Efficacy and safety of the Bruton’s tyrosine kinase (BTK) degrader NX-5948 in patients with relapsed/refractory chronic lymphocytic leukemia: updated results from an ongoing Phase 1a/b study

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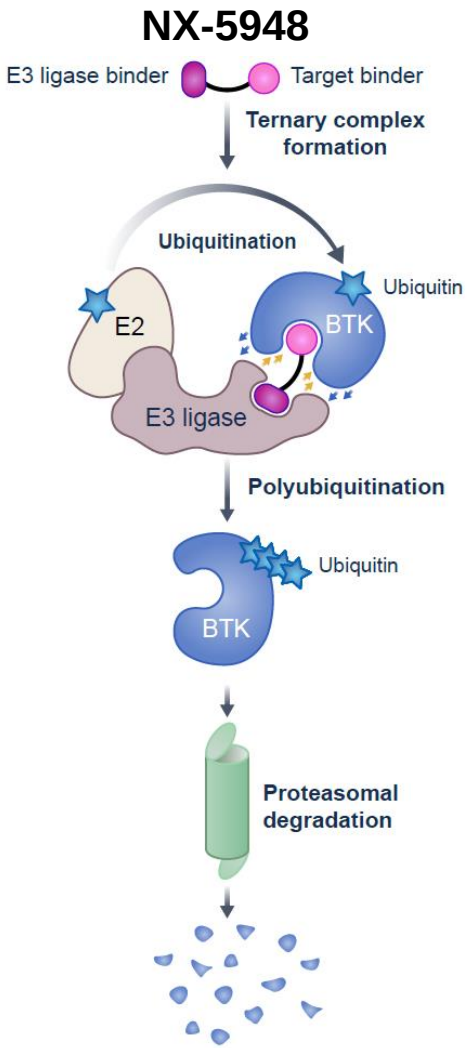
ASH 2024 Annual Meeting, San Diego CA – December 9, 2024

Background

Novel BTK degrader NX-5948 addresses current unmet need in CLL treatment



- The current standard of care in CLL focuses on utilizing the inhibitors of two key signaling pathways – BTK and BCL2
- Unmet need still exists in the CLL treatment landscape:
  - Covalent and non-covalent BTKi resistance mutations[1] are found in more than half of patients who progress on BTKi therapies[2]
  - Some mutations in *BTK* can maintain intact B-cell receptor signaling through a scaffolding function of BTK[3]
  - The number of BCL2i refractory and double (BTKi/BCL2i) refractory patients is growing[4]
- Novel BTK degrader NX-5948 offers an additional treatment modality:
  - Can overcome treatment-emergent BTKi resistance mutations[5] and disrupt BTK scaffolding[3,5]

BCL2, B-cell lymphoma 2; **BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CLL**, chronic lymphocytic leukemia

References
1. Noviski et al. 20th Biennial International Workshop on CLL Meeting, Boston, MA. October 6–9, 2023
2. Molica et al. 66th ASH Annual Meeting, December 7–10, 2024
3. Montoya et al. Science 2024;383
4. Hayama and Riches. Onco Targets 2024;17
5. Linton K, et al. Oral presentation at European Hematology Association Hybrid Congress; 16 June 2024

NX-5948-301: Trial Design

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

Phase 1a dose escalation (completed enrollment)

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

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

CLL/SLL 200 mg QD Prior BTKi and BCL2i	**CLL/SLL 600 mg QD** Prior BTKi and BCL2i
WM 3L+ post-BTKi	**WM** 2L post-BTKi

MCL
Prior BTKi and anti-CD20 CIT

MZL
Prior anti-CD20 CIT and ≥2 prior LoT

DLBCL
Prior anthracycline, anti-CD20 CIT + 1 LoT

FL
Prior anti-CD20 CIT + 1 LoT

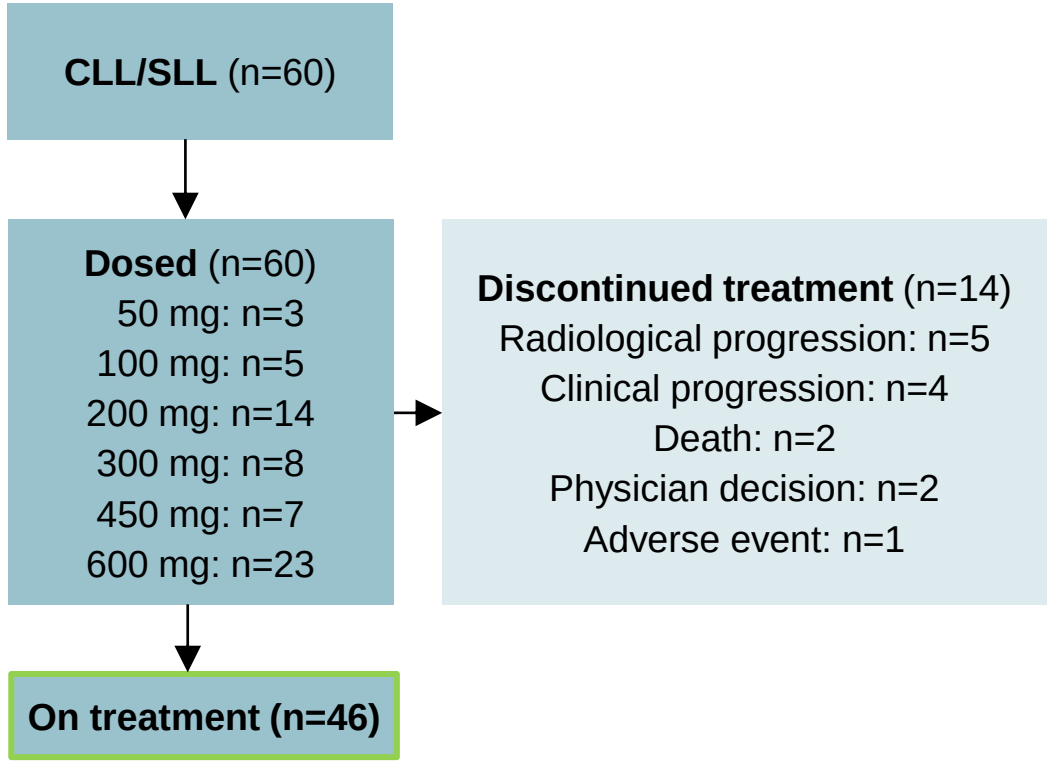
PCNSL/SCNSL
Patients who have progressed or had no response to ≥1 prior LoT

BCL2i, BCL2 inhibitor; **BTKi**, BTK inhibitor; **CIT**, chemo-immunotherapy; **CLL**, chronic lymphocytic leukemia; **DLBCL**, diffuse large B-cell lymphoma; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **FL**, follicular lymphoma; **LoT**, lines of treatment; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **NHL**, non-Hodgkin's lymphoma; **PCNSL**, primary CNS lymphoma; **QD**, once daily; **SCNSL**, secondary CNS lymphoma; **SLL**, small lymphocytic lymphoma; **WM**, Waldenstrom's macroglobulinemia

CLL Patient Disposition and Demographics

Phase 1a and 1b

Patient disposition



Patient demographics

Characteristics	Patients[a] (n=60)
Median age, years (range)	67.0 (35–88)
Sex, n (%)	
Male	38 (63.3)
Ethnicity, n (%)	
Hispanic or Latino	4 (6.7)
Race, n (%)	
Black or African American	5 (8.3)
White	51 (85.0)
Other	4 (6.7)

[a]Population demographics in CLL cohort were comparable to those in the overall population

CLL, chronic lymphocytic leukemia; **SLL**, small lymphocytic lymphoma

Baseline Disease Characteristics

Multiple prior lines of therapy and high prevalence of baseline mutations

Characteristics	Patients with CLL/SLL[a] (n=60)
ECOG PS, n (%)	
0	24 (40.0)
1	36 (60.0)
CNS involvement, n (%)	5 (8.3)
Median prior lines of therapy (range)	4.0 (1–12)
Previous treatments[b], n (%)	
BTKi	59 (98.3)
cBTKi	59 (98.3)
ncBTKi[c]	17 (28.3)
BCL2i	50 (83.3)
BTKi and BCL2i	49 (81.7)
CAR-T therapy	3 (5.0)
Bispecific antibody	4 (6.7)
PI3Ki	18 (30.0)
Chemo/chemo-immunotherapies (CIT)	43 (71.7)
Mutation status[d] (n=57), n (%)	
TP53	23 (40.4)
BTK	22 (38.6)
PLCG2	7 (12.3)
BCL2	6 (10.5)

[a]Baseline disease characteristics in CLL cohort were comparable to those in the overall population; [b]Patients could have received multiple prior treatments; [c]All patients who received ncBTKi have also previously received cBTKi; [d]Mutations presented here were centrally sequenced.

BCL2, B-cell lymphoma 2**; BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CAR-T**, chimeric antigen receptor T-cell; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group (ECOG) performance status; **ncBTKi**, non-covalent BTKi; **PI3Ki**, phosphoinositide 3-kinase inhibitor; **PLCG2**, phospholipase C gamma 2; **SLL**, small lymphocytic lymphoma

NX-5948 Safety Profile

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

TEAEs, n (%)	**Patients with CLL/SLL (n=60)**			**Overall population (N=125)**		
	Any grade	**Grade ≥3**	**SAEs**	**Any grade**	**Grade ≥3**	**SAEs**
Purpura/contusion[a]	22 (36.7)	–	–	42 (33.6)	–	–
Fatigue[b]	16 (26.7)	–	–	29 (23.2)	2 (1.6)	–
Petechiae	16 (26.7)	–	–	28 (22.4)	–	–
Thrombocytopenia[c]	10 (16.7)	1 (1.7)	–	26 (20.8)	7 (5.6)	–
Rash[d]	14 (23.3)	1 (1.7)	1 (1.7)	24 (19.2)	2 (1.6)	1 (0.8)
Neutropenia[e]	14 (23.3)	11 (18.3)	–	23 (18.4)	18 (14.4)	–
Anemia	11 (18.3)	4 (6.7)	–	21 (16.8)	10 (8.0)	–
Headache	10 (16.7)	–	–	21 (16.8)	1 (0.8)	1 (0.8)
COVID-19[f]	10 (16.7)	–	–	19 (15.2)	2 (1.6)	2 (1.6)
Diarrhea	12 (20.0)	1 (1.7)	–	18 (14.4)	1 (0.8)	–
Cough	9 (15.0)	–	–	16 (12.8)	1 (0.8)	–
Pneumonia[g]	4 (6.7)	2 (3.3)	2 (3.3)	10 (8.0)	6 (4.8)	6 (4.8)
Lower respiratory tract infection	3 (5.0)	1 (1.7)	1 (1.7)	9 (7.2)	3 (2.4)	2 (1.6)
Fall	1 (1.7)	1 (1.7)	1 (1.7)	8 (6.4)	2 (1.6)	2 (1.6)
Hypertension	2 (3.3)	1 (1.7)	–	7 (5.6)	5 (4.0)	–
Hyponatremia	–	–	–	3 (2.4)	2 (1.6)	–
Pulmonary embolism	1 (1.7)	1 (1.7)	1 (1.7)	2 (1.6)	2 (1.6)	2 (1.6)
Subdural hematoma	1 (1.7)	–	1 (1.7)	2 (1.6)	1 (0.8)	2 (1.6)

- Tolerable safety profile consistent with prior disclosures
- 1 case of Grade 1 AFib in a CLL patient with pre-existing AFib
- 6 TEAEs resulted in drug discontinuation (1 CLL; 5 NHL)
- 2 Grade 5 AEs (1 pulmonary embolism; 1 case pending) deemed not related to NX-5948

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

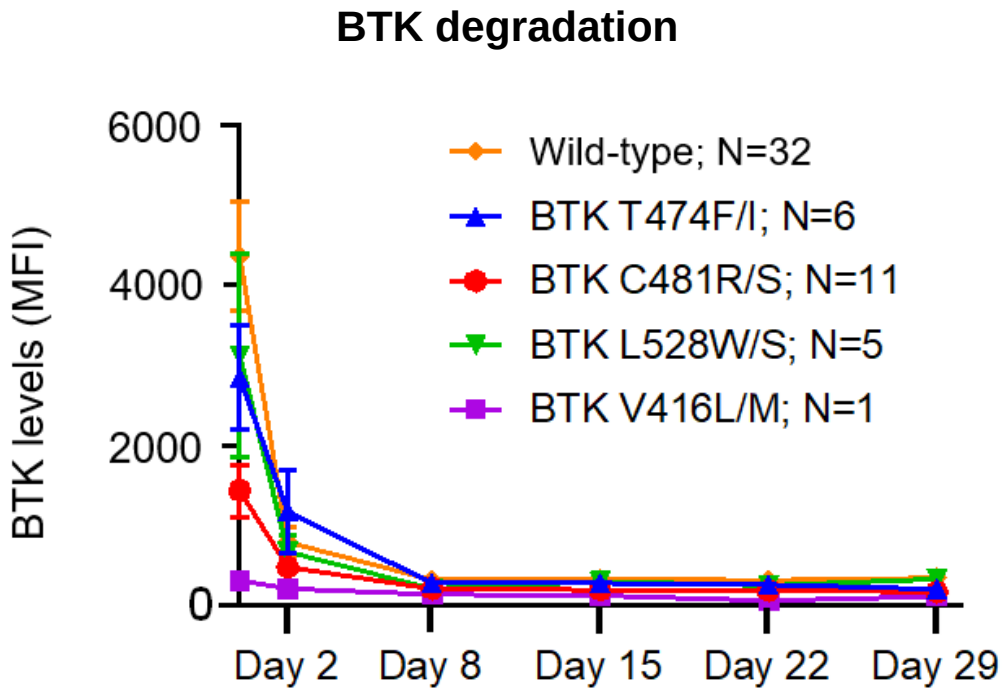
AE, adverse event; **AFib**, atrial fibrillation; **CLL**, chronic lymphocytic leukemia; **NHL**, non-Hodgkin's lymphoma; **SAE**, serious adverse event; **SLL**, small lymphocytic lymphoma; **TEAE**, treatment emergent AE

NX-5948 Degrades Wild-Type and Mutated BTK

NX-5948 degrades gatekeeper, kinase-proficient and kinase-dead BTK mutations

	Patients with CLL/SLL (n=57)[c]
Baseline mutation status, n (%)	
BTK mutations[1,a,b]	22 (38.6)
C481S	12 (21.1)
C481R	2 (3.5)
L528W	4 (7.0)
L528S	1 (1.8)
T474I	5 (8.8)
T474F	1 (1.8)
V416M	1 (1.8)
V416L	1 (1.8)
G541V	1 (1.8)

[a]Patients could have multiple prior treatments and BTK mutations; BTK mutations were tested at baseline by next-generation sequencing centrally. ≥5% allelic frequency is reported
[b]Patients can have more than one resistance mutation
[c]Patients with available mutation status



Note: Some patients have multiple BTK mutations

Reference
1. Montoya et al. Science 2024;383

BTK, Bruton's tyrosine kinase; **CLL**, chronic lymphocytic leukemia; **MFI**, mean fluorescence intensity; **SLL**, small lymphocytic lymphoma

Data cutoff: 10 Oct 2024

NX-5948 Overall Response Assessment

Response rate deepens with longer time on treatment

CLL response-evaluable patients	**Primary ORR analysis[b]** ≥1 response assessment(s) at 8 weeks (n=49)[c]	**Exploratory ORR analysis[b]** ≥2 response assessments at 16 weeks (n=38)[c]
Objective response rate (ORR),[a] % (95% CI)	75.5 (61.1–86.7)	84.2 (68.7–94.0)
Best response, n (%)		
CR	0 (0.0)	0 (0.0)
PR	36 (73.5)	32 (84.2)
PR-L	1 (2.0)	0 (0.0)
SD	10 (20.4)	4 (10.5)
PD	2 (4.1)	2 (5.3)

[a]Objective response rate includes CR + PR + PR-L

[b]Patients who progressed prior to their first response assessment and patients who discontinued for any reason after their first response assessment are included in the denominators

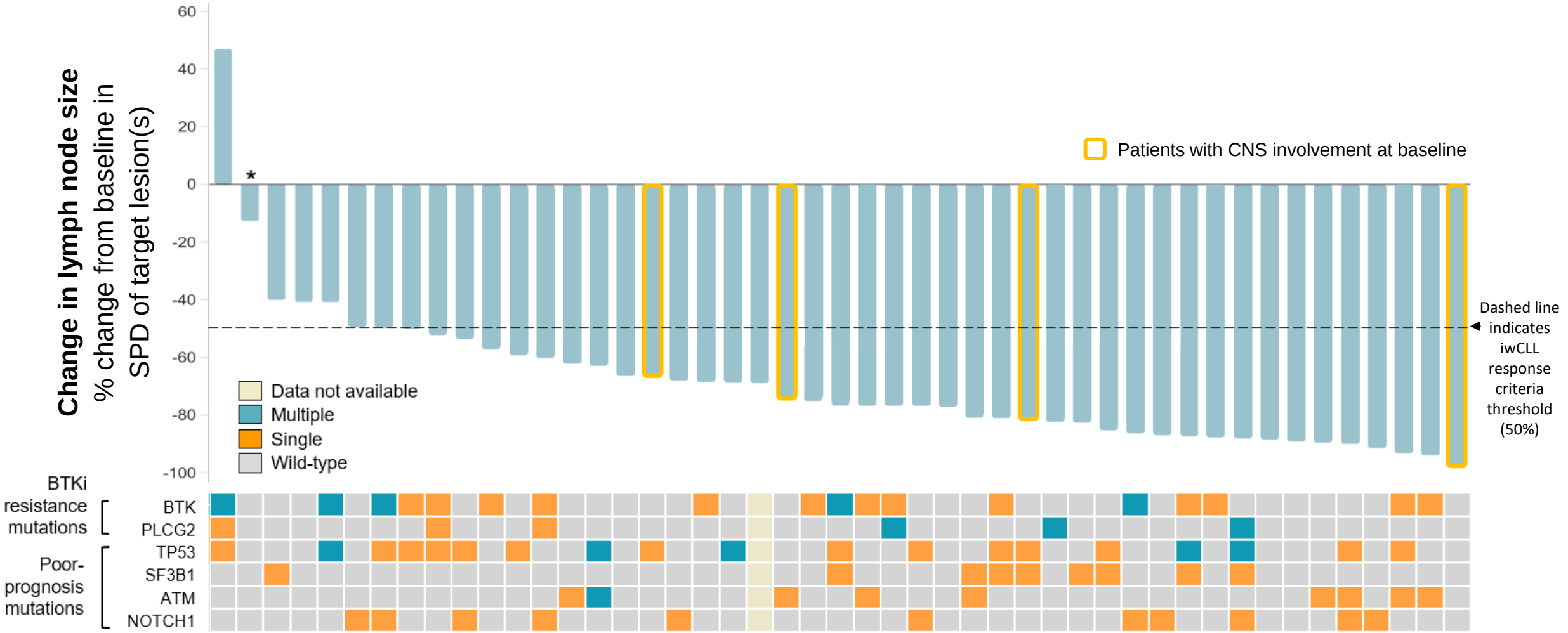
[c]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL criteria, while they may not be represented in waterfall plot

CLL, chronic lymphocytic leukemia; **CR**, complete response; **iwCLL**, International Workshop on CLL; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **PR-L**, partial response with rebound lymphocytosis; **SD**, stable disease

Data cutoff: 10 Oct 2024

Lymph Node Assessment and High-Risk Molecular Features

Clinical activity in patients with CLL including those with baseline mutations and CNS involvement



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

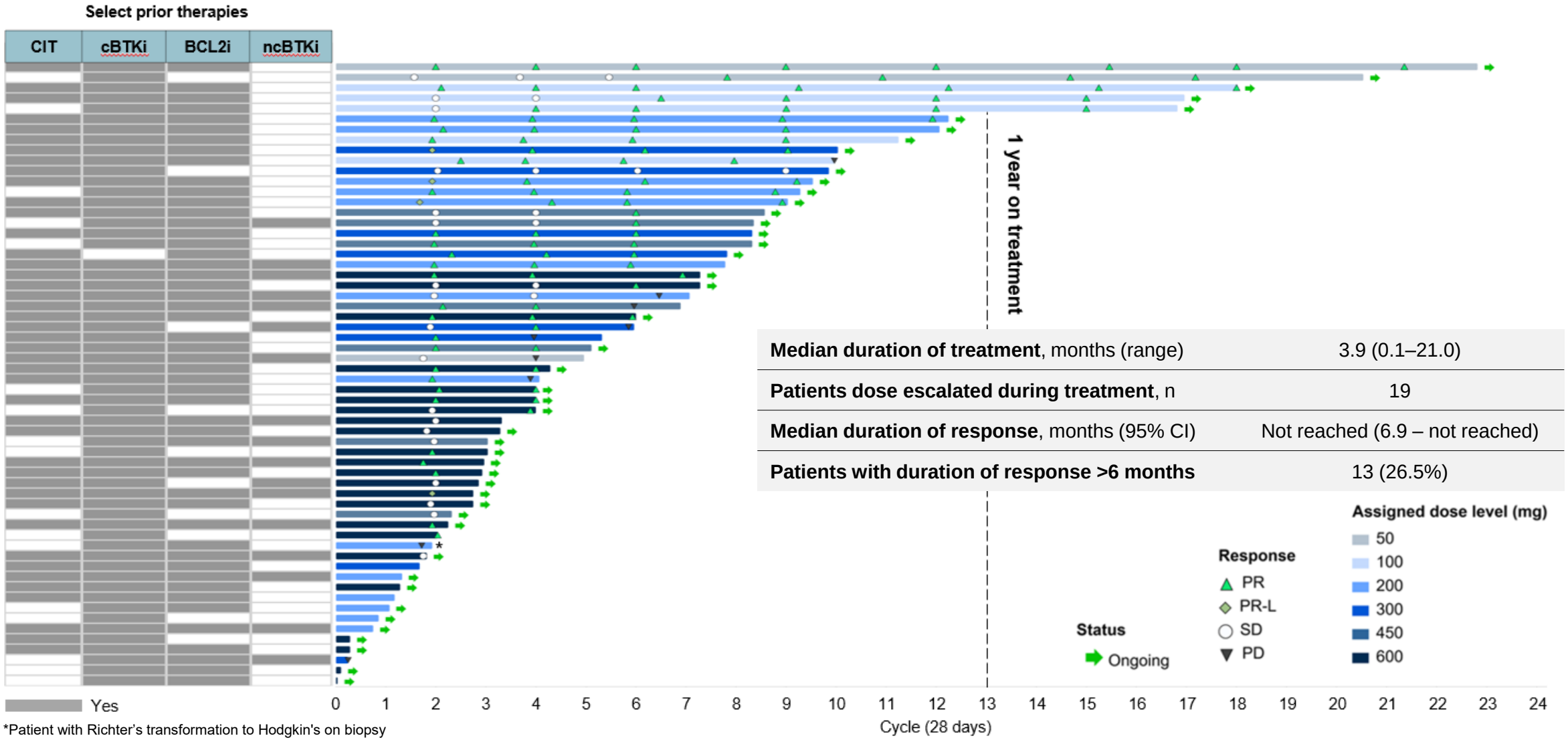
Note: patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL criteria, while they may not be represented in waterfall plot

ATM, Ataxia-telangiectasia mutated; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **iwCLL**, International Workshop on CLL; **NOTCH1**, neurologic locus notch homolog protein 1; **PLCG2**, phospholipase C gamma 2; **SPD**, sum of products diameters

Data cutoff: 10 Oct 2024

NX-5948 Duration of Treatment

Durable responses regardless of prior therapy



Median duration of treatment, months (range)	3.9 (0.1–21.0)
Patients dose escalated during treatment, n	19
Median duration of response, months (95% CI)	Not reached (6.9 – not reached)
Patients with duration of response >6 months	13 (26.5%)

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

BCL2i, BCL2 inhibitor; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CIT**, chemo/chemo-immunotherapies; **ncBTKi**, non-covalent BTKi; **PD**, progressive disease; **PR**, partial response; **PR-L**, PR with rebound lymphocytosis; **SD**, stable disease; **CI**, confidence interval

Data cutoff: 10 Oct 2024

Conclusions

- In this ongoing Phase 1 study, the BTK degrader NX-5948 demonstrated an encouraging clinical profile in a heavily pre-treated population of patients with CLL
- NX-5948 was well tolerated across B-cell malignancies, with no additional safety signals observed with longer duration on study or increased dose
- Robust and deepening clinical responses were observed in a heavily pretreated CLL patient population including patients with baseline BTK and PLCG2 mutations, high risk molecular features and CNS involvement
  - 75.5% ORR deepening to 84.2% ORR in patients with longer follow-up
- Durable responses achieved in patients with high unmet clinical need, post-BTKi, BCL2i
  - 13 patients with duration of response 6+ months and 5 patients remaining on treatment beyond 1 year

Phase 1b dose expansion is underway and pivotal trial(s) initiation is planned in 2025

Acknowledgments

- 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, the Netherlands, Poland and Spain 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.