical Biomarker?

- Proximal to the target
- Dose-responsive
- Directly relates to the biologic mechanism of action
- Translates from animal models to humans

As the first to target CBL-B, Nurix is leading the field in biomarker discovery for this new mechanism of action

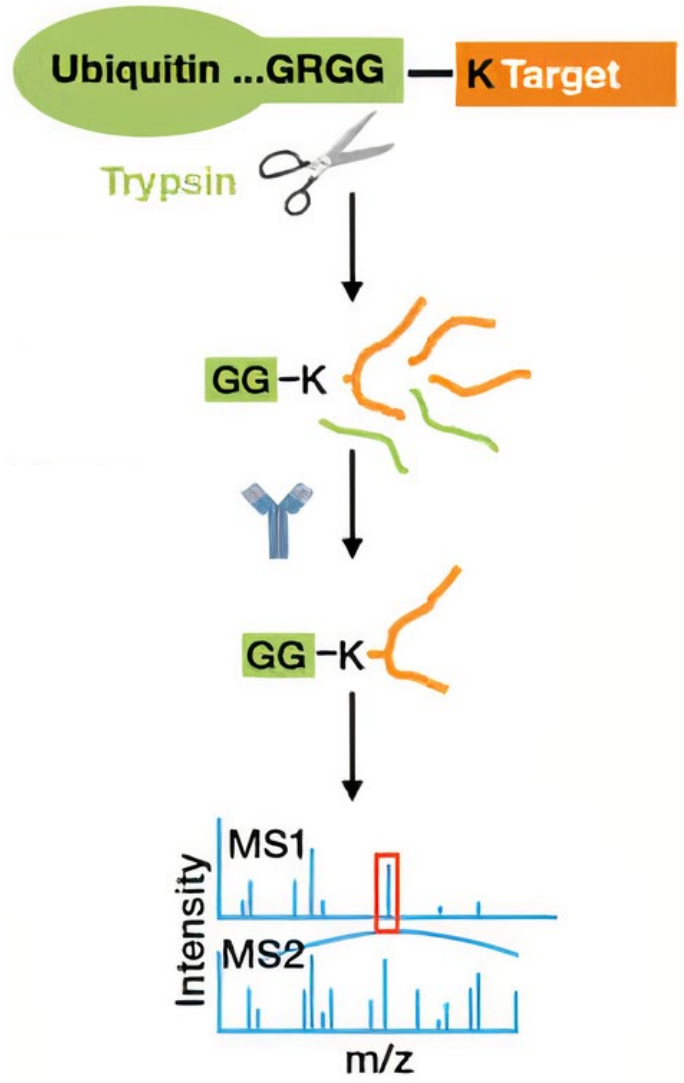
Proprietary Biomarkers Measure CBL Inhibition

- Agnostic screening campaigns identified robust, reproducible and novel proximal biomarkers of CBL-B inhibition
  - ⇢ Ubiscan identified direct ubiquitination substrates of CBL-B E3 ligase
  - ⇢ Phosphoscreen demonstrated increased levels of activated proteins caused by CBL-B inhibition
- Nurix developed robust assays to detect multiple propriety proximal biomarkers of CBL-B inhibition in peripheral blood
- In animal models, changes in these biomarkers correlated with anti-tumor efficacy and informed Phase 1a dose levels
- Dose-proportional biomarker changes are observed in our ongoing Phase 1a trial

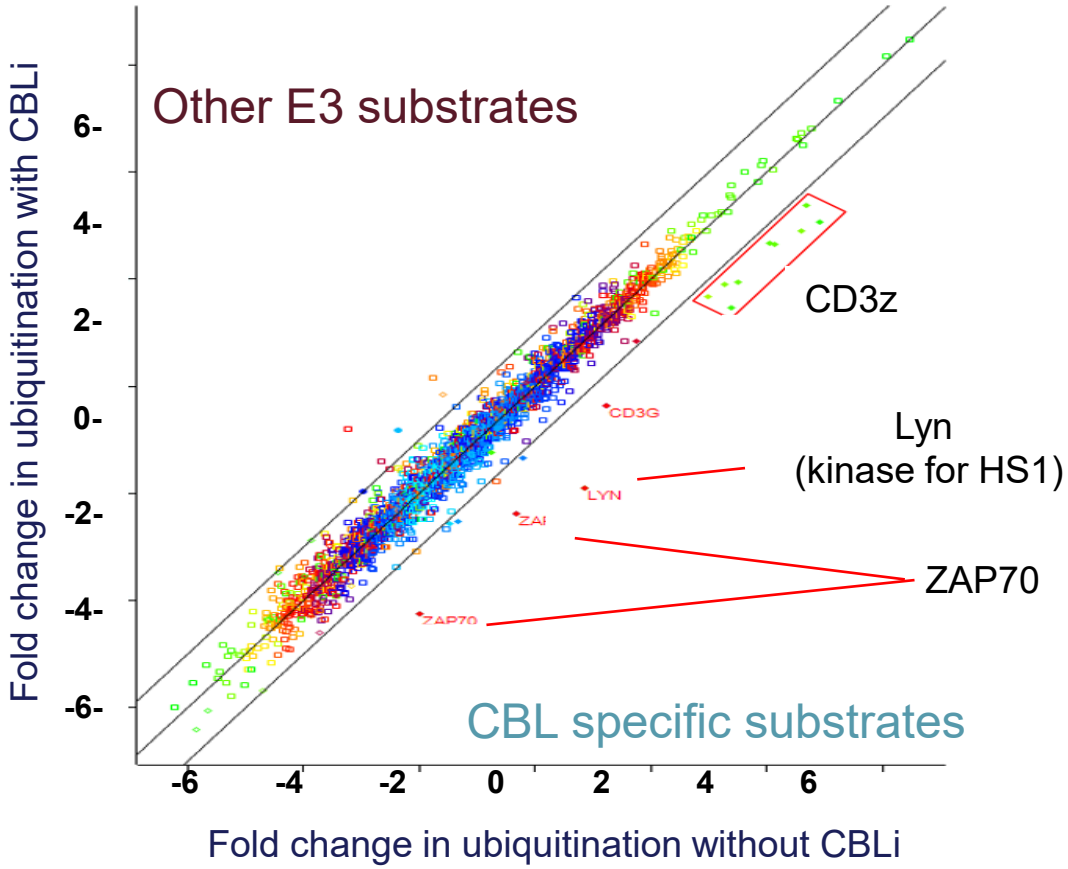
UbiScan Is a Method to Identify Direct Ubiquitination Substrates

1. CBL-B ubiquitinates proteins and targets them for degradation
2. Proteins that are ubiquitinated can be detected by ubiscan because they have GG or “diGly scar”
3. Antibodies recognizing the “scar” can be used to isolate CBL-B targeted proteins which are identified using mass spectroscopy
4. Inhibition of CBL-B decreases the ubiquitination of CBL-B substrates

Overview of UbiScan Technology



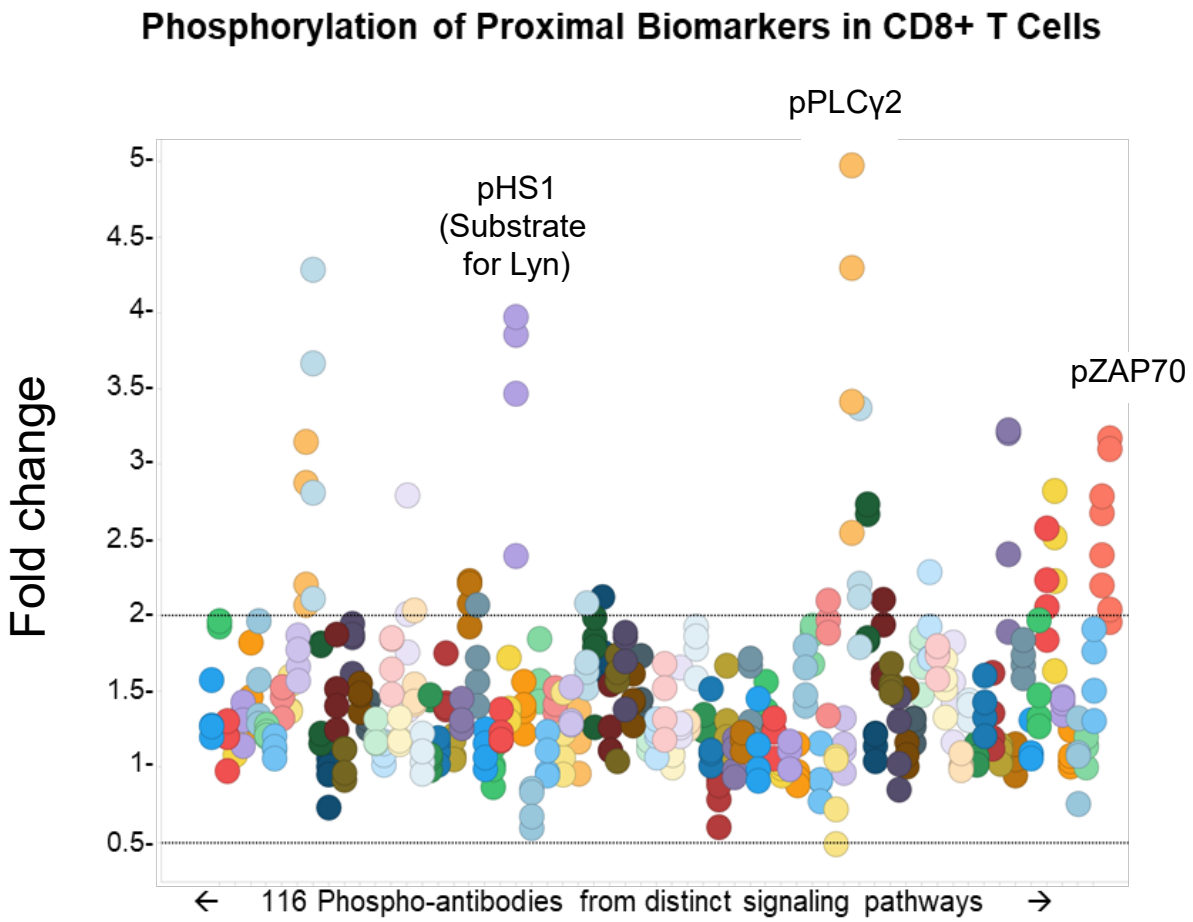
UbiScan Identified Direct CBL Substrates Within the T Cell Receptor (TCR) Signaling Cascade



Decreased signal represents direct substrates ubiquitinated by CBL-B ligase activity

Inhibiting CBL-B decreases ubiquitination of important T Cell receptor signaling molecules

Phospho-Protein Flow Cytometry Assay Identified Proximal Biomarkers



- Stimulated human PBMCs with or without CBL-B inhibition
- Cells were stained with a panel of phospho-specific antibodies for proteins downstream the TCR signaling
- Expression levels were assessed by flow cytometry
- Overlapping results from orthogonal assays (Ubiscan) provided confidence in proximal biomarker signals

Signals Identified in Ubiscan & Phosphoscreen Were Specific to Stimulated T Cells

In presence of CBL inhibitor, stimulation of the TCR results in the phosphorylation of:

ZAP70

- Key organizer of downstream TCR signaling

PLCγ2

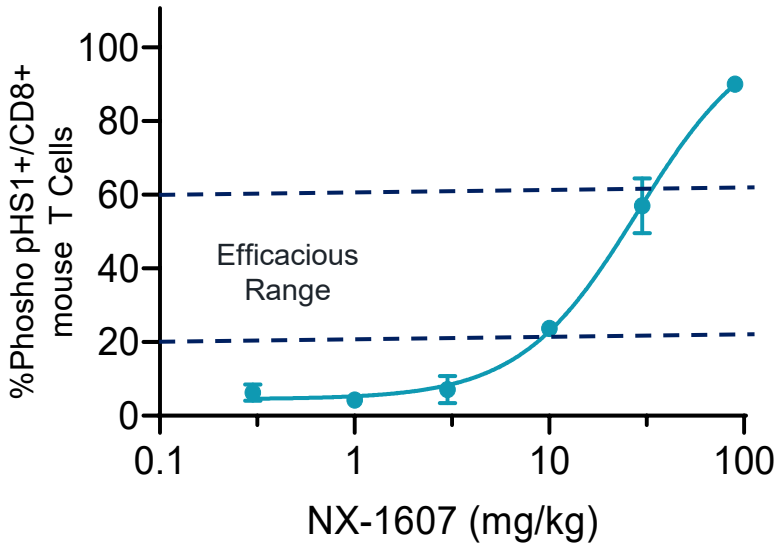
- Expressed in both T cells and B cells
- Associates with LAT and SLP-76 & becomes phosphorylated upon TCR stimulation

HS1

- Substrate of LYN receptor, and an essential actin-regulatory adaptor protein at the immune synapse, via VAV1

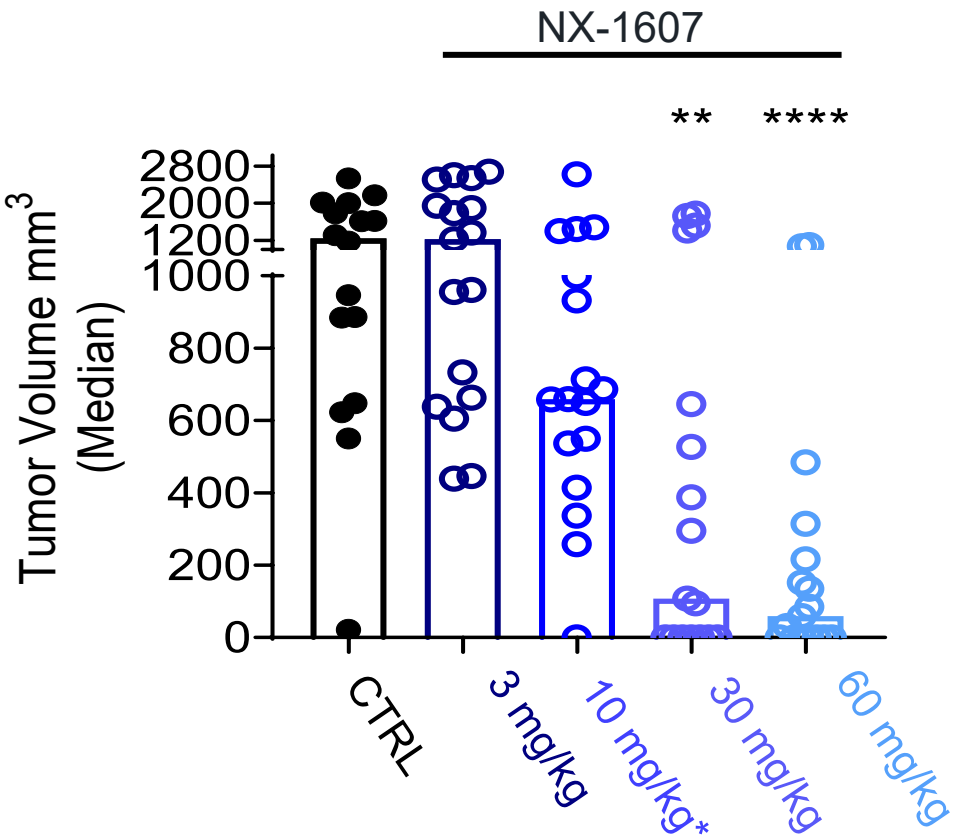
Dose Dependent Increases of CBL-B Proximal Biomarker Correlates with Antitumor Effects of NX-1607

Pharmacodynamic relationship in mice following NX-1607 dosing



In vivo efficacy observed between 10-60 mpk which corresponds to ~20-60% pHS1+ CD8+ T Cells

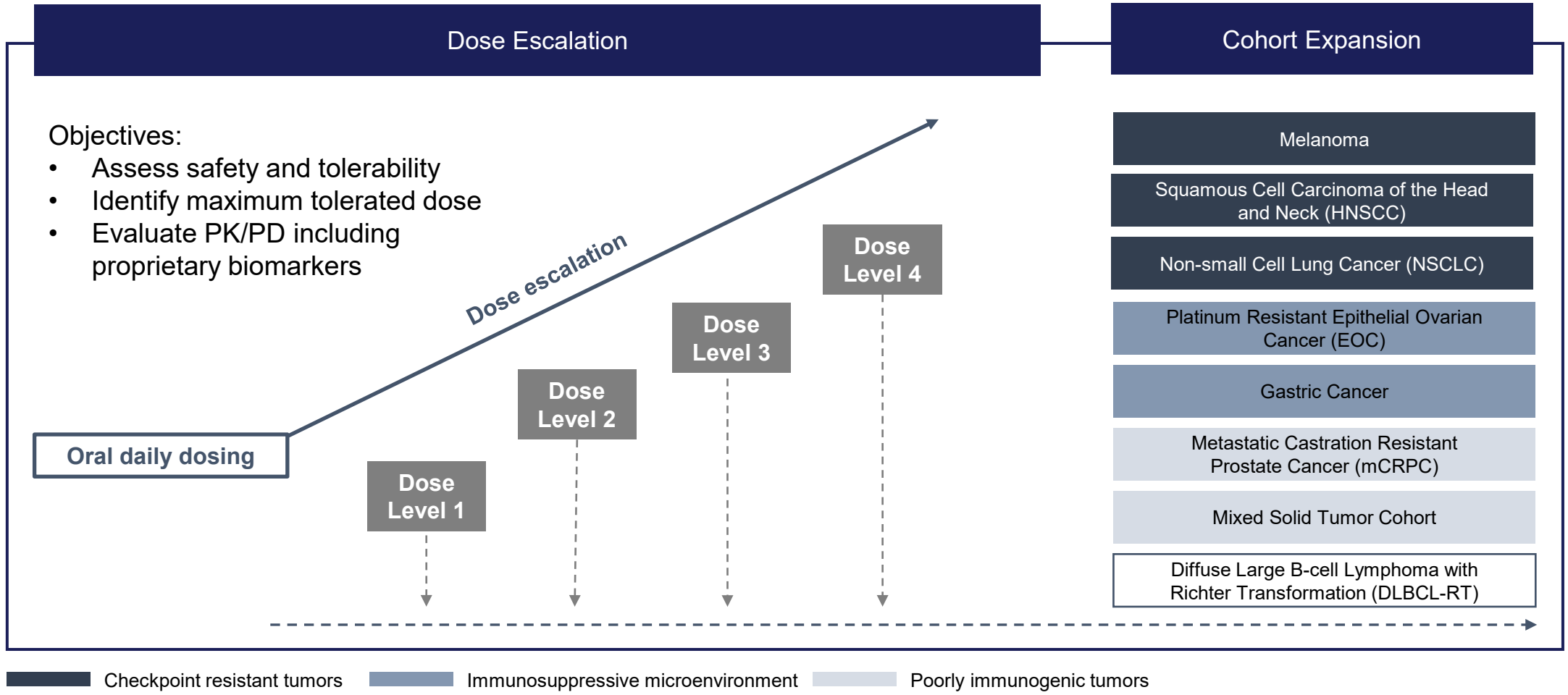
Antitumor activity in mice



A20 - B cell lymphoma model

NX-1607-101: Phase 1 first-in-human clinical trial design

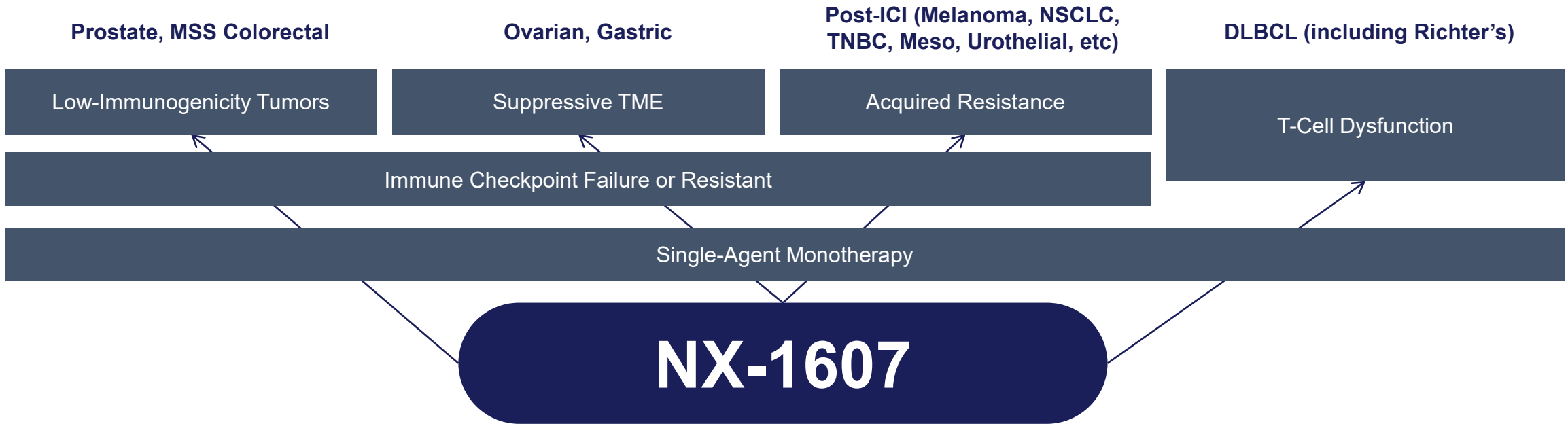
Two-Part Phase 1 Monotherapy Trial of NX-1607 in Relapsed or Refractory Tumors



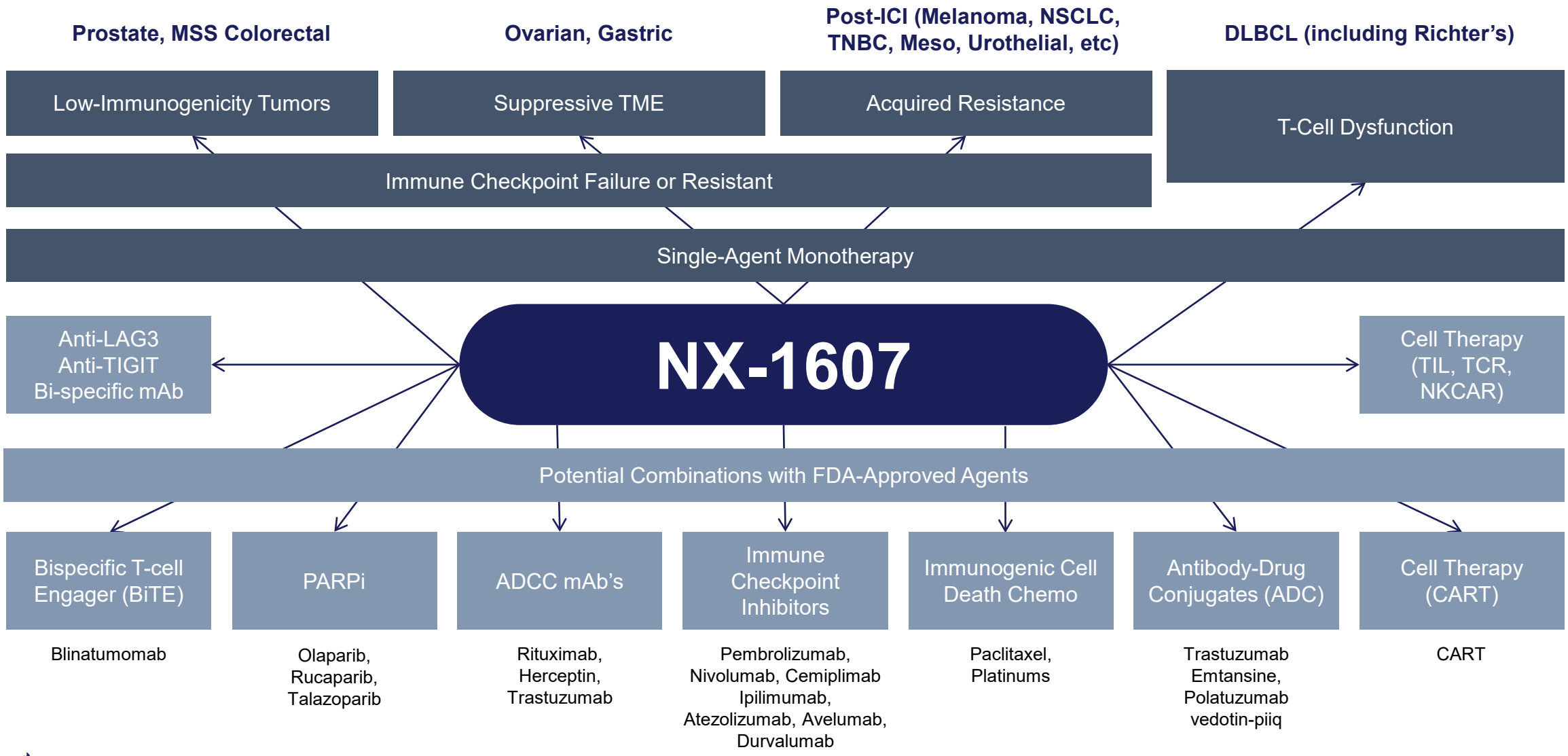
NX-1607-101 Initial Clinical Experience

- Dose escalation is ongoing
- Consistent with preclinical models, we are observing dose-dependent increases of proximal biomarkers
- Expect to select Phase 1b dose in H2 2022
- Clinical update in mid-2022 will report PK and biomarkers

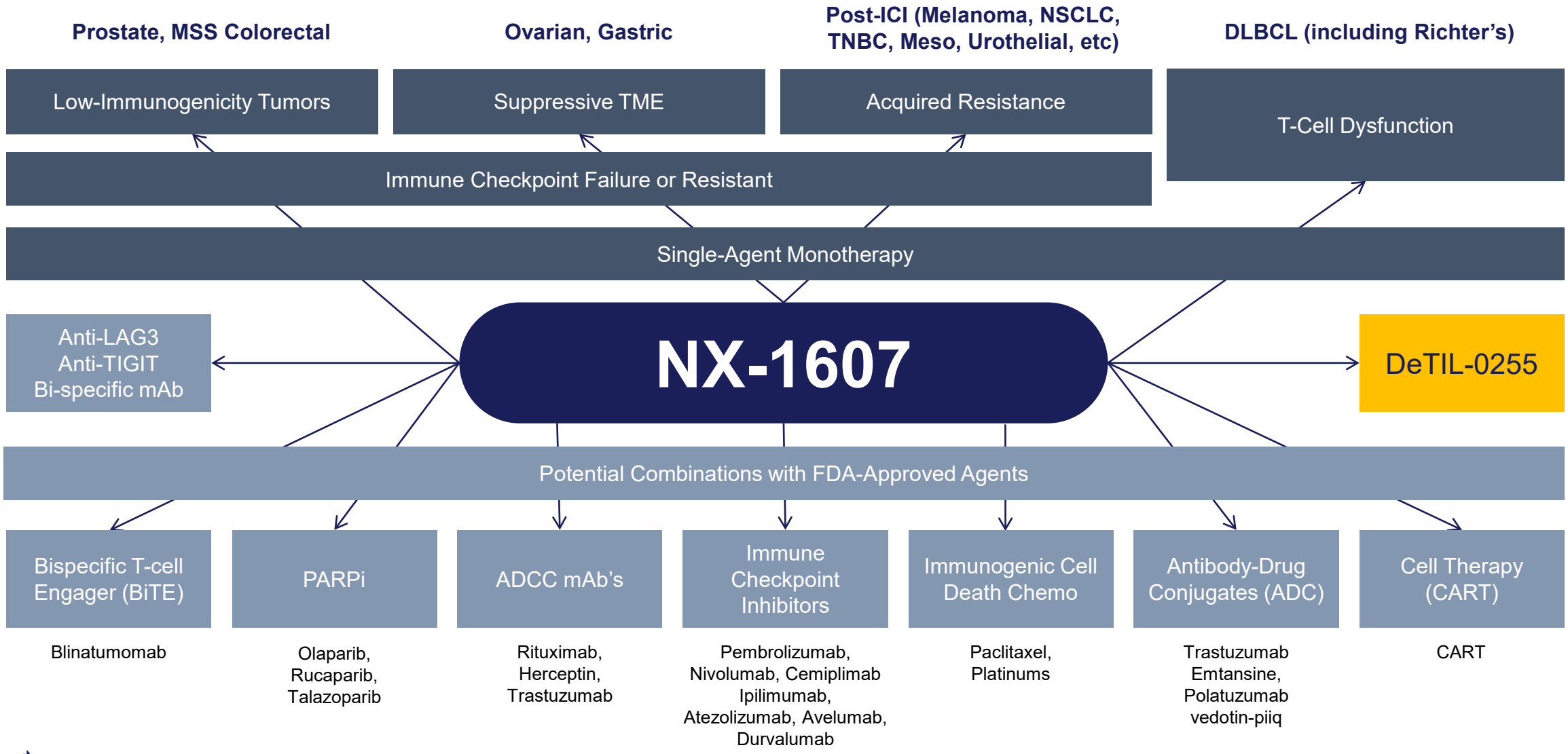
CBL-B Inhibition Has the Potential To Be the Small Molecule Centerpiece of Immuno-Oncology Therapy



CBL-B Inhibition Has the Potential To Be the Small Molecule Centerpiece of Immuno-Oncology Therapy



CBL-B Inhibition Has the Potential to Be the Small Molecule Centerpiece of Immuno-Oncology Therapy

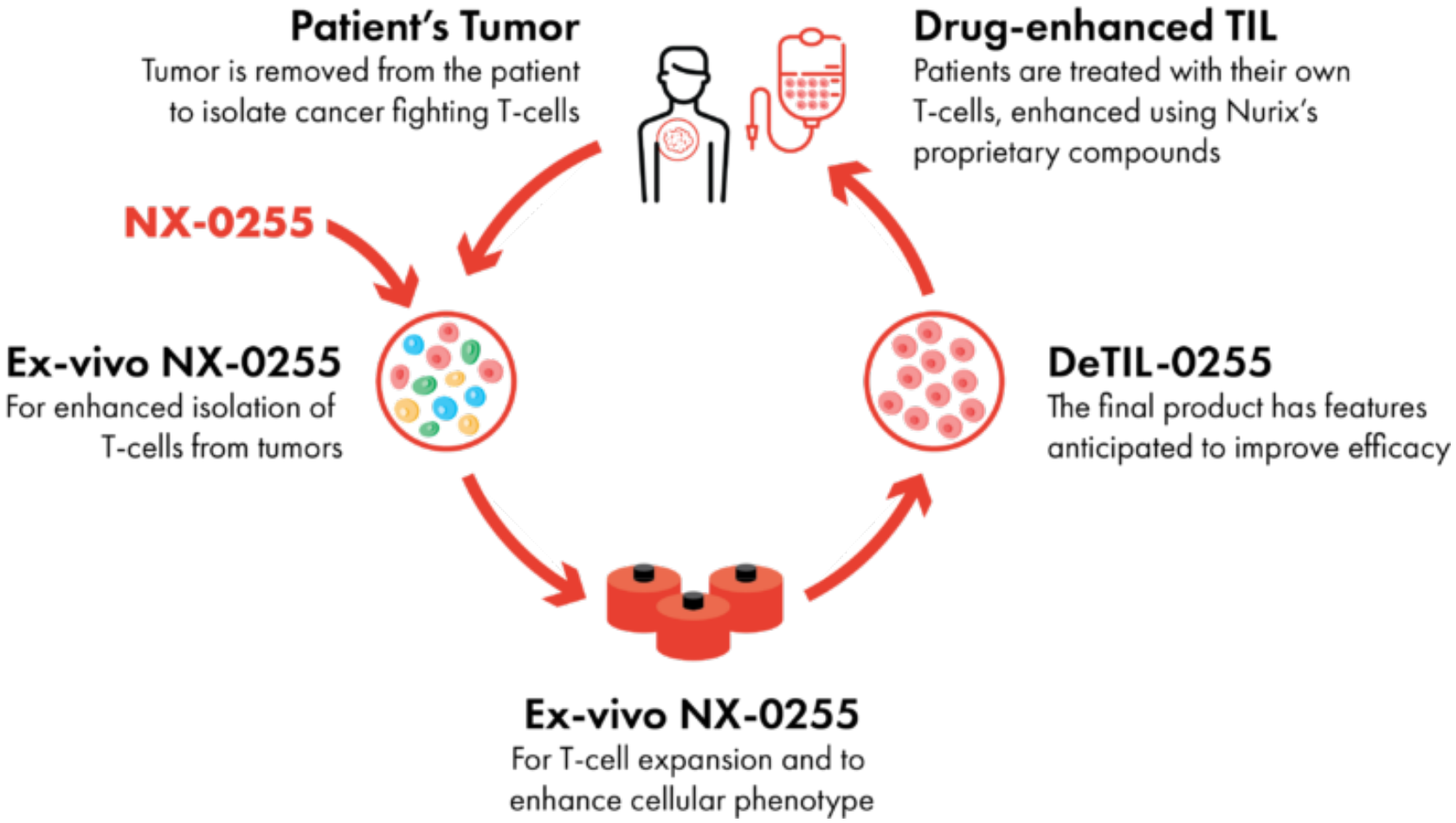


DeTIL-0255: Drug Enhanced Cell Therapy in the Clinic

Michael T Lotze, MD, FACS
Chief Cellular Therapy Officer
Nurix Therapeutics

Drug-Enhanced Tumor Infiltrating Lymphocytes (DeTIL-0255)

A one-time patient-derived cell therapy



Tumor Infiltrating Lymphocytes (TIL) – T Cell Therapy with Durable Responses and Potential to Cure Patients with Solid Tumors

Sponsor	TIL for Patient with Metastatic Melanoma	N	ORR	CR%	Median OS
NCI US	Autologous Reactive TIL	43	**49%**	12%	62
NCI US		51	**45%**	24%	36.6
NCI US		20	**35%**	5%	n/a
Sheba Israel	Unselected TIL	57	**40%**	9%	15.2
Herlev Denmark	Unselected TIL; IL-2 Decrescendo	25	**42%**	12%	21.8
MD Anderson US	Unselected TIL	74	**42%**	11%	17.3
Iovance US	Unselected TIL	66	**36%**	3%	17.4

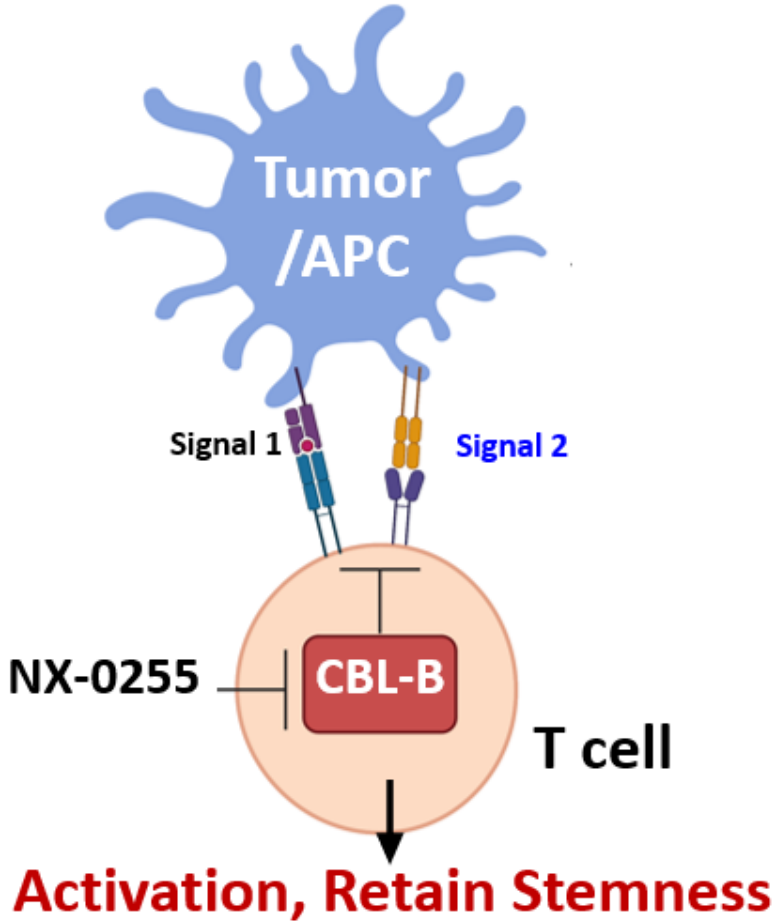
TIL Administration Has Been Less Effective in the Post-Checkpoint Setting For Patients With Solid Tumors

- TIL has the potential to cure patients with solid tumors
- Checkpoint inhibitor therapy has reduced the efficacy of subsequent TIL administration
- The current TIL regimen is not suitable for most solid tumor patients
- TIL cell exhaustion due to continuous antigen exposure and lack of suitable intra-tumoral dendritic cells (lack of costimulatory molecules) leading to:
  - ⇢ Suboptimal manufacturing success rate
  - ⇢ Poor persistence of T cells
  - ⇢ Unpredictable efficacy and durability

DeTIL-0255: Cell Therapy Product Designed To Overcome Major Limitations of Current TIL Therapy

Desirable phenotype with mixture of increased stem-like T cells *and* potent effector T cells

DeTIL-0255 can integrate effectively in a regimen for patients with virtually any cancer type



More Effective Expansion of Potent and Stem-like Human DeTIL-0255 Compared with TIL

- Increased diversity, cell number, and stem-like properties
- Decreased exhaustion
- Enhanced effector function
- Increased activation

Exhaustion	
Marker	% of CD8+
Total PD-1+	↓
Total PD-1+ TIM-3+	↓
Total PD-1+ LAG-3+	↓

Cytotoxic Function	
Marker	Absolute No. of CD8
CD107a+	↑
GrB+	↑
Perforin+	↑
CD107a+ GrB+	↑
CD107a+ Perforin	↑
GrB+ Perforin	↑
GrB+ Perforin CD107A+	↑

Chemokine Secretion	
Secretion	pg/mL
RANTES	↑
MCP-1	↑
IL-8	↑

Cytokine Secretion	
Secretion	pg/mL
7 CRS-associated cytokines (IL-2, IL-4, IL-6, IL-9, IL-10, IFN-γ, TNF-α)	—

Tumor Reactivity	
CD8	% of CD8+
Total 41BB+	↑

- Increased CD226/DNAM expression

Arrows indicate a statistically significant ($P<0.05$) change in DeTIL-0255 compared with TIL.
CRS, cytokine release syndrome; DeTIL-0255, drug-enhanced tumor-infiltrating lymphocytes; GrB, granzyme B; IFN-γ, interferon gamma; IL, interleukin; LAG-3, lymphocyte-activation gene 3;

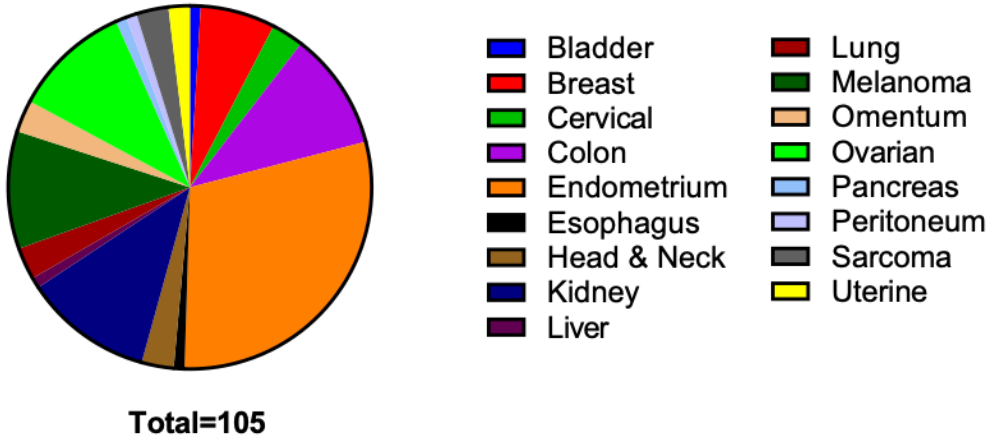
Whelan et al Poster 98 SITC 2021

Potency Assay Prospectively Designed to Meet Regulatory Requirements

- Tumor-specific
- Demonstrates the biologic activity of DeTIL-0255
- Reproducible
- Developed prospectively
- Matrix testing of DeTIL-0255 properties including phenotype and function
- Ongoing validation in our clinical trial

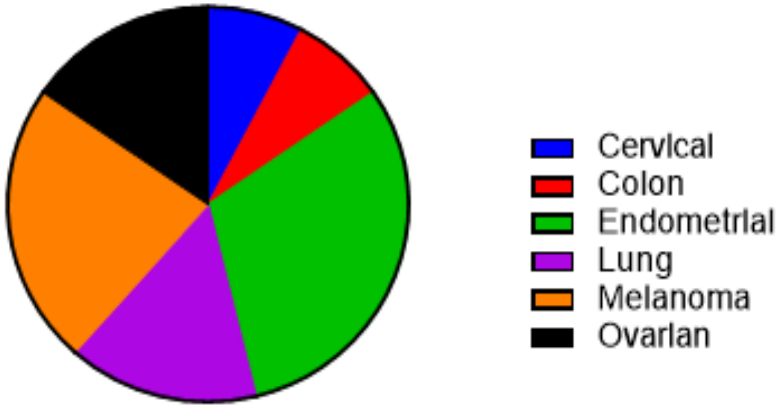
Universal DeTIL-0255 Expansion Allowing Application to Multiple Tumor Types

Pilot Runs



Total=105

Full-scale runs



Total=13

All tumors harbor TIL which can be expanded in pilot and full-scale runs

Pilot scale:
100% of 105 tumors demonstrate T cell expansion

Full-scale:
100% of 13 tumors demonstrate successful DeTIL-0255 production

Introduction of DeTIL-0255 into the Clinic

- Drug-enhanced TIL product utilizes our proprietary CBL-B inhibitor in manufacturing
- Cellular therapy with phenotypic and functional properties associated with superior activity in conventional TIL therapies
- 100% success rate in pilot and full-scale manufacturing runs
- Potency assay designed to meet all regulatory requirements with anticipated validation in ongoing clinical trial
- Successfully manufactured DeTIL and initiated treatment of the first patient in our clinical trial; the second patient DeTIL is manufactured and will be administered soon

DeTIL-0255-201: First-in-Human Clinical Trial

Robert J Brown, MD
EVP, Head of Clinical Development
Nurix Therapeutics

DeTIL-0255-201: Phase 1 First-in-Human Clinical Trial Design

Two-Part Phase 1 Monotherapy Trial of DeTIL-0255 in Relapsed or Refractory Gynecological Cancers

Safety Run in (3-6 patients)

Objectives:
- Assess safety and tolerability
- Assess preliminary efficacy

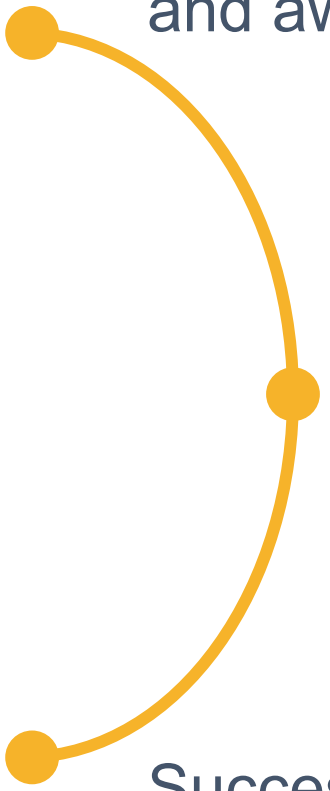
In-hospital treatment (~3 weeks)

Excisional Biopsy → DeTIL production (22 days) → Conditioning chemotherapy (Cy / Flu) → DeTIL infusion 1 x 10^9 cells to 150 x 10^9 cells → IL-2 infusions

Cohort Expansion

- Platinum Resistant Epithelial Ovarian Cancer (~ 18 patients)
- Recurrent, Metastatic or Persistent Cervical Cancer (~ 18 patients)
- Advanced or Recurrent Endometrial Cancer (~ 18 patients)

Successful Infusion in First Patient In DeTIL-0255-201



First patient with ovarian cancer has cleared DLT period and awaiting tumor assessment

Successful expansion and desirable phenotype including CD4+ and CD8+ T cells with characteristics of memory and stem-like cells

Successfully manufactured DeTIL-0255 for second patient

DeTIL-0255 Holds the Promise of Superior Antitumor Activity in the Clinic

- Displays characteristics associated with better outcomes in TIL therapy
  - ⇢ Superior stem-like and memory phenotype
  - ⇢ Enhanced effector function
  - ⇢ Increased persistence and activity
- Clinical trial with DeTIL-0255 designed to demonstrate safety and signs of efficacy in patients with gynecologic malignancies
- Addition of oral NX-1607 may further improve efficacy and safety, reduce burden of treatment for patients
  - ⇢ Reduce chemotherapy, replace or reduce use of high-dose IL2

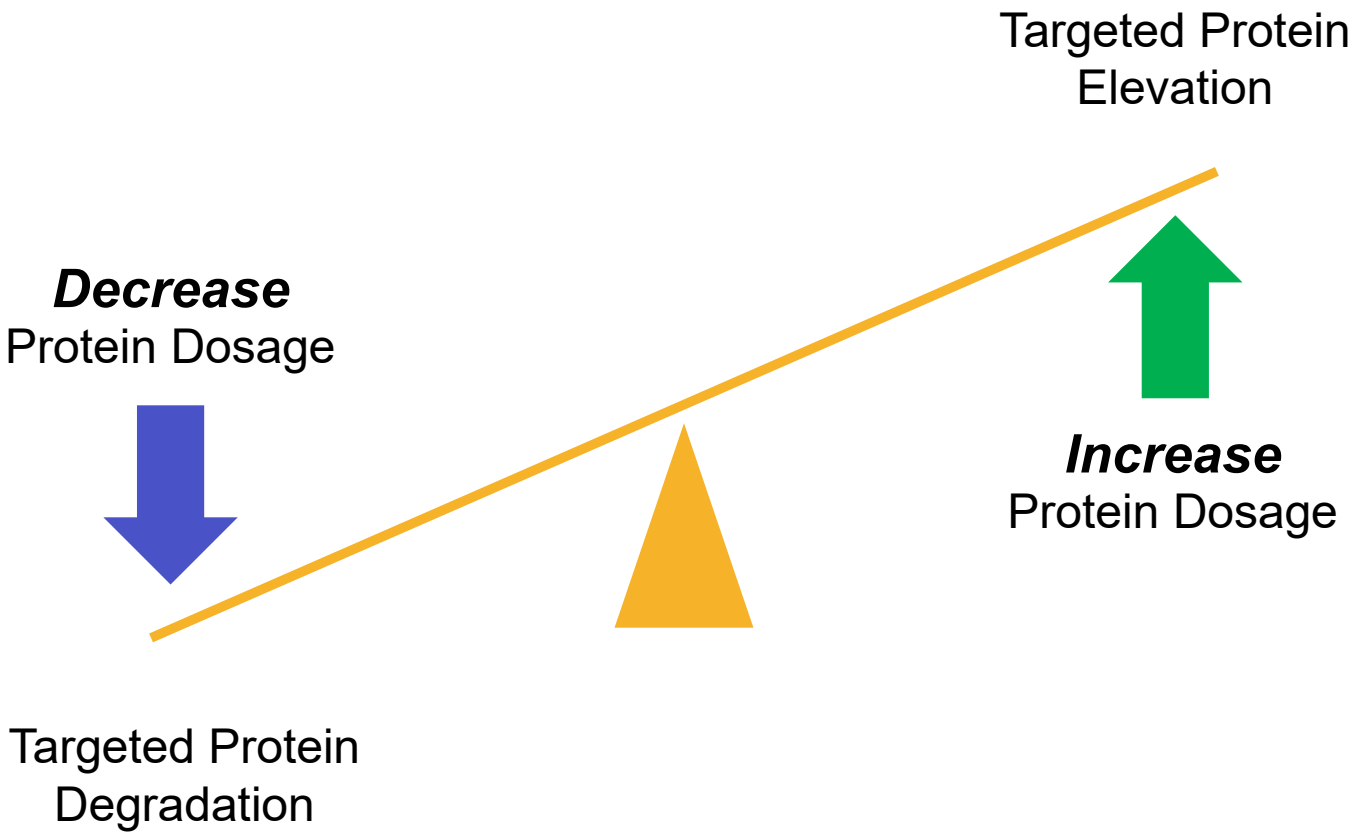
nurix

Leader in Targeted Protein Modulation

The Genesis: Powerful DELigase R&D Platform

Gwenn M Hansen, PhD
Chief Scientific Officer
Nurix Therapeutics

Our Platform Enables Two Complementary Protein Modulation Approaches for Therapeutic Discovery



E3 ligases are the rheostat of the proteome

Ligase Modulators can either

Eliminate or Enhance

a pathway function

Our CBL and BTK drugs are just the beginning

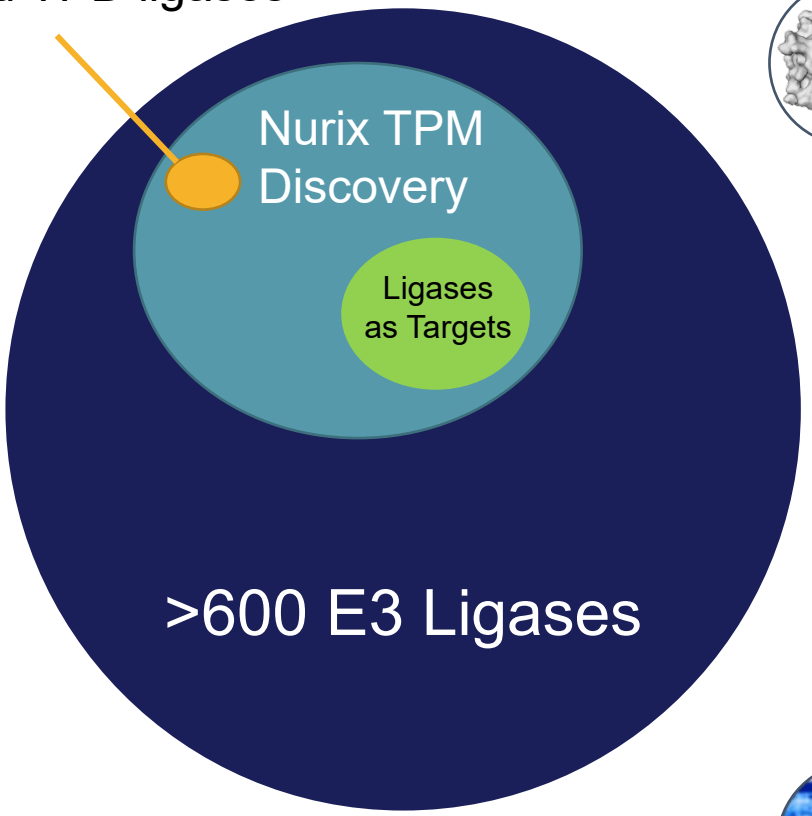
Nurix's platform can address classically druggable and undruggable protein classes and has delivered multiple Protein Modulators

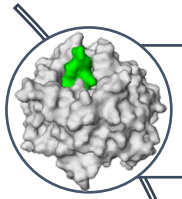
Key Questions About Nurix's Platform

- How is Nurix advancing the field of ligase discovery to become the leader in Targeted Protein Modulation?
- What is driving the productivity of Nurix's DELigase platform?
- Why did Nurix focus on and internalize DEL technology?
- How is Nurix innovating to address the challenges of discovery?
- What future targets will emerge from Nurix's discovery engine?
- How might protein modulation be impactful in treating disease?

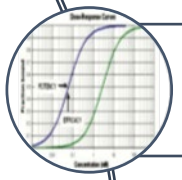
Unique TPM Opportunities Can Be Unlocked by Harnessing or Inhibiting Additional E3 Ligases

Precedented TPD ligases

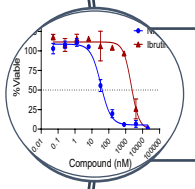




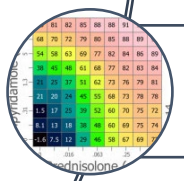
Unlock novel targets and pathways



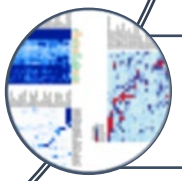
Improve target coverage and selectivity



Overcome inhibitor resistance



Neosubstrate synergy with target biology



Enhance selectivity through ligase specificity

Nurix Has the Most Comprehensive Ligase Discovery Pipeline

Ligand Discovery | Ligand Optimization | Degrader Profiling | DC nominatio | Clinic

CBL Inhibitors and BTK Degraders

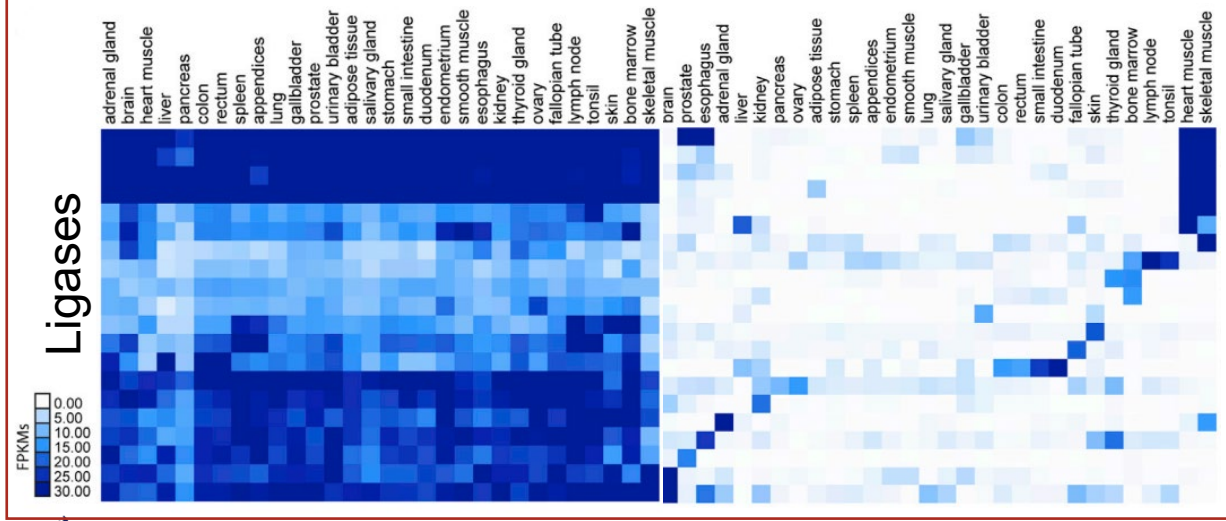
20 Ligases

11 Ligases

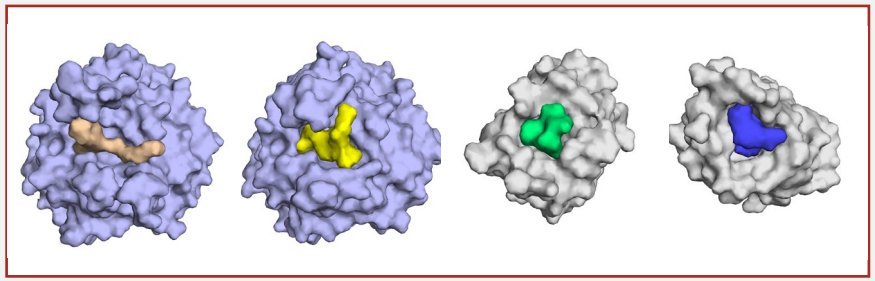
27 Ligases

60 Ligases in Discovery Pipeline

Broadly-expressed vs Selectively expressed



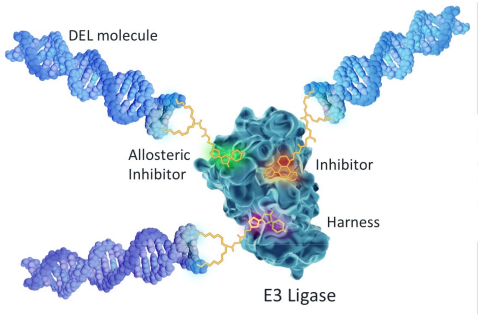
Examples:



Multiple ligands identified for novel ligases with broad expression and high processivity in cancer and normal tissues

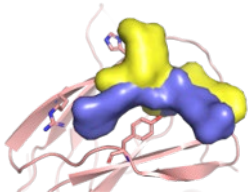
Nurix's DELigase Protein Modulation Discovery Platform

DEL Discovery



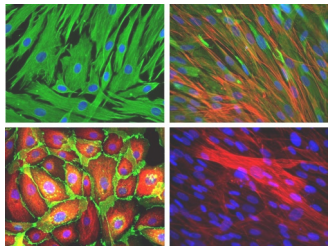
> 5 billion drug-like compounds that can be easily screened against hundreds of proteins to identify starting points therapeutic discovery

Rational and Empirical Chemistry



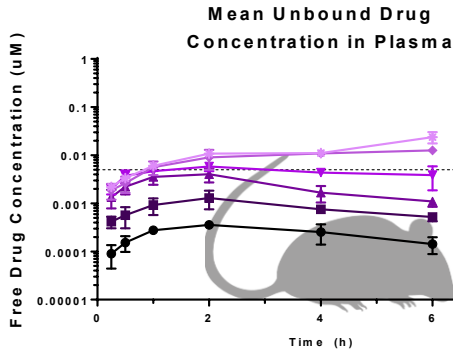
Structure Based Drug Design combined with chemistry automation enables broad exploration of lead-like chemical space for each program

Direct-to-Cell Biology Capabilities



High throughput cellular assays monitor protein levels and biological phenotypes to assess impact on biology

Scaled Screening for in vivo exposure

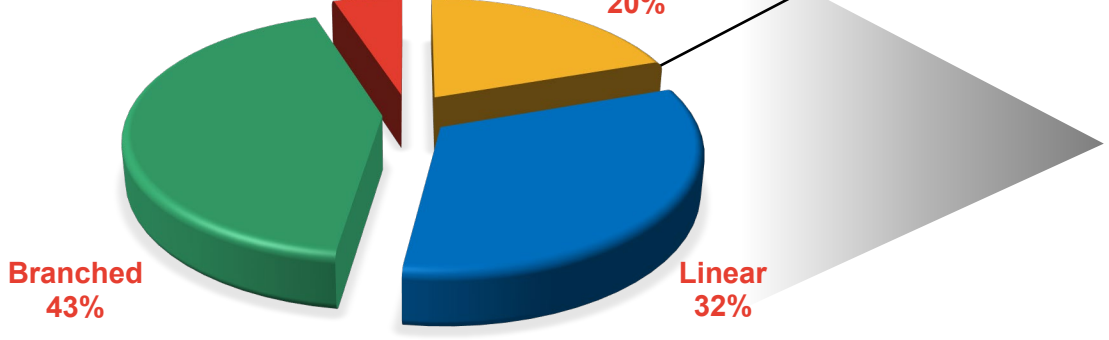


Capacity to screen for ideal in vivo drug exposure profile and assess impact on disease biology

Integrated Discovery Engine To Unlock Relevant Targets

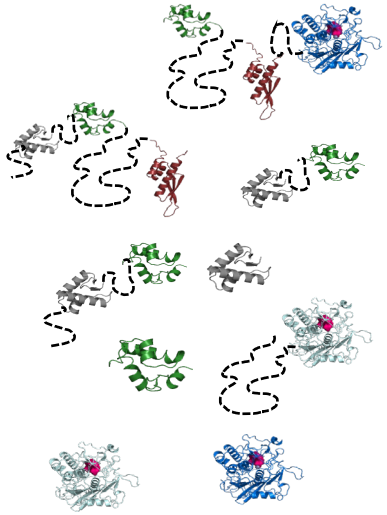
1. Proprietary Starting Points
   - Designed for Difficult Targets
   - Drug-Like
   - Degrader-Like

Scaffold Libraires Proving Essential for Delivering Ligands for Undruggable Targets (75% sole source)



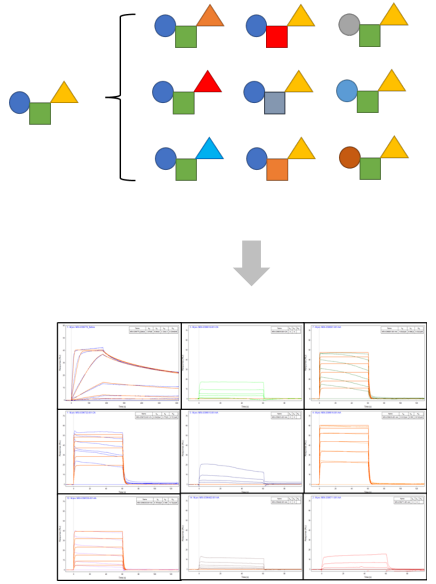
Libraries Contain Significant Chemical Diversity

2. Versatile Discovery
   - Simultaneous identification of unique mechanisms of action
   - Not limited by biochemical tractability of the Target or Ligase



Screening Explores Significant Protein Diversity

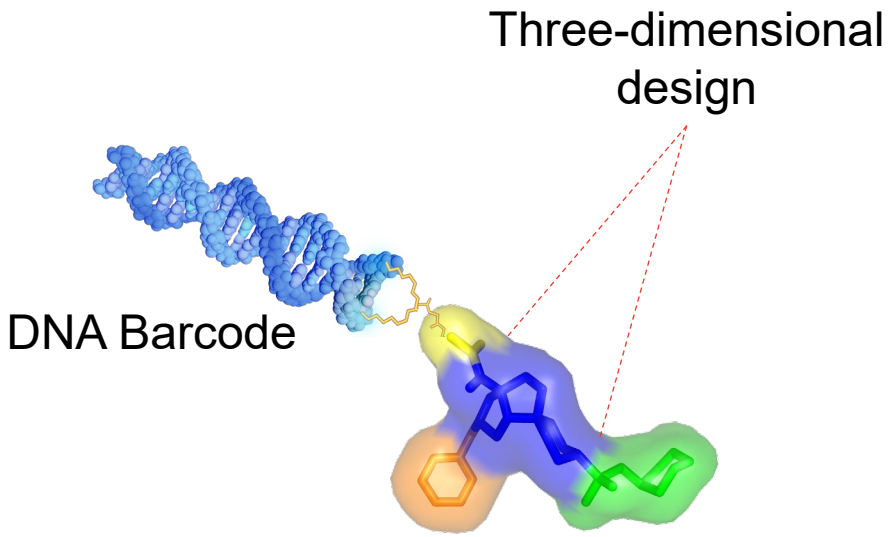
3. Efficient Follow-up
   - Combinatorial design enables automation and computation

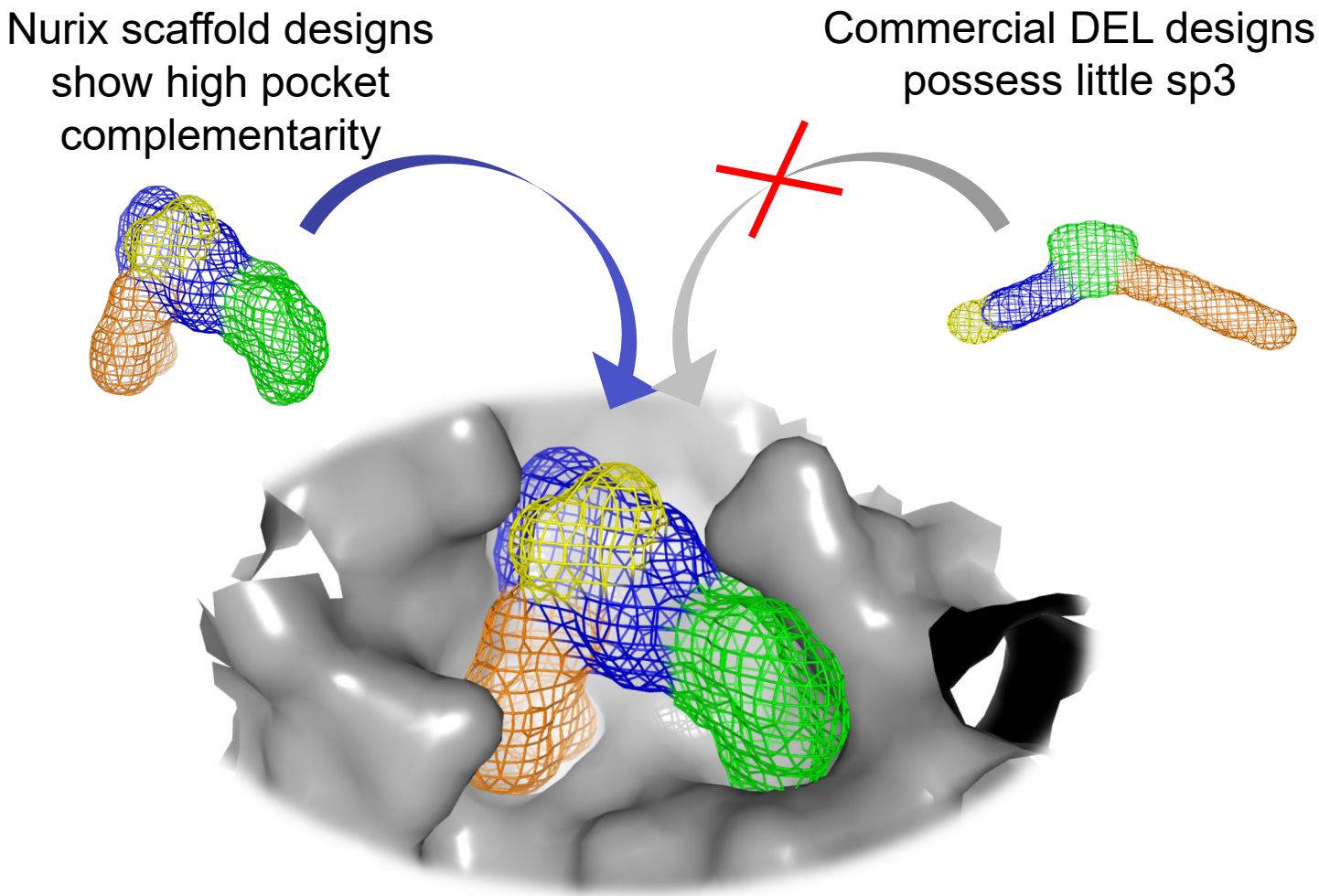


Lead Identification via Automation

Custom Scaffold-Based DELs Enable Nurix To Identify Binders to Challenging Protein Surfaces

Our proprietary scaffold DELs provide unique geometry and high sp3 character, allowing molecules to achieve optimal pocket fit

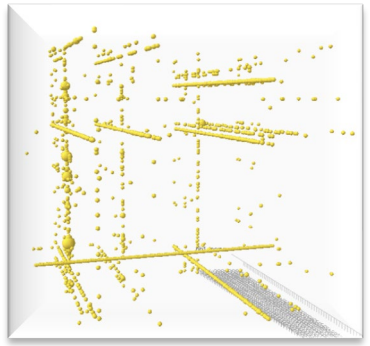




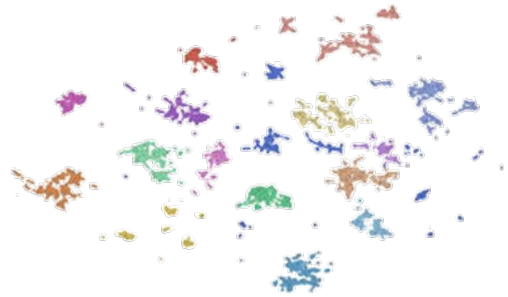
Ligand-bound X-ray structure of DEL hit

Leveraging Computational Methods To Search Beyond DEL Space to Discover Potent and Diverse CRBN Binders

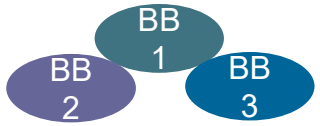
Nurix's Discovery Workflow Allows Access to Chemical Space Beyond Existing Compound Collections



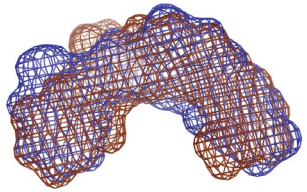
DEL Screen for Binders



Automated Structure Analysis and Clustering

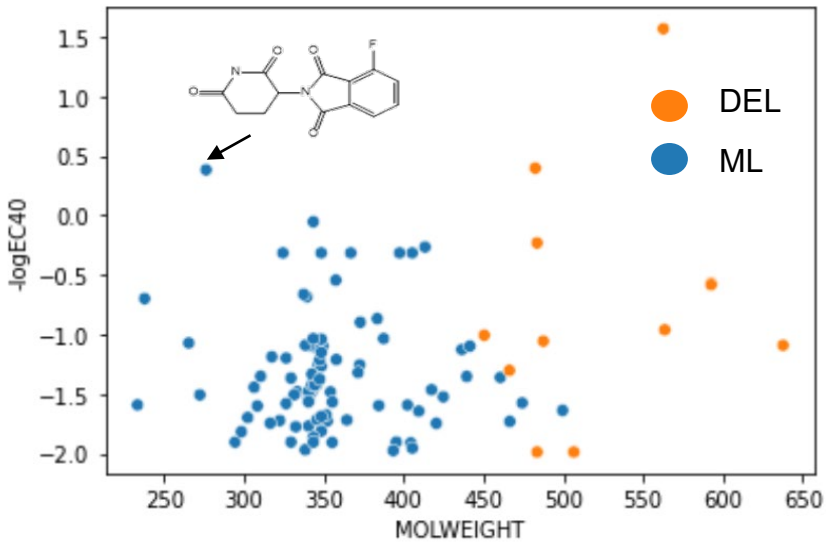


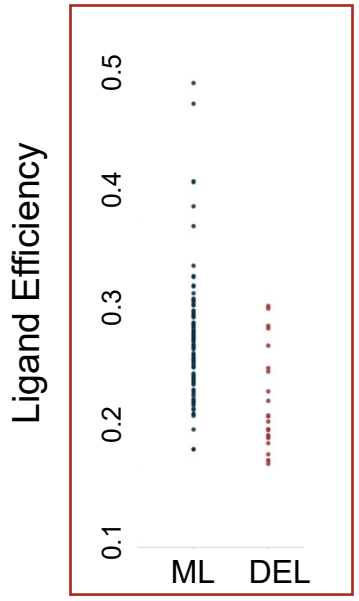
Traditional Hit Resynthesis



Machine Learning and Similarity Virtual Screening

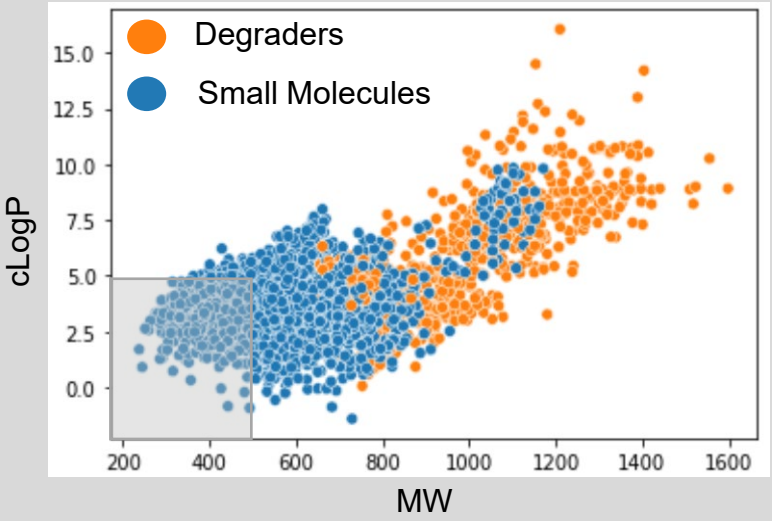
Combining traditional and computationally-driven discovery allows us to discover more binders in desirable chemical property space





Predicting Solubility in Unique Chemical Space with Machine Learning

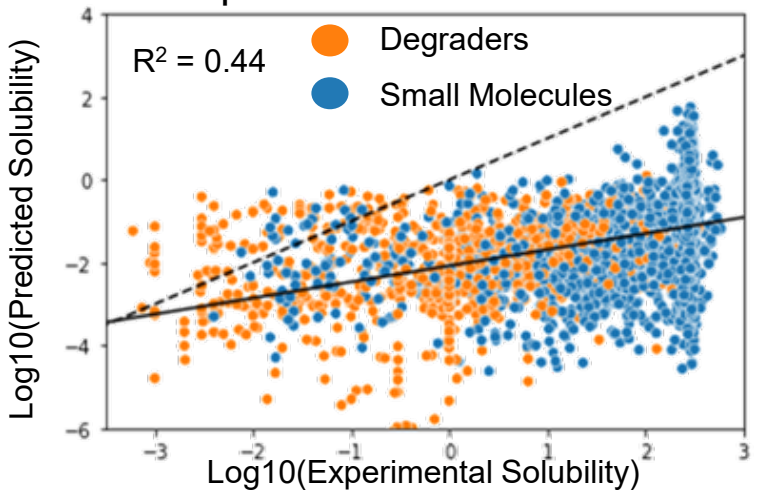
Problem:
Degraders occupy non-traditional chemical space



- Common approaches for property prediction fail for these classes of compound
- Lack of intuition introduces inefficiency in Lead Optimization campaigns

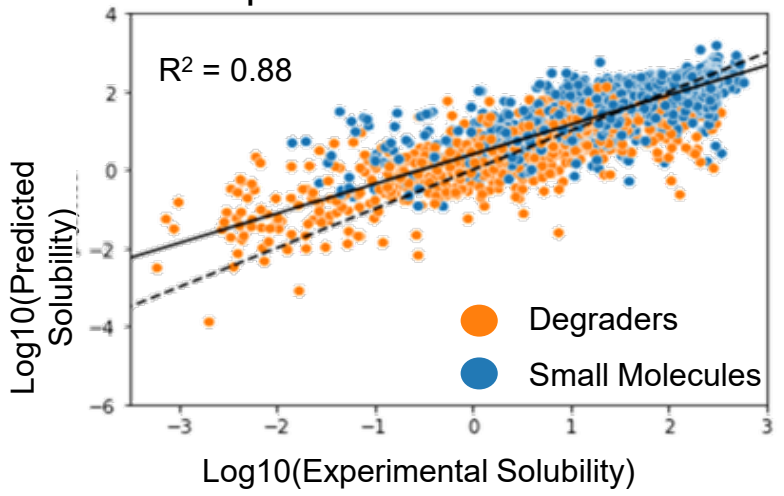
Leading Chem-informatics Software

Experiment vs Prediction:



Nurix's Machine Learning Models

Experiment vs Prediction:



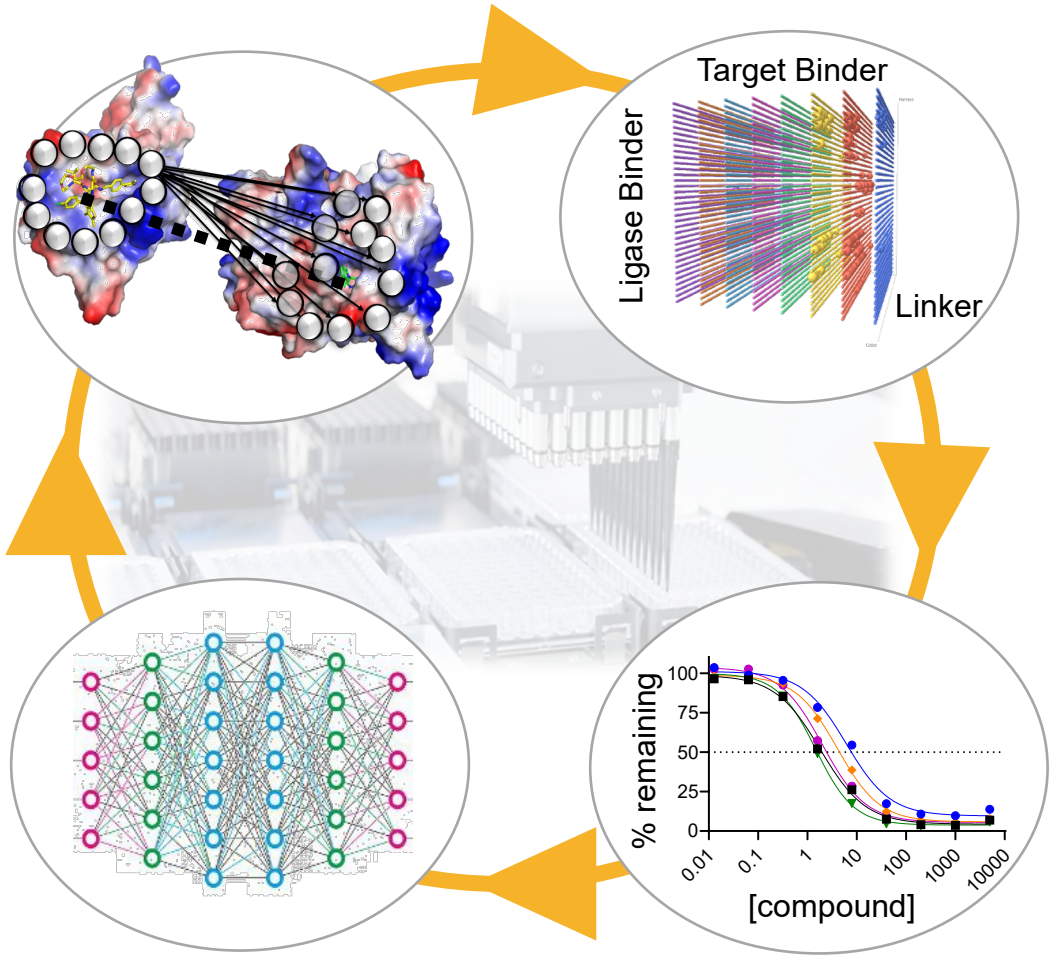
Solution:
Application of modern machine learning frameworks improve our understanding of structure-to-property relationships, enabling better hit selection and more efficient degrader design and optimization

Nurix Is Applying Automation to Better Define the Parameters of Degrader Design to Advance our Programs to the Clinic

Challenge: Identifying and optimizing degraders remains largely an empirical process

DESIGN SCOPE

Theoretical range of degrader chemical space more fortuitous than rational



SYNTHESIZE AT SCALE

Automation enables Nurix to sample unprecedented chemical space

WRITE THE RULEBOOK

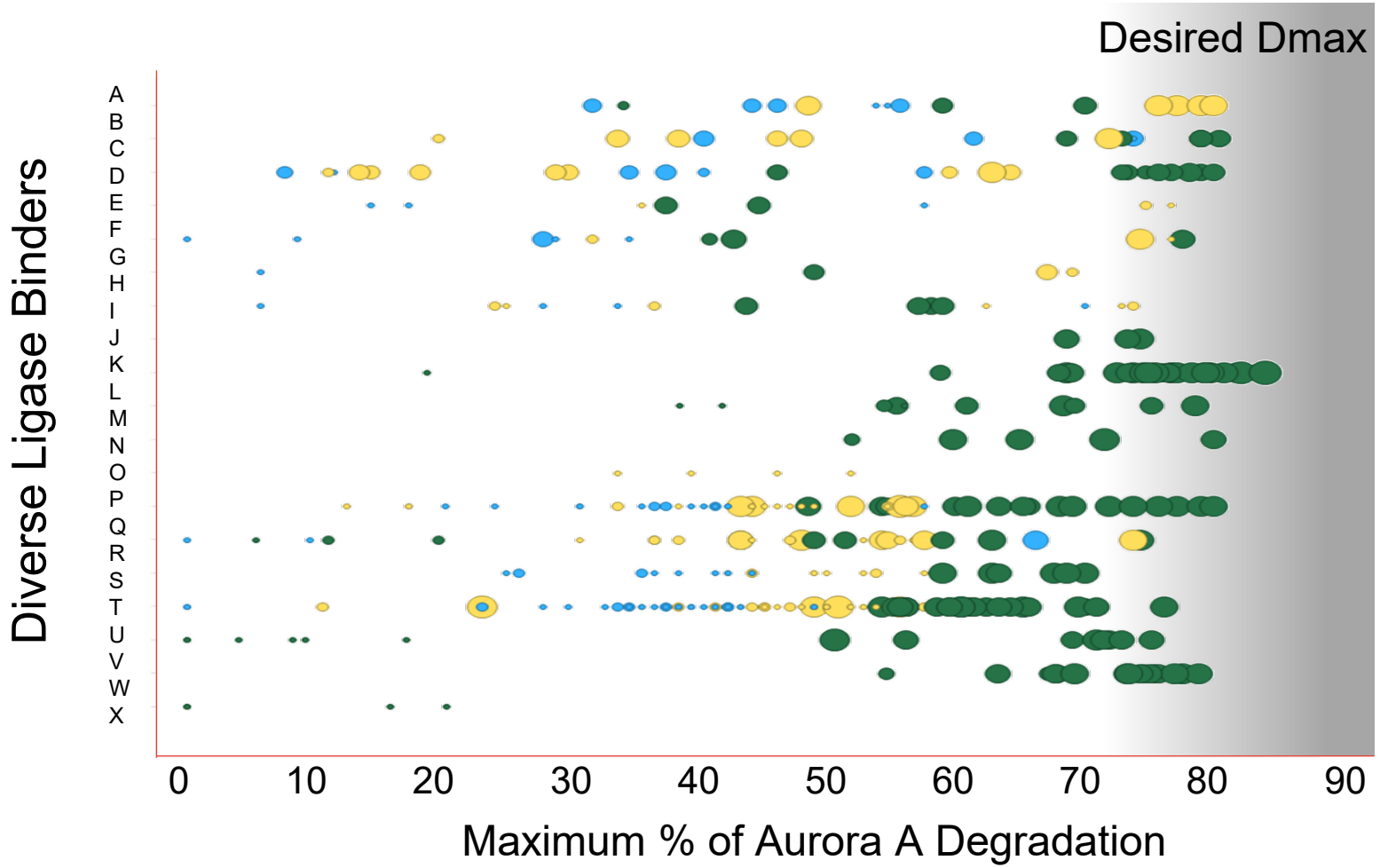
Machine Learning transforms large datasets into degrader rulebook for improved design

DISCOVER LEADS

Empirical data reveals degraders with optimal performance

Lead-Like Aurora A Degraders Discovered by Applying Automation to Nurix's Compound Synthesis Workflow

Power of Applying Automation to Quickly Identify Ideal Design Space



Aurora A Binders:

Binder 1

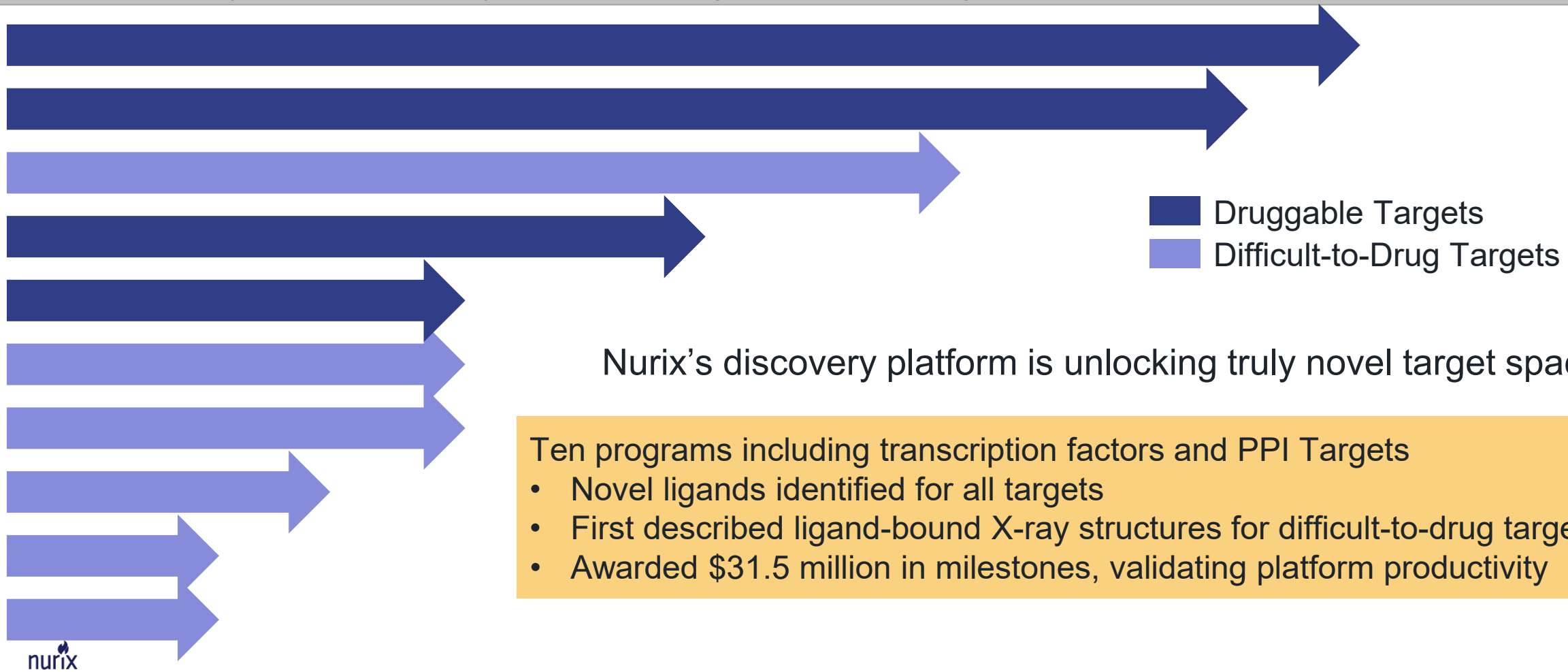
Binder 2

Binder 3

Size of point = potency

In collaboration with MYCN thought leaders and Alex's Lemonade Stand Foundation

Collaboration Pipeline Has Demonstrated Value of Platform, Particularly with Targets Considered Undruggable



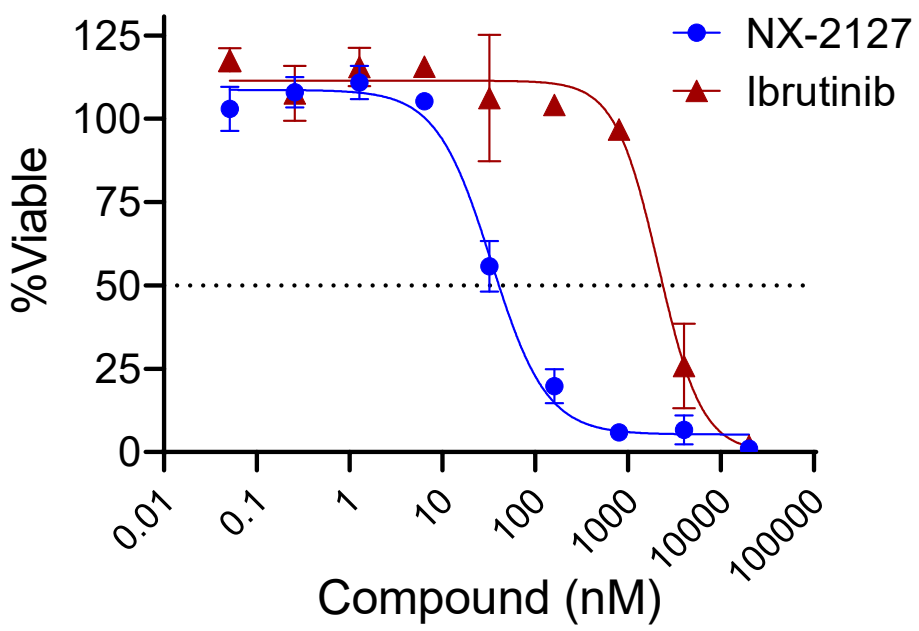
Nurix's discovery platform is unlocking truly novel target space

Ten programs including transcription factors and PPI Targets

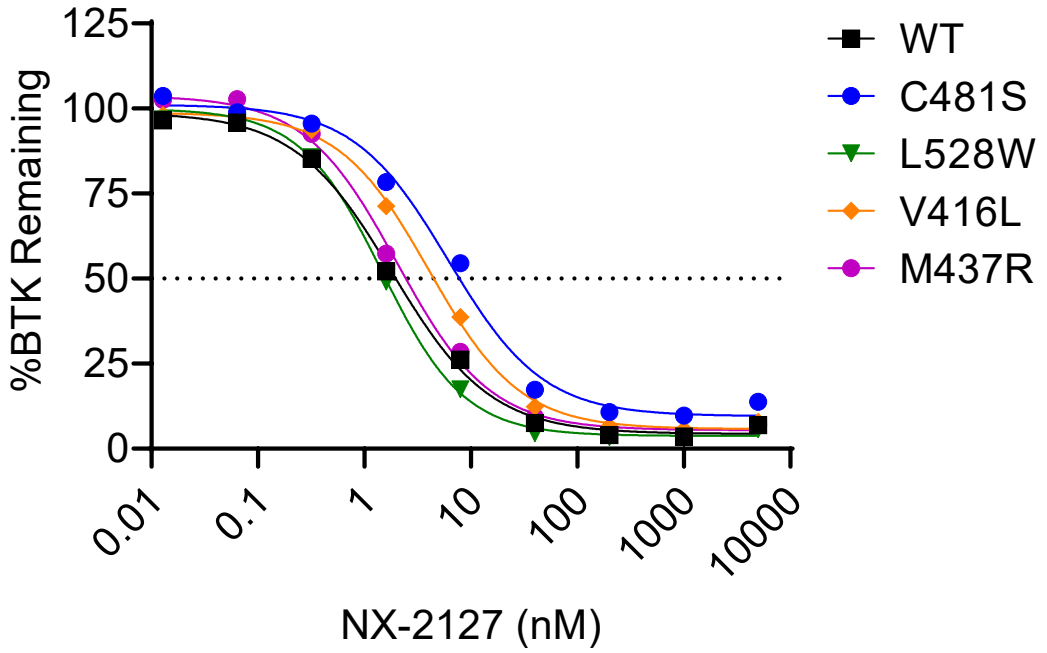
- Novel ligands identified for all targets
- First described ligand-bound X-ray structures for difficult-to-drug targets
- Awarded $31.5 million in milestones, validating platform productivity

Nurix Is Confirming the Value of Degraders to Solve Inhibitor Resistance

NX-2127 kills lymphoma cells harboring BTK-C481S mutation



NX-2127 degrades multiple novel BTK mutations emerging post BTKi-treatment



Leading the Field of Protein Modulation

Delivering multiple modalities of therapeutics across the broadest target space

- Largest pipeline of E3 ligase targets
- Best in class for integrating DEL within a discovery engine incorporating automation, machine learning, and structure-based drug design
- Proven platform performance for unprecedented targets
- Our clinical candidates are helping to illustrate the value of degraders to solve inhibitor resistance

nurix

Leader in Targeted Protein Modulation

Financial Snapshot & Conclusions

Building From a Position of Strength

R&D Day
New York, NY
May 26, 2022

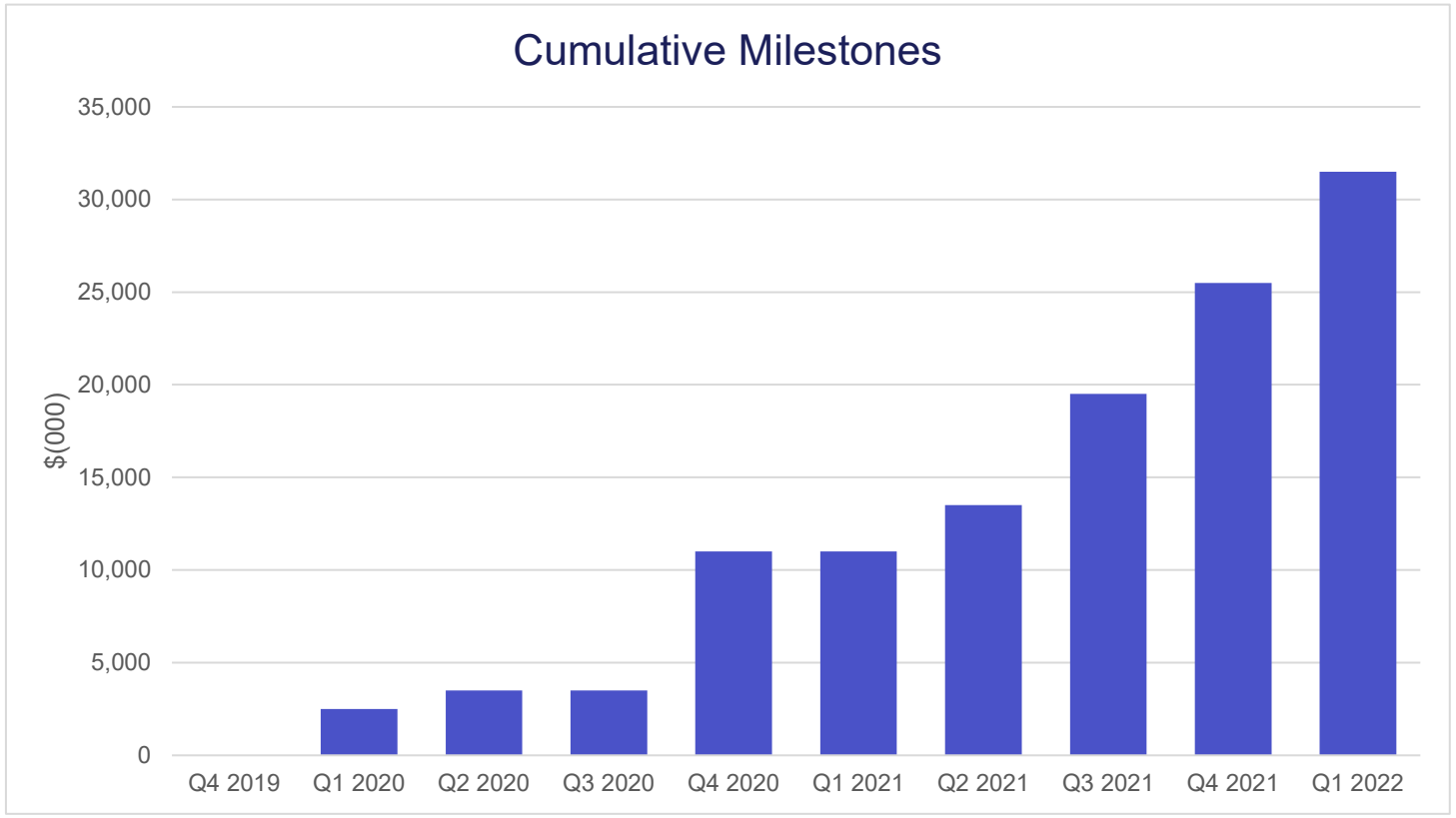
Financial Snapshot

Hans van Houte
Chief Financial Officer
Nurix Therapeutics

Nurix Is in a Strong Financial Position

$386M in cash and investments on February 28, 2022

- Funded through key readouts for all four clinical programs
- Execution on R&D collaborations drives success-based cash flow



R&D collaboration details:

- Gilead $55M upfront and $2.3B in additional payments including early discovery milestones
- Sanofi $77M upfront and expansion payments and $2.5B in addition payments including early discovery milestones
- Nurix option for 50/50 U.S. co-development for two drug candidates per partner
- Nurix clinical programs excluded

Nurix Continues To Successfully Fund Through Appropriate Mix of Equity and Collaboration Revenue at Every Stage of Growth

Equity Capital

- Series A: $6M
- Series B: $25M
- Series C: $17M
- Series D: $120M
- IPO: $232M
- Follow on: $150M

Collaborations

- Celgene collaboration: $150M
- Gilead collaboration: $45M
- Sanofi collaboration: $55M
- Sanofi expansion: $22M
- Ongoing milestones: $31.5M

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 mid-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

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A Bright Future

Arthur T Sands, MD, PhD
President, CEO and Board Director
Nurix Therapeutics

Key Messages for Today

1

Resistance has met its match
with targeted protein modulation

2

We have positive and exciting findings
from the first trial of a TPD in a hematologic malignancy

3

We set the stage for the **next breakthrough in immune oncology**
with **more to come** from our powerful platform

What to Expect From Nurix in 2022 and Beyond

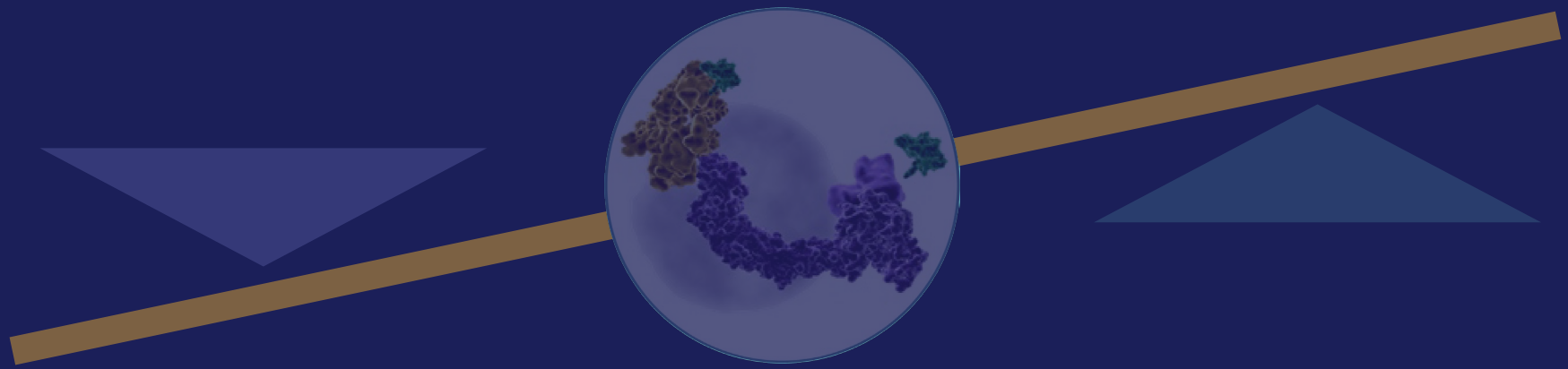
- Advancing technology and pipeline to remain leaders in Targeted Protein Modulation
- Driving toward definitive clinical results
- Building commercial-ready organization
- Reaping fruits of current partnership programs
- Future alliances/partnerships

2022-BEYOND
CONQUERING CANCER

Nurix is committed to building a patient-focused, science-driven oncology company powered by our leadership position in Targeted Protein Modulation

Thank You

Q&A



Leader in Targeted Protein Modulation

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