Latest Results from an Ongoing First-in-Human Phase 1a/b Study of NX-5948, a Selective Bruton's Tyrosine Kinase (BTK) Degrader, 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

EHA Hybrid Congress – June 16, 2024

Disclosures

Disclosures of: Kim Linton

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	X		X			X	X
BeiGene			X			X	
BMS			X			X	
Celgene			X			X	X
Genmab	X		X			X	X
Kite/Gilead			X			X	
Hartley Taylor							X
Roche	X		X			X	X
Takeda	X						

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

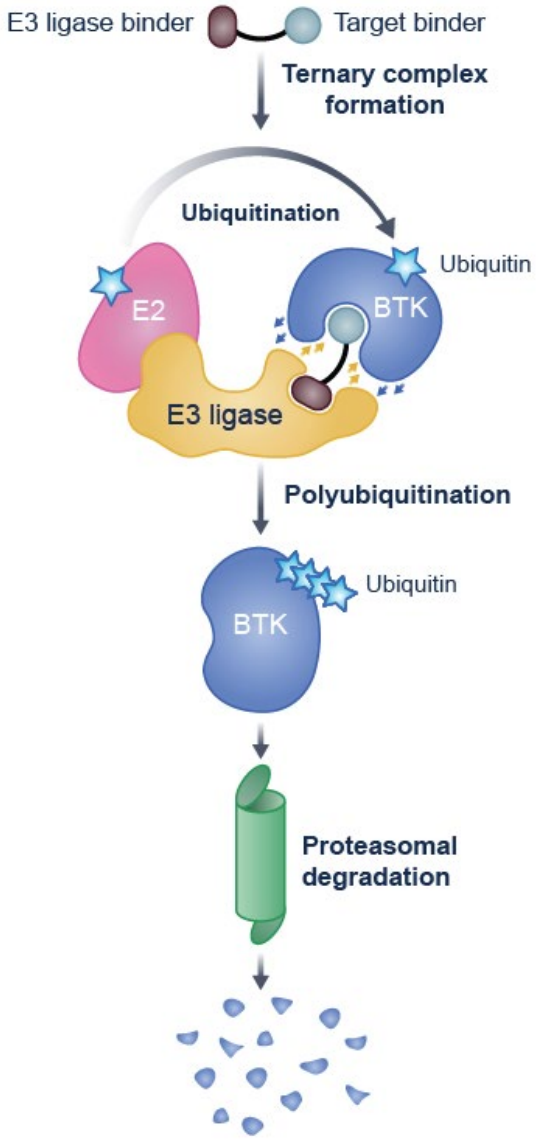
- Emerging patterns of resistance limit the utility of currently available therapies:
  - BTK mutations confer resistance to both covalent and non-covalent BTK inhibitors (cBTKi and ncBTKi)[1]
  - Some mutations lead to ‘kinase dead’ or ‘kinase overactive’ BTK mutants with intact B-cell receptor signaling through a scaffolding function of BTK[2]

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)

- 600 mg QD
- 450 mg QD
- 300 mg QD
- 200 mg QD
- 100 mg QD
- 50 mg QD

NHL/WM
(up to 66 patients)

- 600 mg QD
- 450 mg QD
- 300 mg QD
- 200 mg QD
- 100 mg QD
- 50 mg QD

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

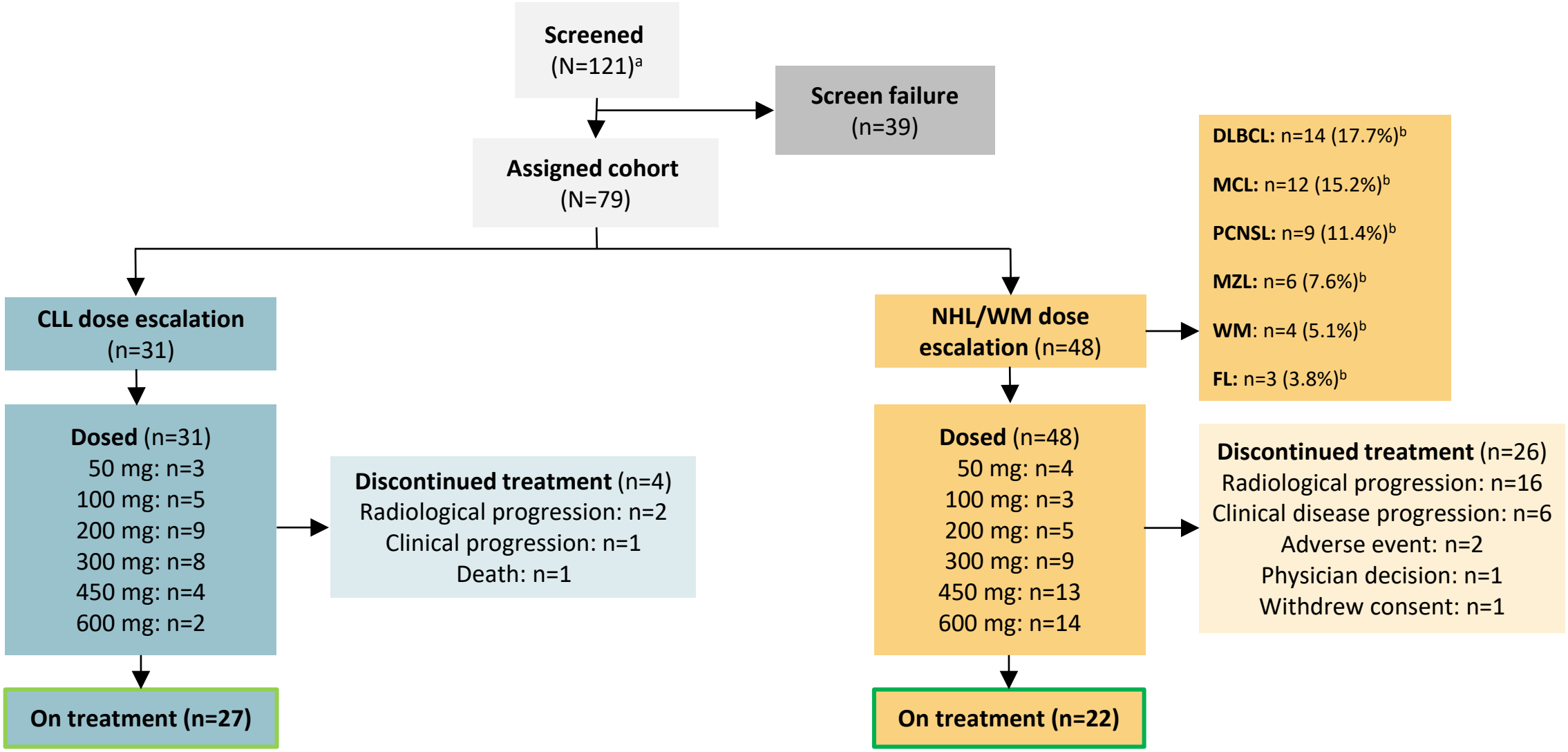
FL
Prior anti-CD20 CIT + 1 LoT

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

CLL, chronic lymphocytic leukemia; **SLL**, small lymphocytic lymphoma; **NHL**, non-Hodkgin's lymphoma; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **WM**, Waldenstrom's macroglobulinemia; **DLBCL**, diffuse large B-cell lymphoma; **FL**, follicular lymphoma; **PCNSL**, primary CNS lymphoma; **SCNSL**, secondary CNS lymphoma; **CIT**, chemo-immunotherapy; **LoT**, lines of treatment; **BCL2i**, Bcl-2 inhibitor; **ECOG PS**, Eastern Cooperative Oncology Group (ECOG) performance status

Patient Disposition

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



[a]Includes 3 patients at screening but not yet enrolled on study at time of data cutoff; [b]Percent 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)

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

Data cutoff: 17 April 2024

NX-5948 Is Well Tolerated

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

	Patients with CLL (n=31)			Overall population (N=79)		
TEAEs, n (%)	**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

[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [c]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [d]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [e]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'; [f]Aggregate 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.

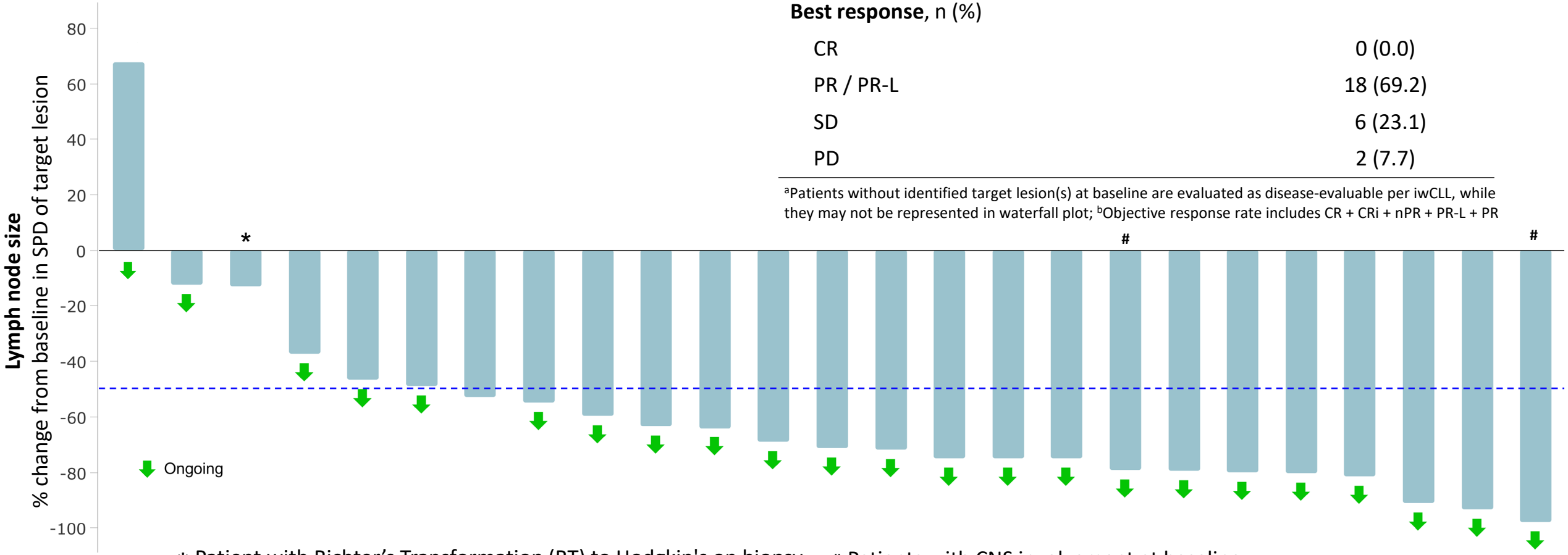
Data cutoff: 17 April 2024

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)

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



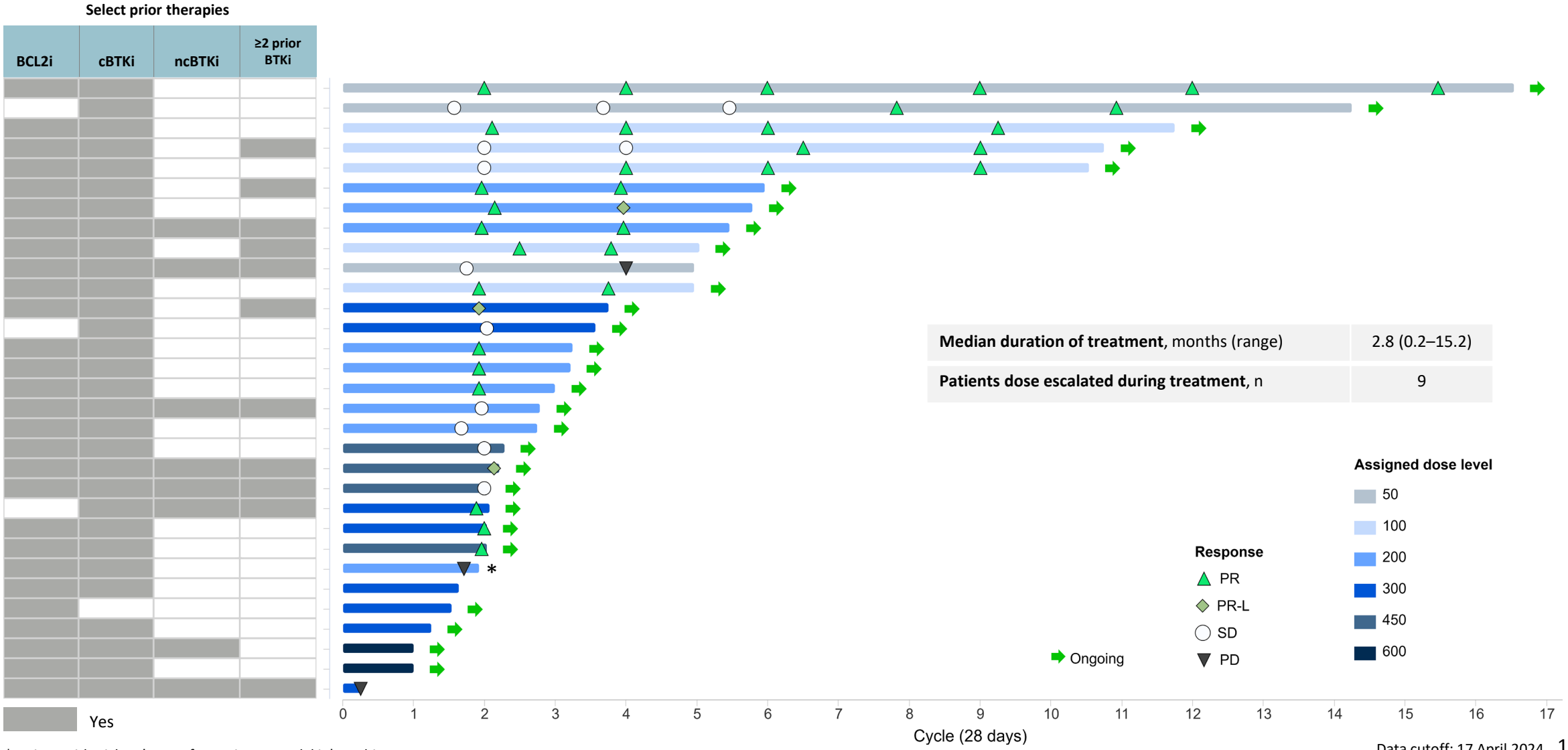
∗ Patient with Richter's Transformation (RT) to Hodgkin's on biopsy # Patients with CNS involvement at baseline

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.

Data cutoff: 17 April 2024

NX-5948 Efficacy: Duration of Treatment

Durable responses seen in heavily pretreated patients with CLL

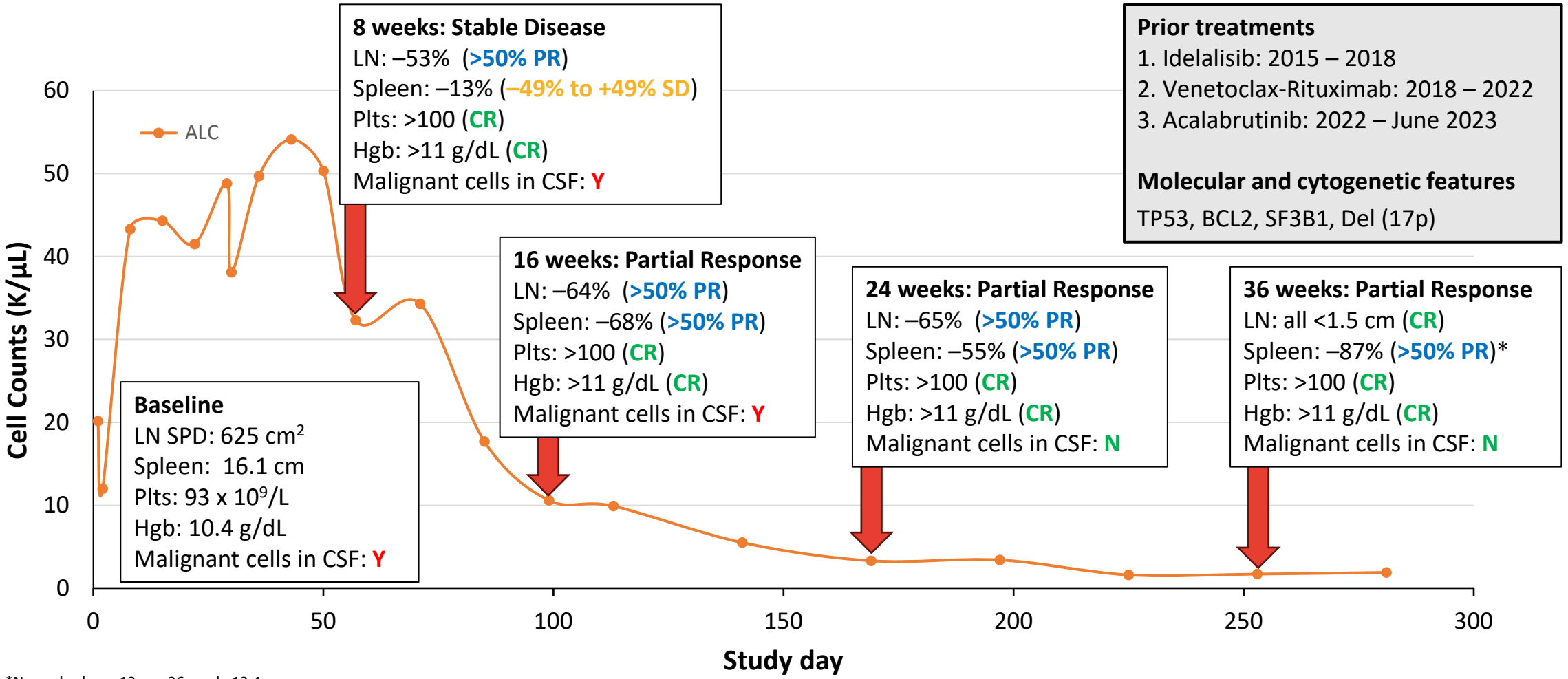


*Patient with Richter's transformation to Hodgkin's on biopsy

Data cutoff: 17 April 2024

Case Study: Patient with CLL and CNS Involvement

Deepening response over time approaching complete response criteria



*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

LN, lymph nodes; **Plts**, platelets; **Hgb**, hemoglobin; **CSF**, cerebrospinal fluid

References

Hansen GM. Oral presentation at AACR Annual Meeting 2024, San Diego, CA. April 9, 2024

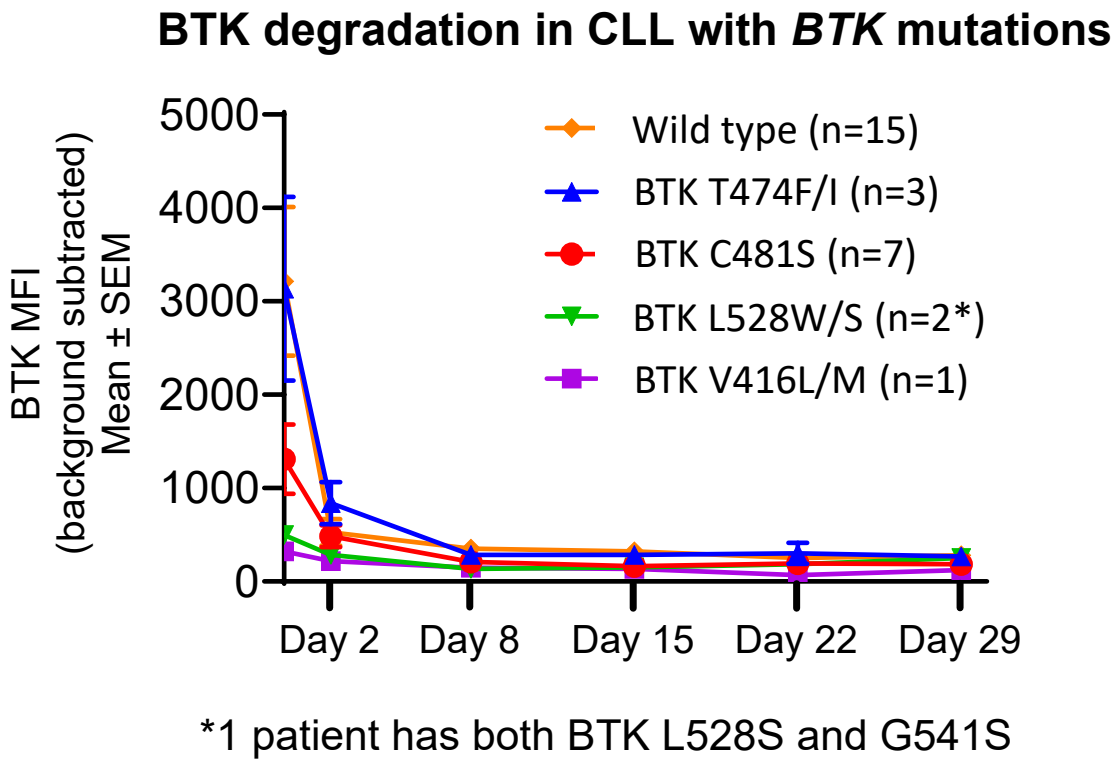
Data cutoff: 17 April 2024

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)

[a]Patients could have multiple BTK mutations; BTK mutations were tested at baseline by NGS centrally. ≥5% allelic frequency is reported.
[b]L528W, L528S; [c]T474F,T474I; [d]V416L, V416M.

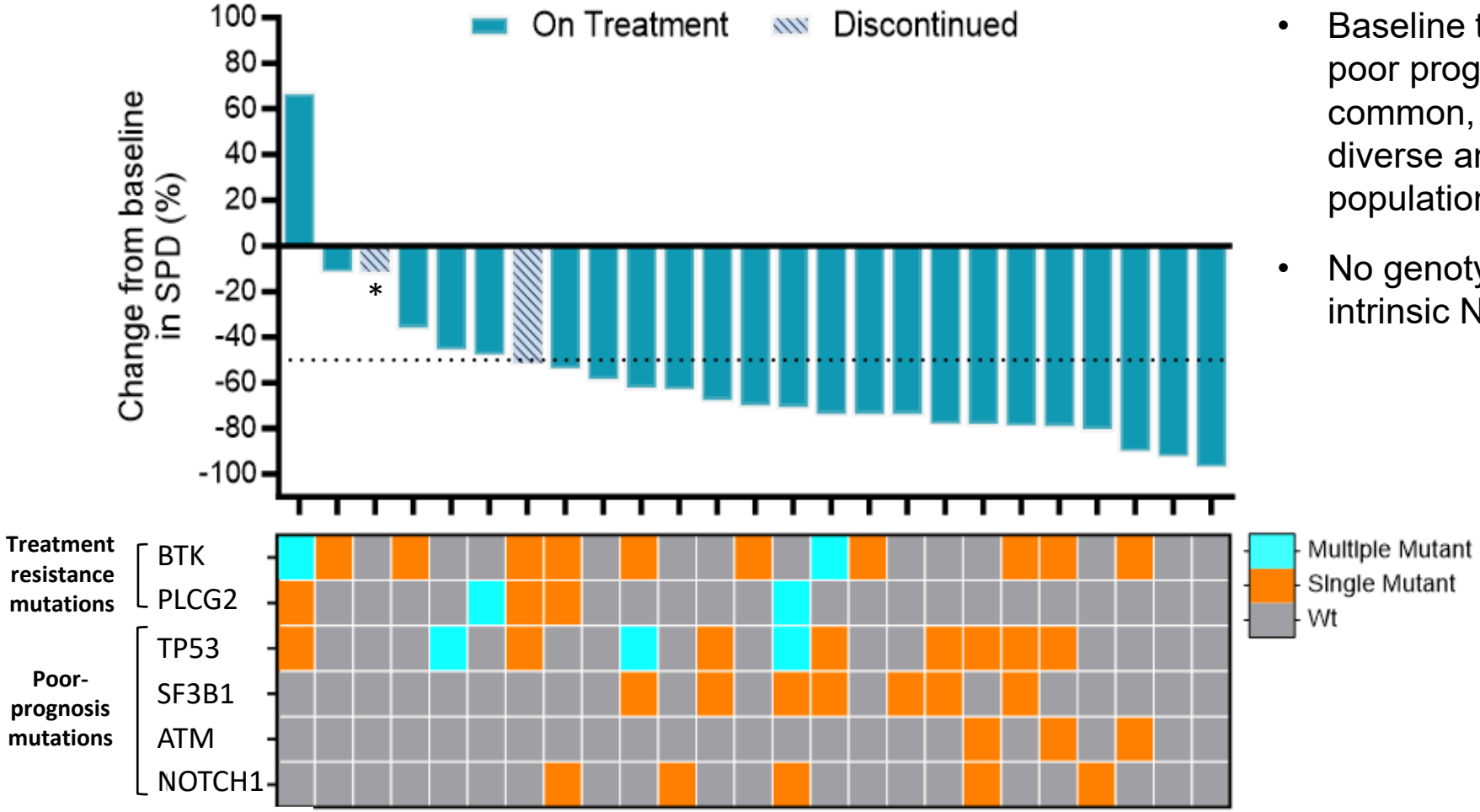


*1 patient has both BTK L528S and G541S

MFI, mean fluorescence intensity

Clinical Activity in Patients with Baseline Mutations

Treatment resistance and poor-prognosis genetic mutations



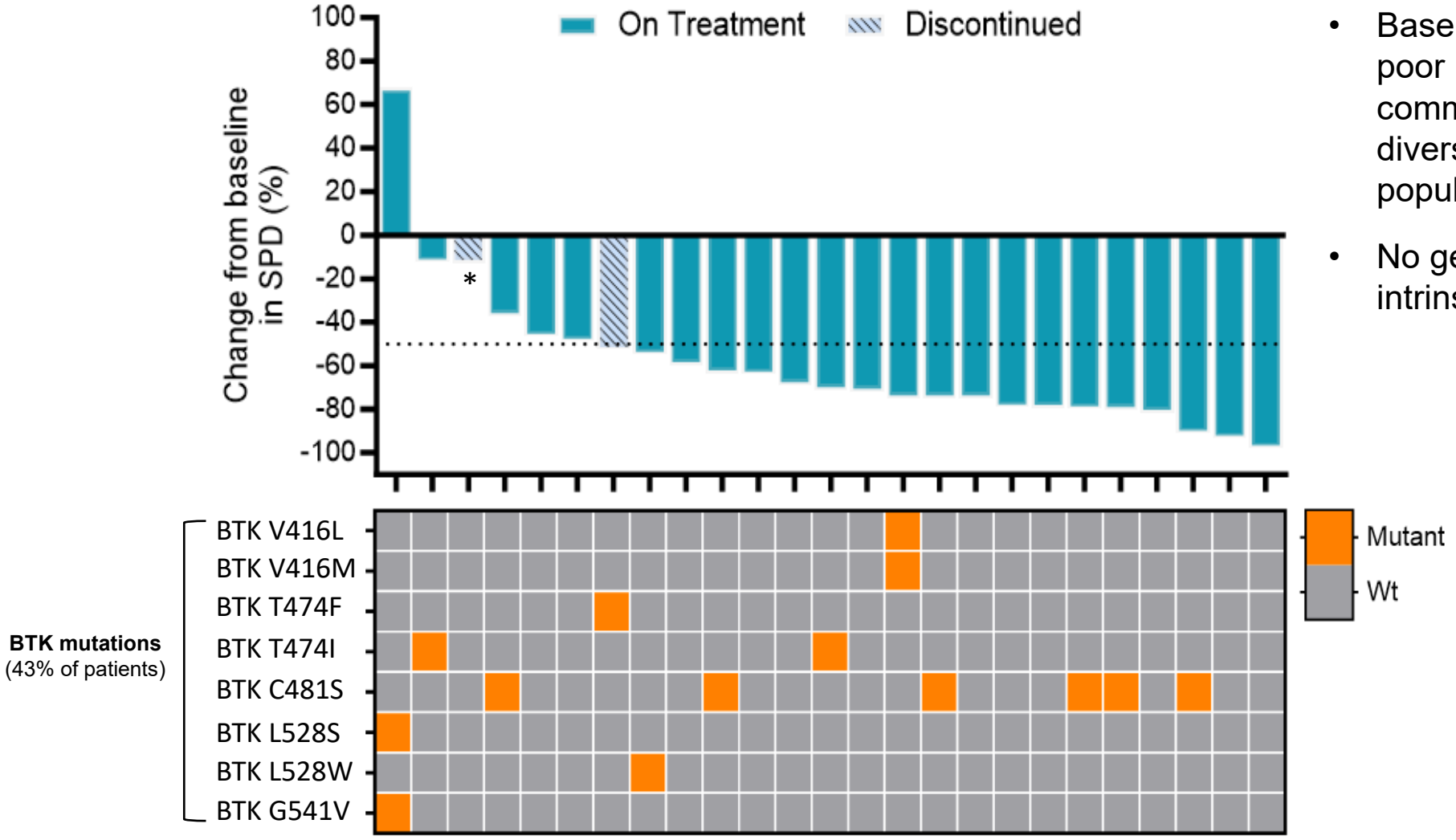
- Baseline treatment-resistance and poor prognosis mutations were common, indicating a genetically diverse and hard-to-treat CLL patient population
- No genotypic profile was linked to intrinsic NX-5948 resistance

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

Data cutoff: 17 April 2024

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

Data cutoff: 17 April 2024

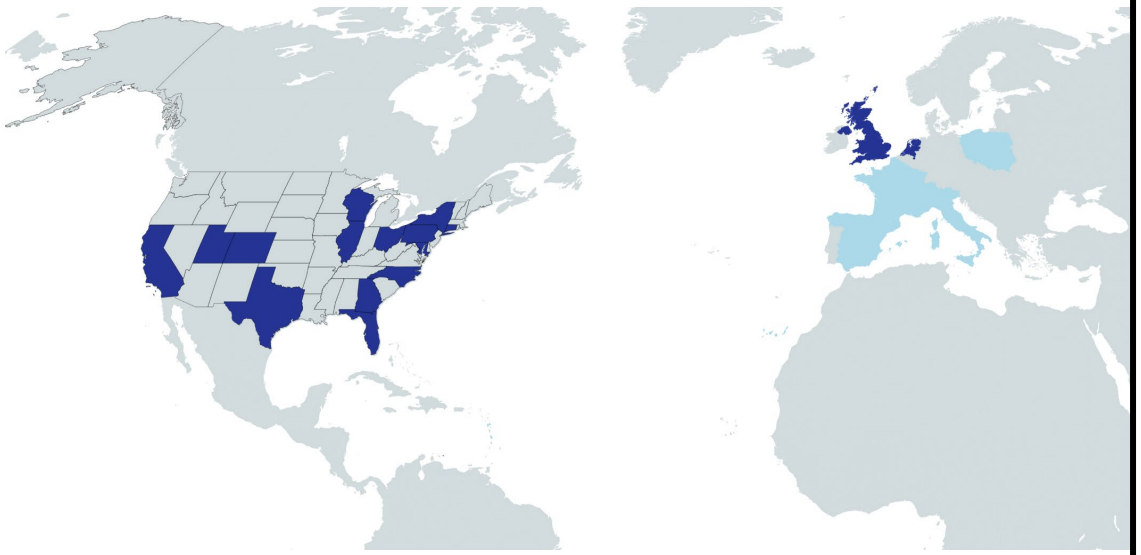
Conclusions:

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

Acknowledgements

- The authors are grateful to the patients and their families who enrolled in this trial
- The authors would also like to thank:
  - All NX-5948 investigators and study sites in the US, UK and the Netherlands for participating in this clinical research
  - Nurix employees working on developing NX-5948 and supporting the clinical trial
- The NX-5948-301 study is sponsored by Nurix Therapeutics, Inc
- Medical writing/editing support for this presentation was provided by Miller Medical Communications Ltd., which was funded by Nurix Therapeutics, Inc



Participating Global Sites

USA

Cayuga Cancer Center, Ithaca, NY

City of Hope National Medical Center, Duarte, CA

Colorado Blood Cancer Institute Medical Group, Denver, CO

Duke Cancer Institute, Durham NC

Emory Winship Cancer Institute, Atlanta, GA

Feinberg School of Medicine, Northwestern University, Chicago, IL

Huntsman Cancer Institute, Salt Lake City, UT

MD Anderson Cancer Center, Houston, TX

Medical College of Wisconsin, Milwaukee, WI

Memorial Sloan Kettering Cancer Center, New York , NY

Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL

Taussig Cancer Institute, Cleveland Clinic Main Campus, Cleveland, OH

UCSF Helen Diller Comprehensive Cancer Center, San Francisco, CA

University of Cincinnati, Cincinnati, OH

University of Pennsylvania, Philadelphia, PA

Yale School of Medicine, New Haven, CT

UK

Barts Cancer Institute, Queen Mary University of London

Beatson West of Scotland Cancer Centre, Glasgow, Scotland

Clatterbridge Cancer Centre, Liverpool

Derriford Hospital, Plymouth

Oxford University Hospitals NHS Foundation Trust, Oxford

Royal Marsden NHS Foundation Trust, Sutton

Sarah Cannon Research Institute, London

St. James's Hospital, Leeds

The Christie Hospital and Manchester Cancer Research Centre, Division of Cancer Sciences, Manchester

University Hospital Southampton NHS Trust, Southampton

The Netherlands

Erasmus MC Cancer Institute, University Medical Center Rotterdam, department of Hematology; on behalf of the Lunenburg Lymphoma Phase I/II Consortium – HOVON /LLPC

Radboud UMC, Nijmegen

UMC Utrecht

University of Groningen