



Nurix Therapeutics

NX-5948 Clinical Update

European Hematology Association Congress

EHA2024

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Agenda

I. Introduction

Arthur T. Sands, MD, PhD
Chief Executive Officer, Nurix Therapeutics



II. NX-5948 clinical presentation from EHA

Kim Linton, MBChB, MRCP, PhD, FRCP
University of Manchester and The Christie NHS Foundation Trust



III. Patient journey and program next steps

Paula G. O'Connor, MD
Chief Medical Officer, Nurix Therapeutics



IV. Concluding remarks & Q&A

Nurix Is Advancing a Pipeline of Propriety and Partnered Programs in Oncology and Inflammation & Immunology

MOA	Oncology program	Target	Therapeutic area	Discovery – Lead Op	IND enabling	Phase 1a	Phase 1b
TPD	NX-5948	BTK	B-cell malignancies				
	NX-2127	BTK-IKZF	B-cell malignancies				
TPE	NX-1607	CBL-B	Immuno-Oncology				
TPD	Multiple	Undisclosed	Undisclosed				
	Multiple	Undisclosed	Undisclosed				
	Multiple	Undisclosed	Undisclosed				
DAC	Multiple	Undisclosed	Oncology				



MOA	I&I program	Target	Therapeutic area	Discovery – Lead Op	IND enabling	Phase 1a	Phase 1b
TPD	NX-5948	BTK	Inflammation / autoimmune				
	NX-0479 / GS-6791	IRAK4	Rheumatoid arthritis and other inflammatory diseases				
	STAT6 degrader	STAT6	Type 2 inflammatory diseases				
	Undisclosed	Undisclosed	Inflammation / autoimmune				



Executive Summary

NX-5948, an emerging best-in-class profile in CLL

- NX-5948 has demonstrated positive results from the ongoing Phase 1a clinical trial in patients with an objective response rate of 69.2% in heavily pretreated CLL patients including those with BTK inhibitor resistance mutations
- Clinical responses in CLL patients were rapid and deepening with longer time on treatment and NX-5948 has been well tolerated with extended treatment durations in many patients
- With an emerging best-in-class profile, Nurix is expanding to Phase 1b in CLL with plans to initiate pivotal development in 2025

Kim Linton, MBChB, MRCP,
PhD, FRCP
University of Manchester and
The Christie NHS Foundation Trust



Latest Results from an Ongoing First-in-Human Phase 1a/b Study of NX-5948, a Selective Bruton's Tyrosine Kinase (BTK) Degradator, in Patients with Relapsed/Refractory CLL and Other B-cell Malignancies

Kim Linton, Graham P. Collins, Francesco Forconi, Nirav N. Shah, Karan Dixit, Talha Munir, Zulfa Omer, Dima El-Sharkawi, Jeanette Doorduijn, Alvaro Alencar, Pam McKay, John Riches, Mary Gleeson, David Lewis, Allison Winter, Sarah Injac, Ted Shih, Srinand Nandakumar, May Tan, Ganesh Cherala, Erin Meredith, Alexey Danilov

Unmet Clinical Need: Relapsed/Refractory CLL

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

- Targeted therapy focusing on two key pathways (BTK/BCL2) is standard of care in CLL and has changed the treatment landscape in front-line and relapsed/refractory settings
- Emerging patterns of resistance limit the utility of currently available therapies:
 - BTK mutations confer resistance to both covalent and non-covalent BTK inhibitors (cBTKi and ncBTKi)¹
 - Some mutations lead to ‘kinase dead’ or ‘kinase overactive’ BTK mutants with intact B-cell receptor signaling through a scaffolding function of BTK²

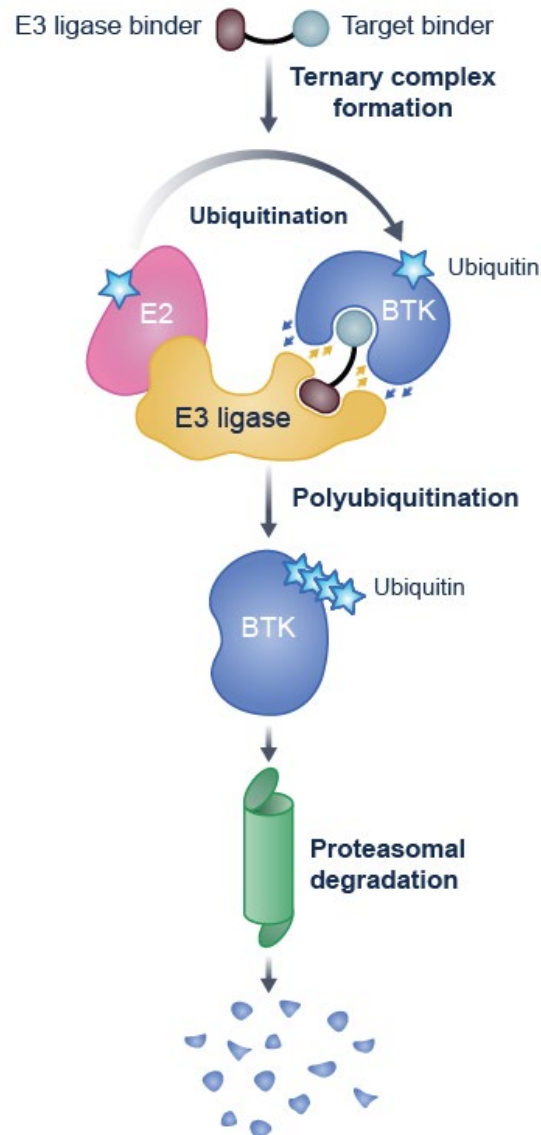
There is a need for a new treatment modality that can target both emerging resistant mutations and BTK scaffolding activity

References

1. Noviski et al. XX Biennial International Workshop on CLL Meeting, Boston, MA. October 6-9, 2023 (Poster #2020)
2. Montoya et al. Science 2024;383

NX-5948 Mechanism of Action

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



BTK degraders can overcome treatment-emergent resistance mutations

BTK degraders address BTK scaffolding function

BTK degraders show emerging activity in various B-cell malignancies

BTK degraders have the potential to replace BTK inhibitors in the clinic

NX-5948-301: Trial Design

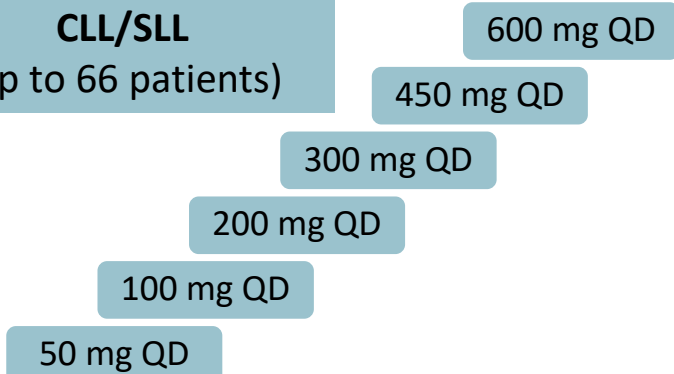
Phase 1a/b trial in adults with relapsed/refractory B-cell malignancies

Phase 1a dose escalation

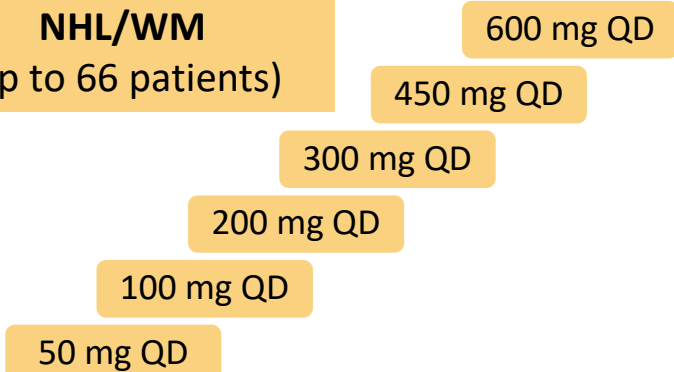
Key eligibility criteria

- Age ≥18 years
- Relapsed/Refractory disease
- ≥2 prior lines of therapy (≥1 for PCNSL)
- ECOG PS 0–1 (ECOG PS 0–2 for PCNSL)

CLL/SLL
(up to 66 patients)



NHL/WM
(up to 66 patients)



Potential Phase 1b dose expansion (N = up to 160 patients)

CLL/SLL dose A
Prior BTKi and BCL2i

CLL/SLL dose B
Prior BTKi and BCL2i

MCL

Prior BTKi and anti-CD20 CIT

MZL

Prior anti-CD20 CIT and ≥2 prior LoT

WM

Prior BTKi and ≥2 prior LoT

DLBCL

Prior anthracycline, anti-CD20 CIT + 1 LoT

FL

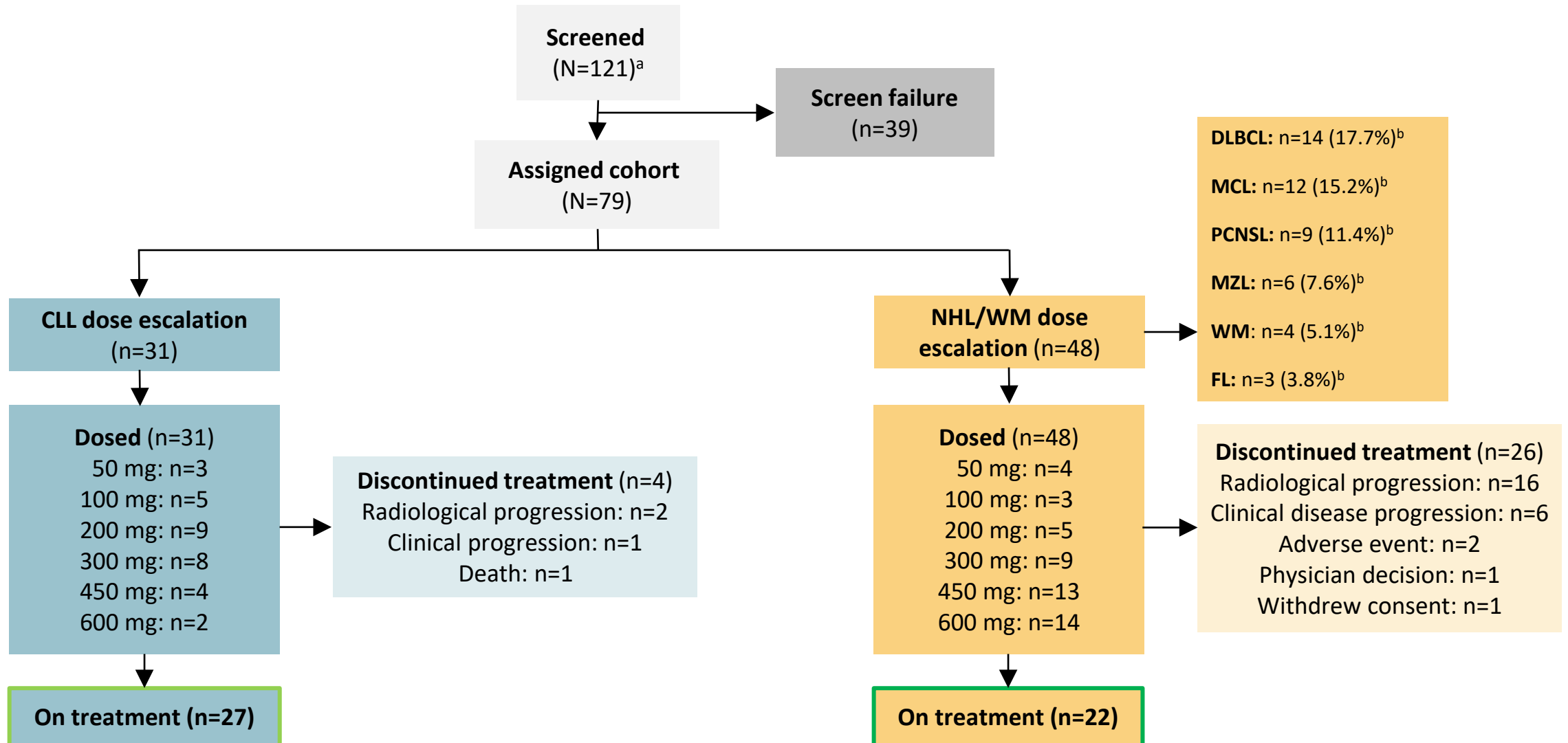
Prior anti-CD20 CIT + 1 LoT

PCNSL/SCNSL

Who have progressed or had no response to ≥1 prior LoT

Patient Disposition

Patients were dosed in CLL (n=31) and NHL/WM (n=48) dose-escalation cohorts



^aIncludes 3 patients at screening but not yet enrolled on study at time of data cutoff; ^bPercent of total patient population

Baseline Demographics/Disease Characteristics

Elderly population with multiple prior lines of targeted therapies

Characteristics	Patients with CLL (n=31)	Patients with NHL/WM (n=48)	Overall population (N=79)
Median age, years (range)	69.0 (35–88)	66.5 (42–87)	67.0 (35–88)
Male, n (%)	19 (61.3)	33 (68.8)	52 (65.8)
ECOG PS, n (%)			
0	13 (41.9)	13 (27.1)	26 (32.9)
1	18 (58.1)	33 (68.8)	51 (64.6)
CNS involvement, n (%)	2 (6.5)	10 (20.8)	12 (15.2)
Median prior lines of therapy (range)	4.0 (2–14)	4.0 (2–13)	4.0 (2–14)
Previous treatments^a, n (%)			
BTKi	30 (96.8)	29 (60.4)	59 (74.7)
≥2 BTKi	11 (35.5)	NA	NA
Pirtobrutinib	7 (22.6)	7 (14.6)	14 (17.7)
BCL2i	28 (90.3)	7 (14.6)	35 (44.3)
BTKi and BCL2i	27 (87.1)	7 (14.6)	34 (43.0)
CAR-T therapy	2 (6.5)	11 (22.9)	13 (16.5)
Bispecific antibody	1 (3.2)	7 (14.6)	8 (10.1)
PI3Ki	9 (29.0)	4 (8.3)	13 (16.5)
Chemo/chemo-immunotherapies	24 (77.4)	48 (100.0)	72 (91.1)
Mutation status, n (%)			
TP53	14/30 (46.7)	4/42 (9.5)	18/72 (25.0)
BTK	13/30 (43.3)	0/42 (0.0)	13/72 (18.1)
PLCG2	6/30 (20.0)	2/42 (4.8)	8/72 (11.1)

^aPatients could have received multiple prior treatments; **NA**, not applicable; **PI3Ki**, PI3 kinase inhibitor; **CAR-T**, chimeric antigen receptor T-cell.

NX-5948 Is Well Tolerated

TEAEs in ≥10% of overall population or grade ≥3 TEAEs or SAEs in >1 patient

TEAEs, n (%)	Patients with CLL (n=31)			Overall population (N=79)		
	Any grade	Grade ≥3	SAEs	Any grade	Grade ≥3	SAEs
Purpura/contusion ^a	13 (41.9)	–	–	28 (35.4)	–	–
Thrombocytopenia ^b	7 (22.6)	1 (3.2)	–	21 (26.6)	7 (8.9)	–
Neutropenia ^c	7 (22.6)	6 (19.4)	–	16 (20.3)	12 (15.2)	–
Fatigue	7 (22.6)	–	–	14 (17.7)	2 (2.5)	–
Anemia	6 (19.4)	1 (3.2)	–	13 (16.5)	3 (3.8)	–
Petechiae	7 (22.6)	–	–	13 (16.5)	–	–
Rash ^d	8 (25.8)	–	1 (3.2)	13 (16.5)	1 (1.3)	1 (1.3)
Headache	6 (19.4)	–	–	12 (15.2)	–	–
Cough	4 (12.9)	–	–	11 (13.9)	1 (1.3)	–
Diarrhea	5 (16.1)	1 (3.2)	–	9 (11.4)	1 (1.3)	–
COVID-19 ^e	2 (6.5)	–	–	8 (10.1)	2 (2.5)	2 (2.5)
Hypertension	1 (3.2)	1 (3.2)	–	6 (7.6)	4 (5.1)	–
Pneumonia ^f	2 (6.5)	1 (3.2)	1 (3.2)	5 (6.3)	4 (5.1)	4 (5.1)

- 1 DLT (non-protocol mandated drug hold; NHL)
- 2 TEAEs resulting in drug discontinuation (both NHL)
- 1 related SAE (TLS based on labs, no clinical sequelae)
- Grade 5 AE (pulmonary embolism, not deemed NX-5948 related)
- No additional safety signal with higher doses

^aPurpura/contusion includes episodes of contusion or purpura; ^bAggregate of 'thrombocytopenia' and 'platelet count decreased'; ^cAggregate of 'neutrophil count decreased' or 'neutropenia';

^dAggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; ^eAggregate of 'COVID-19' and 'COVID-19 pneumonia'; ^fAggregate of 'pneumonia' and 'pneumonia klebsiella'

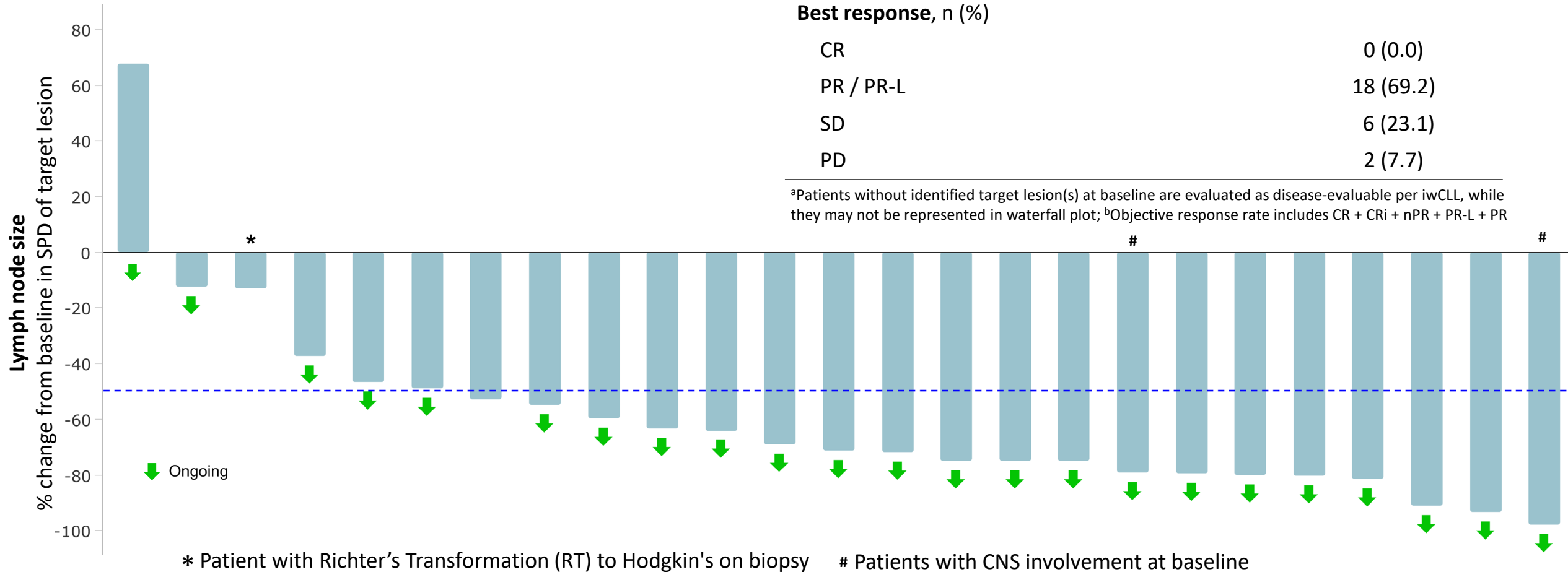
AE, adverse event; TEAE, treatment emergent adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event; TLS, tumor lysis syndrome.

NX-5948 Efficacy: Clinical Response

Broad antitumor activity in CLL as demonstrated by significant lymph node reduction and ORR

CLL disease-evaluable patients ^a	n=26
Objective response rate (ORR)^b, % (95% CI)	69.2 (48.2–85.7)
Best response, n (%)	
CR	0 (0.0)
PR / PR-L	18 (69.2)
SD	6 (23.1)
PD	2 (7.7)

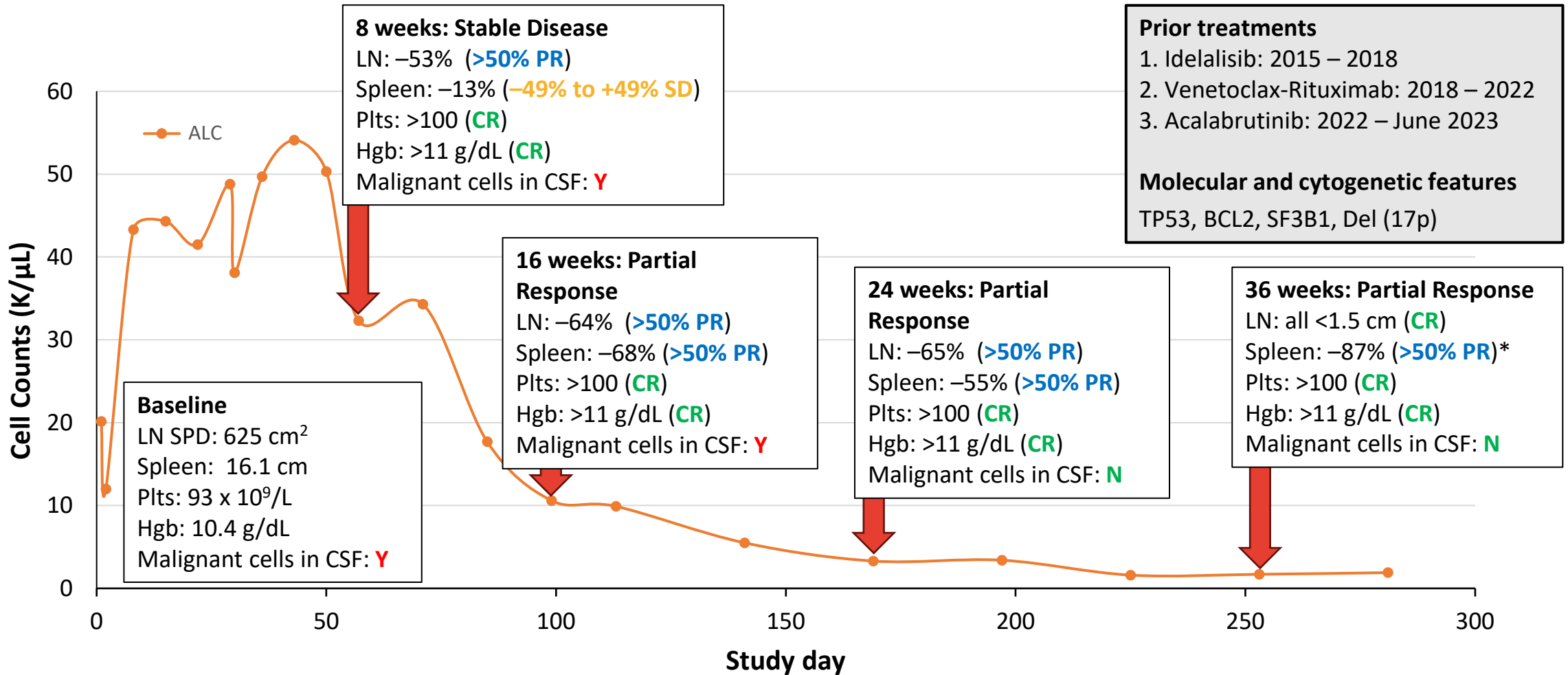
^aPatients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL, while they may not be represented in waterfall plot; ^bObjective response rate includes CR + CRi + nPR + PR-L + PR



SPD, sum of products diameters; CR, complete response; CRi, complete response with incomplete marrow recovery; PR, partial response; nPR, nodular partial response; PR-L, partial response with rebound lymphocytosis; SD, stable disease; PD, progressive disease.

Case Study: Patient with CLL and CNS Involvement

Deepening response over time approaching complete response criteria



Prior treatments

1. Idelalisib: 2015 – 2018
2. Venetoclax-Rituximab: 2018 – 2022
3. Acalabrutinib: 2022 – June 2023

Molecular and cytogenetic features

TP53, BCL2, SF3B1, Del (17p)

*Normal spleen: 13 cm; 36 week: 13.4 cm
 The overall response assessments are from the investigators while the individual parameter response assessment criteria are calculated per iwCLL from the data entered

References

Mutation Status and BTK Degradation

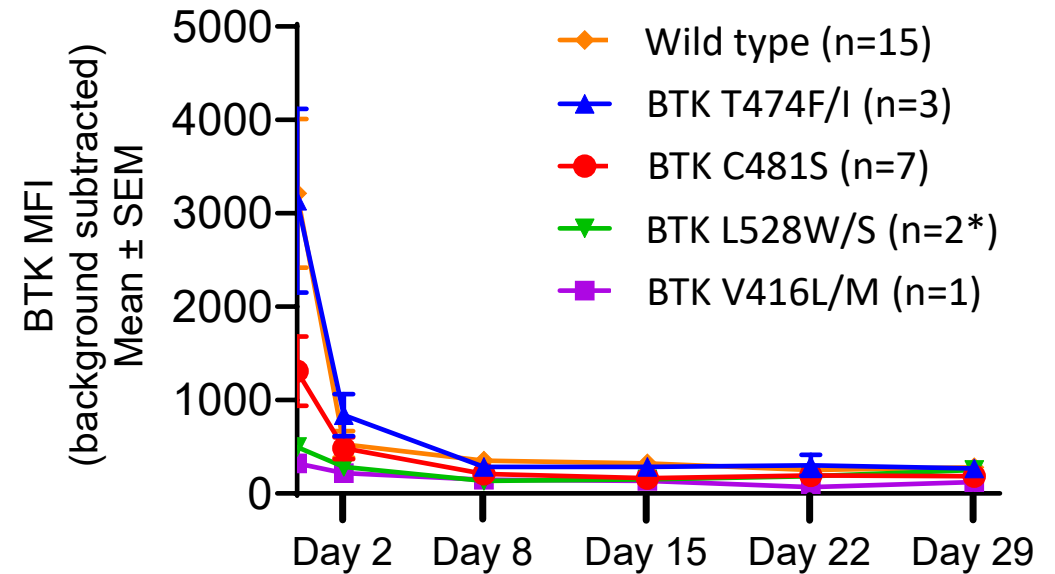
NX-5948 induces rapid and robust degradation of wild-type and mutant BTK

	Patients with CLL (n=30)
Mutation status, n (%)	
BTK ^a	13 (43.3)
C481S	7 (23.3)
L528 ^b	2 (6.7)
T474 ^c	3 (10.0)
V416 ^d	1 (3.3)
G541V	1 (3.3)

^aPatients could have multiple BTK mutations; BTK mutations were tested at baseline by NGS centrally. $\geq 5\%$ allelic frequency is reported.

^bL528W, L528S; ^cT474F, T474I; ^dV416L, V416M.

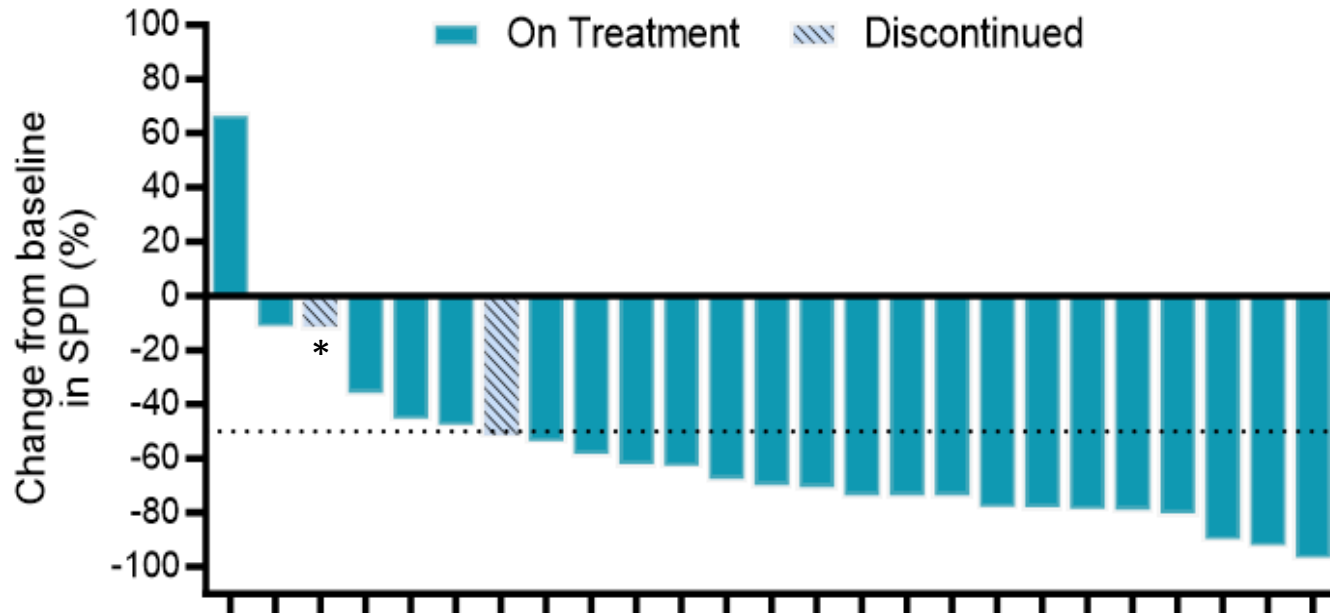
BTK degradation in CLL with *BTK* mutations



*1 patient has both BTK L528S and G541S

Clinical Activity in Patients with Baseline Mutations

Treatment resistance and poor-prognosis genetic mutations



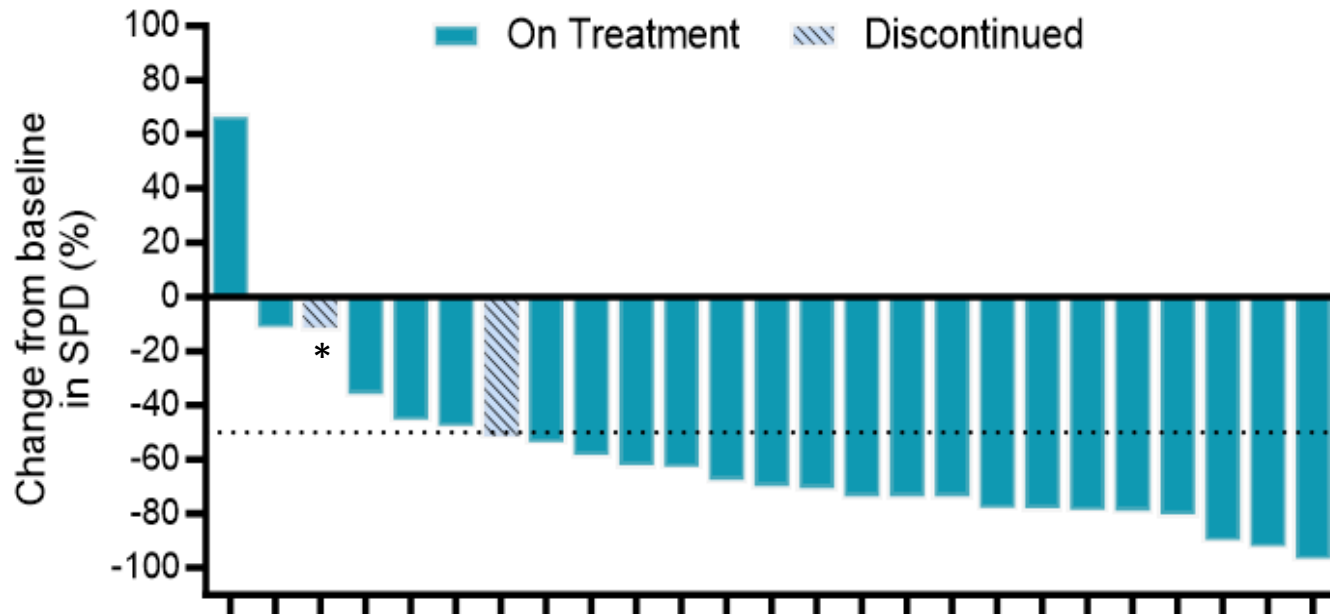
- Baseline treatment-resistance and poor prognosis mutations were common, indicating a genetically diverse and hard-to-treat CLL patient population
- No genotypic profile was linked to intrinsic NX-5948 resistance



*Patient with Richter's transformation to Hodgkin's on biopsy

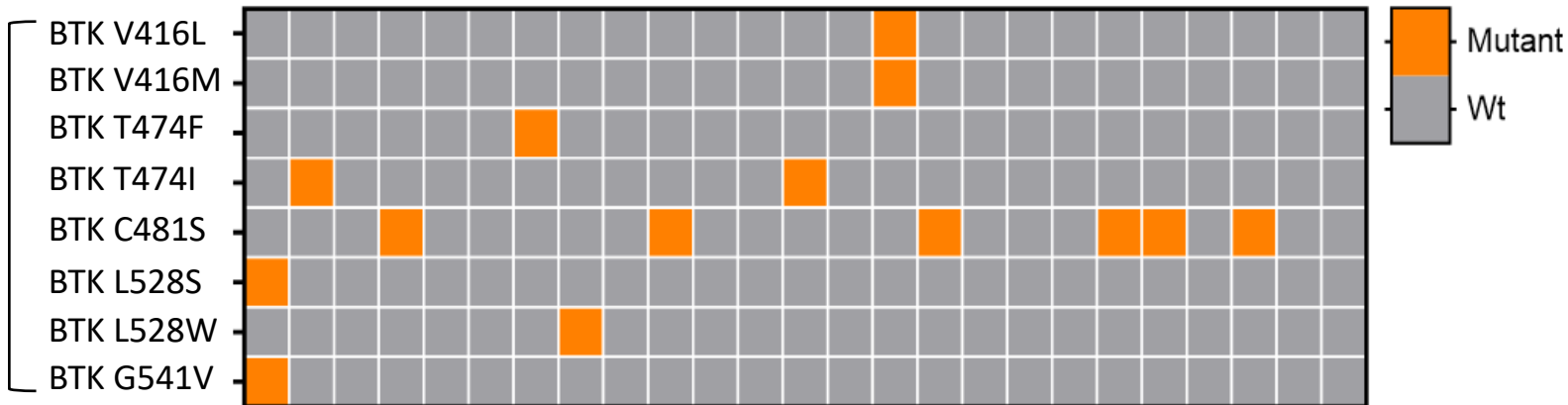
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- No genotypic profile was linked to intrinsic NX-5948 resistance

BTK mutations
(43% of patients)



*Patient with Richter's transformation to Hodgkin's on biopsy

Conclusions:

Positive results from the ongoing Phase 1 study of novel BTK degrader NX-5948

- NX-5948 was well tolerated in patients with NHL and CLL, with no increased safety signal at higher doses
- Deep and durable clinical responses were observed in a difficult-to-treat CLL patient population:
 - Heavily pretreated patient population with unfavorable genetic mutations associated with poor prognosis and BTK inhibitor resistance mutations
 - Robust clinical activity in patients with CLL with 69.2% ORR and all responses ongoing as of April 17, 2024:
 - Rapid responses - majority of responses (15/18) seen at the first scan (8 weeks)
 - Durable and deepening responses with longer time on treatment (27/31 patients still on study)
 - No patient profile associated with intrinsic resistance to NX-5948
- These data support the continued development of NX-5948 in the treatment of CLL where Phase 1b dose expansion is planned. Additional data in NHL/WM will be presented in 2H 2024

Paula G. O'Connor, MD
Chief Medical Officer
Nurix Therapeutics



NX-5948: The Patient Journey

Two additional case studies
highlighting the activity of
NX-5948 to address patients
with high unmet medical
needs



Case Study 1: CLL Patient with Extensive Prior Treatment

Site	City of Hope
Age, M/F	61, male
Diagnosis	CLL
Initial diagnosis	2008
Prior progression	12 Sep 2023
Dose	200 mg daily
IwCLL response	PR
Status	On treatment
Current cycle	Cycle 8

Relevant Medical History

- Atrial fibrillation: Dx Jul 2022
- Hypothyroidism: Dx May 2022
- Hypertension: Dx Jul 2022
- Fatigue: Dx Oct 2023
- Disease related cytopenias: Dx 2022-23

Molecular, Cytogenetics and other baseline features

- Del(11q, 13q)*, IGHV unmutated*
- BTK T474I mutation**
- Bulky disease (5 of 6 target lymph nodes >5 cm in longest diameter)
- Splenomegaly

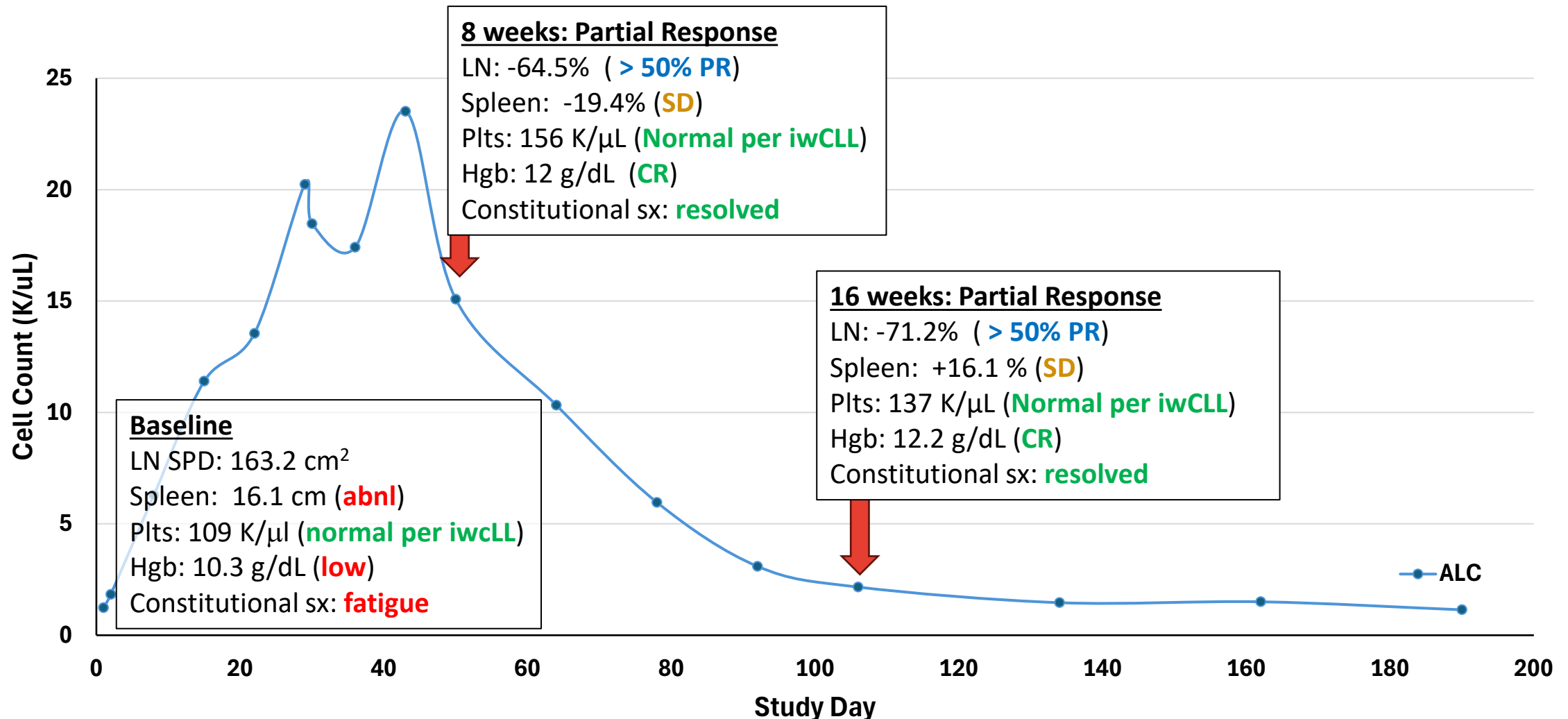
Prior Systemic Therapies

- FCR: 2009-2010
- **Ibrutinib** + rituximab: 2012
- Venetoclax: 2018
- **Acalabrutinib**: 2021
- Chlorambucil + obinutuzumab: 2021
- **Zanubrutinib**: 2022
- Lisocabtagene maraleucel: 2022
- Duvelisib: 2022-23
- **Pirtobrutinib** + obinutuzumab: 2023
- R-CHOP: 2023
- **Pirtobrutinib** + bendamustine + obinutuzumab: 2023

Reason for pirtobrutinib + bendamustine + obinutuzumab discontinuation: Progressive disease

Case Study 1: CLL Patient with Extensive Prior Treatment

Rapid and sustained lymph node reduction with improving hematologic features



The overall response assessments are from the investigators, while the individual parameter response assessment criteria are calculated per iwCLL from the data entered.

Case Study 2: CLL Patient with High-Risk Features

Extensive prior treatment with CIT, nBTKi, BCL2i, and PI3K

Site	Northwestern
Age, M/F	66, M
Diagnosis	CLL
Initial diagnosis	2008
Prior progression	2 Nov 2023
Dose	200 mg daily
IwCLL response	PR
Status	On treatment
Current cycle	Cycle 8

Relevant Medical History

- Supraventricular tachycardia: Jun 2018 - present
- Peripheral neuropathy: Oct 2018 - present
- Hearing loss: Apr 2008 - present
- Tinnitus: Apr 2008 - present
- Chronic kidney disease: Jul 2019 – present

Prior Systemic Therapies

- Campath + rituximab: Nov 2008 – Mar 2009
- Bendamustine + rituximab: Nov 2010 – Mar 2011
- Ibrutinib: Dec 2013- Aug 2018
- Acalabrutinib: Aug 2018 – Aug 2019
- Ublituximab+ umbralisib+ venetoclax: 13 Aug 2019 – 13 Jul 2020

Molecular/ Cytogenetics

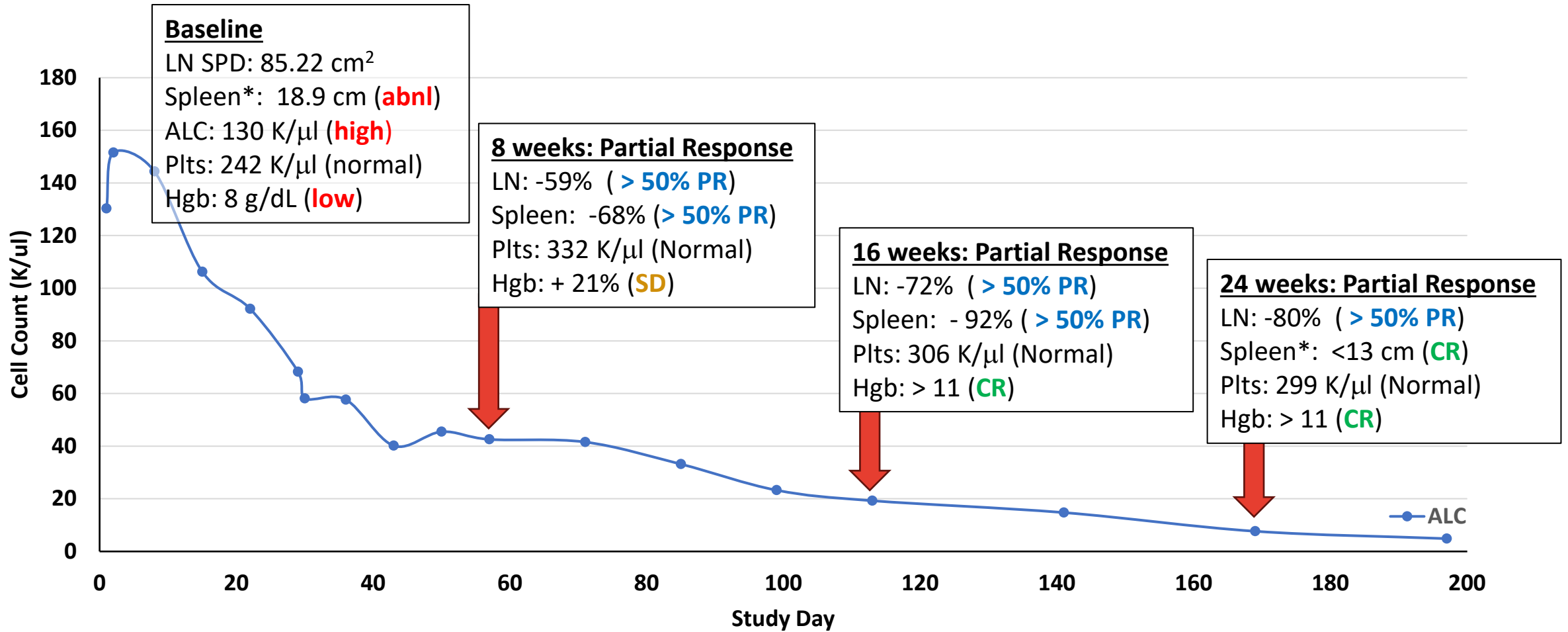
- IgHV unmutated*, Del 11q, Del13q*
- TP53 mutated**, SF3B1 mutated**, NOTCH1 mutated**
- PLCG2 mutated**

Baseline clinical features

- Bulky disease (1 target lymph node >5cm longest diameter, 6 total)
- Splenomegaly

Case Study 2: CLL Patient with High-Risk Features

Early clinical activity deepening over time



Initial lymphocytosis consistent with BTK targeted MOA. *Normal spleen= <13 cm 24 wk: 12.8 cm
The overall response assessments are from the investigators, while the individual parameter response assessment criteria are calculated per iwCLL from the data entered.

NX-5948: Next Steps in CLL



Next Steps: Expand Phase 1b in Select CLL Populations

Enable Pivotal Trial Initiation in 2025

Phase 1b expansion in CLL

CLL/SLL (n = 80-160)

Two monotherapy dose levels to be selected from Phase 1a dose escalation

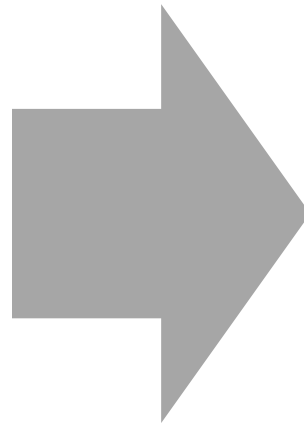
Includes multiple cohorts in clinically meaningful populations e.g. prior BTKi and BCL-2i, BTKi resistance mutations, 2L with high-risk genetics (TP53 mut/del 17p)

Combination basket study

CLL/SLL (n = TBD)

Potential combinations for CLL:

- venetoclax
- obinutuzumab
- rituximab



Pivotal trials in 3L+ CLL

**3L+ monotherapy post-BTKi/post-BCL2i
(Fast Track Designation)**

Single-arm and randomized controlled trial options

Pivotal trials in 1L/2L CLL

1L/2L monotherapy study

Randomized controlled trial

1L/2L fixed duration combinations

Randomized controlled trial

Conclusions: Nurix Plans To Accelerate Development of NX-5948 with First Pivotal Study To Be Initiated in 2025

- CLL: Clear demonstration of clinical activity in difficult to treat populations
 - Advancing to an expanded Phase 1b across a wide range of CLL subpopulations
 - Preparing for initiation of pivotal trial(s) in 2025 in 3L+ CLL where we have Fast Track Designation with a ~70% ORR observed to date
 - Planning for a broad and parallel Phase 3 program across lines of therapy as monotherapy and in combination with other approved agents
- NHL: Broad activity with deep responses seen across NHL subtypes
 - Preparing for Phase 1b expansion in selected NHL subtypes with initial focus on monotherapy in indolent indications
 - Additional data in NHL patients will be presented in 2H 2024

Arthur T. Sands, MD, PhD
Chief Executive Officer
Nurix Therapeutics



Nurix Therapeutics: Planning for Success

- We believe NX-5948 is a potential best-in-class drug that can replace BTK inhibitors and offer patients important treatment options
- We have a team that can successfully accelerate development to move to pivotal trial(s) in 2025
- We have built a robust and growing pipeline of oncology and immunology drugs both wholly-owned and with industry leading partners and retained product rights
- We are appreciative of support from our investors, our investigators, and most importantly from our patients

Questions & Answers

