Clinical Activity of NX-5948: A First-in-Class BTK Degrader

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

Program	Target	MOA	Therapeutic area	Discovery – Lead Op	IND enabling	Phase 1a	Phase 1b
NX-5948	BTK	TPD	B-cell malignancies				
NX-2127	BTK-IKZF	TPD	B-cell malignancies				
NX-1607	CBL-B	TPE	Immuno-Oncology				
BRAF degrader	Pan-mutant BRAF	TPD	Solid tumors				
Multiple	Undisclosed	TPD/DAC	Undisclosed				
Multiple	Undisclosed	TPD	Undisclosed		GILEAD sanofi		
Multiple	Undisclosed	DAC	Oncology		Pfizer		
NX-5948	BTK	TPD	Inflammation / autoimmune				
NX-0479/GS-6791	IRAK4	TPD	RA & inflammatory diseases		GILEAD		
STAT6 degrader	STAT6	TPD	T2 inflammatory diseases		sanofi		
Multiple	Undisclosed	TPD	Inflammation / autoimmune		sanofi		
Undisclosed	Undisclosed	TPD/DAC	Inflammation / autoimmune				

TPD: Targeted Protein Degradation; **TPE**: Targeted Protein Elevation; **DAC**: Degrader Antibody Conjugate; **RA:** Rheumatoid arthritis; **T2:** Type 2

Rationale for BTK Degraders

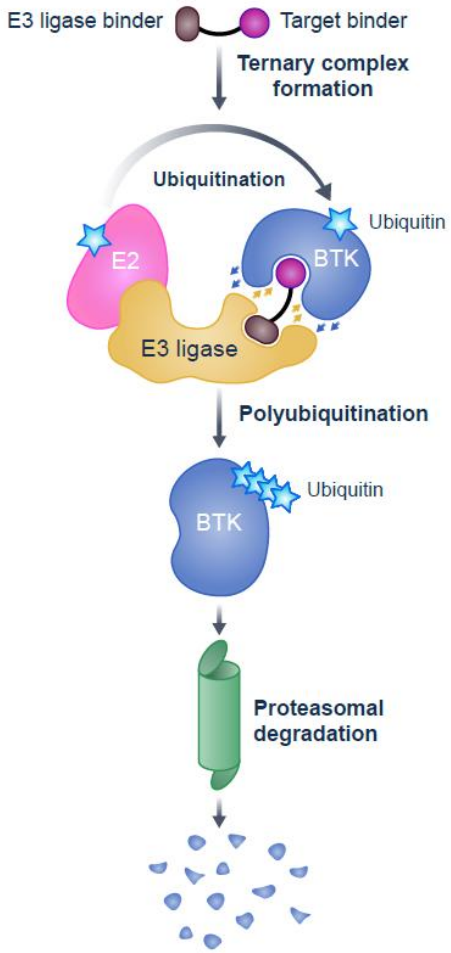
- The BCR signaling pathway mediated by BTK is a key driver in oncogenesis and a validated therapeutic target in multiple lymphoid malignancies
- BTK degraders:
  - Can overcome treatment-emergent BTK inhibitor resistance mutations[1,2]
  - Address BTK scaffolding function – the transduction of BCR signal downstream from BTK in the absence of BTK enzymatic activity[3]
  - Demonstrated emerging activity in various B-cell malignancies including CLL and Waldenstrom's Macroglobulinemia[4,5]

References
1. Noviski et al. NX-5948 and NX-2127 potently degrade a broad array of clinically-relevant BTK mutants that display resistance to inhibitors and other BTK degraders. iwCLL 2023; 2. Hansen G.M. Targeted Protein Degraders for the Treatment of Hematologic Malignancies: Addressing the Mutational Resistance of BTK in the Clinic. TPD Basel Sept 19, 2023; 3. Montoya et al. Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127. Science 2024;383; 4. Searle et al. Initial Findings From a First-in-Human Phase 1a/b Trial of NX-5948, a Selective Bruton's Tyrosine Kinase Degrader, in Patients with Relapsed/Refractory B-Cell Malignancies. ASH 2023; 5. Danilov et al. A First-in-Human Phase 1 Trial of NX-2127, a First-in-Class Bruton's Tyrosine Kinase Dual-Targeted Protein Degrader with Immunomodulatory Activity, in Patients with Relapsed/Refractory B-Cell Malignancies. ASH 2023

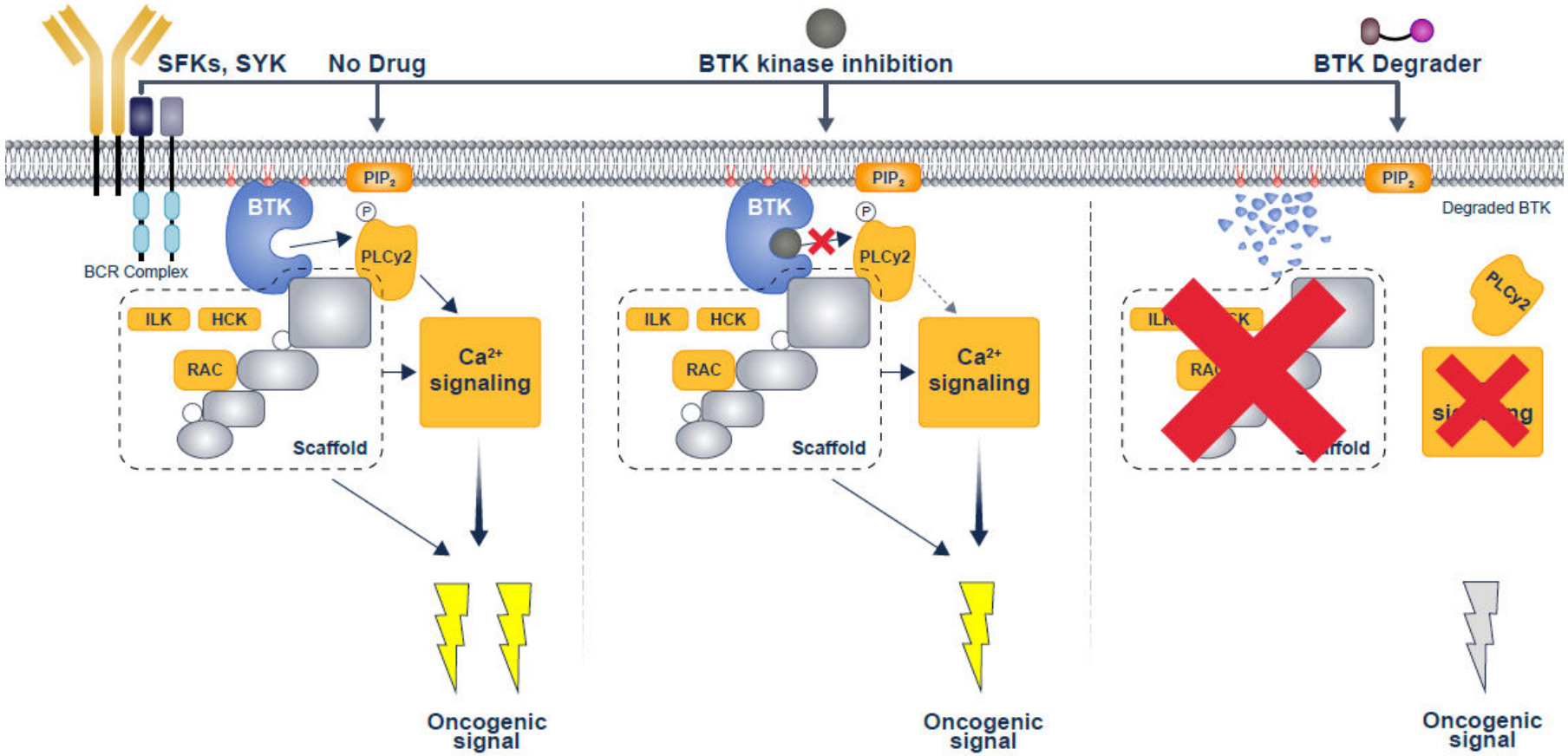
NX-5948 BTK Degrader Mechanism of Action

BTK degraders disrupt BCR signaling by destroying BTK protein and eliminating its immediate and downstream functions

NX-5948



BTK Scaffolding



References

1. Montoya et al. Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127. Science 2024;383
2. Eisen et al. Conditional Requirement for Dimerization of the Membrane-Binding Module of BTK. BioRxiv January 17, 2024
3. Yuan et al. BTK kinase activity is dispensable for the survival of diffuse large B-cell lymphoma. J Biol Chem.2022;298(11):102555

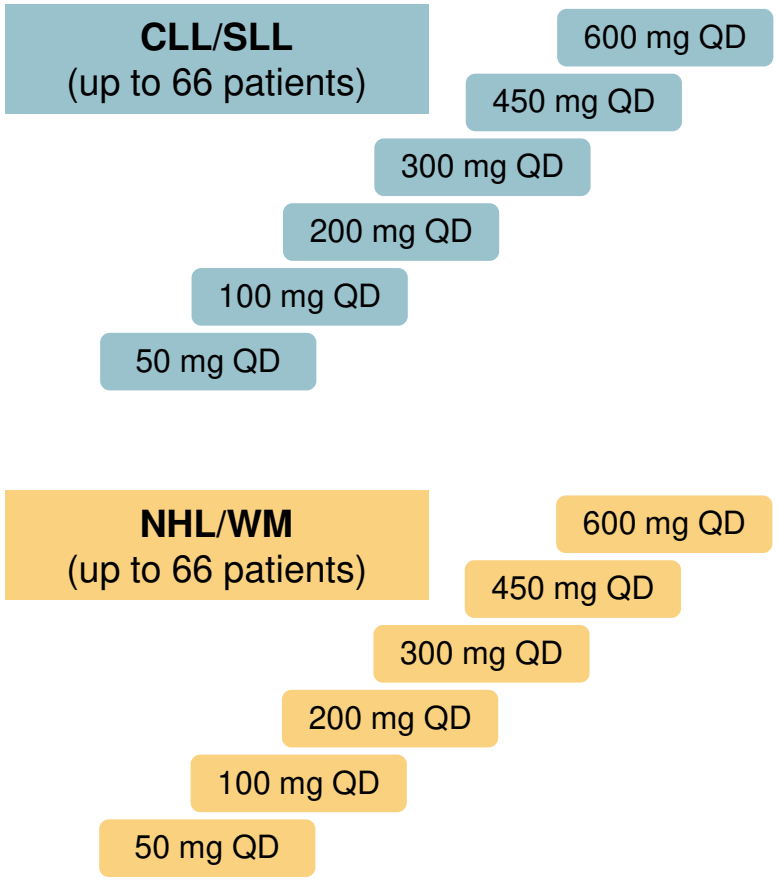
NX-5948-301: Trial Design

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

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)



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
3L+ post-BTKi (Global)

WM
2L post-BTKi (UK)

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
WM Bing-Neel patients allowed

nurix

BCL2i, Bcl-2 inhibitor; **CIT**, chemo-immunotherapy; **CLL**, chronic lymphocytic leukemia; **DLBCL**, diffuse large B-cell lymphoma; **ECOG PS**, Eastern Cooperative Oncology Group (ECOG) 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; **SCNSL**, secondary CNS lymphoma; **SLL**, small lymphocytic lymphoma; **WM**, Waldenstrom's macroglobulinemia

Baseline Demographics/Disease Characteristics

Elderly population with multiple prior lines of targeted therapies and poor prognosis mutations

Characteristics	Overall population (N=79)	Patients with CLL (n=31)	Patients with WM (n=13)
Median age, years (range)	67.0 (35–88)	69.0 (35–88)	74.0 (64–82)
Male, n (%)	52 (65.8)	19 (61.3)	11 (84.6)
ECOG PS, n (%)			
0	26 (32.9)	13 (41.9)	3 (23.1)
1	51 (64.6)	18 (58.1)	10 (76.9)
CNS involvement, n (%)	12 (15.2)	2 (6.5)	0
Median prior lines of therapy (range)	4.0 (2–14)	4.0 (2–14)	3.0 (2–5)
Previous treatments[a], n (%)			
BTKi	59 (74.7)	30 (96.8)	13 (100.0)
Pirtobrutinib	NA	7 (22.6)	3 (23.1)
BCL2i	35 (44.3)	28 (90.3)	1 (7.7)
BTKi and BCL2i	34 (43.0)	27 (87.1)	1 (7.7)
CAR-T therapy	13 (16.5)	2 (6.5)	0 (0.0)
Bispecific antibody	8 (10.1)	1 (3.2)	0 (0.0)
PI3Ki	13 (16.5)	9 (29.0)	0 (0.0)
Chemo/chemo-immunotherapies	72 (91.1)	24 (77.4)	13 (100.0)
Mutation status, n (%)			
TP53	18/72 (25.0)	14/30 (46.7)	NA
BTK	13/72 (18.1)	13/30 (43.3)	NA
PLCG2	8/72 (11.1)	6/30 (20.0)	NA
MYD88	NA	NA	8/13 (61.5)
CXCR4	NA	NA	2/13 (15.4)
	Data cutoff: 17 Apr 2024	Data cutoff: 17 Apr 2024	Data cutoff: 10 Oct 2024

[a]Patients could have received multiple prior treatments

CAR-T, chimeric antigen receptor T-cell; **NA**, not applicable; **PI3Ki**, PI3 kinase inhibitor

Linton K, et al. Oral presentation at European Hematology Association Hybrid Congress; 16 June 2024
O'Connor P. Oral presentation at 12th International Workshop on Waldenstrom's Macroglobulinemia meeting; 19 October 2024

NX-5948 Is Well Tolerated with a Limited Number of Adverse Events Leading to Drug Discontinuation

Frequency of any grade TEAEs in ≥10% of patients or grade ≥3 TEAEs or SAEs in >1 patient

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

- 1 DLT (non-protocol mandated drug hold; maculopapular rash in NHL)
- 2 TEAEs resulting in drug discontinuation (both NHL)
- 1 related SAE (TLS based on labs in CLL, no clinical sequelae)
- Grade 5 AE (pulmonary embolism in CLL, 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'

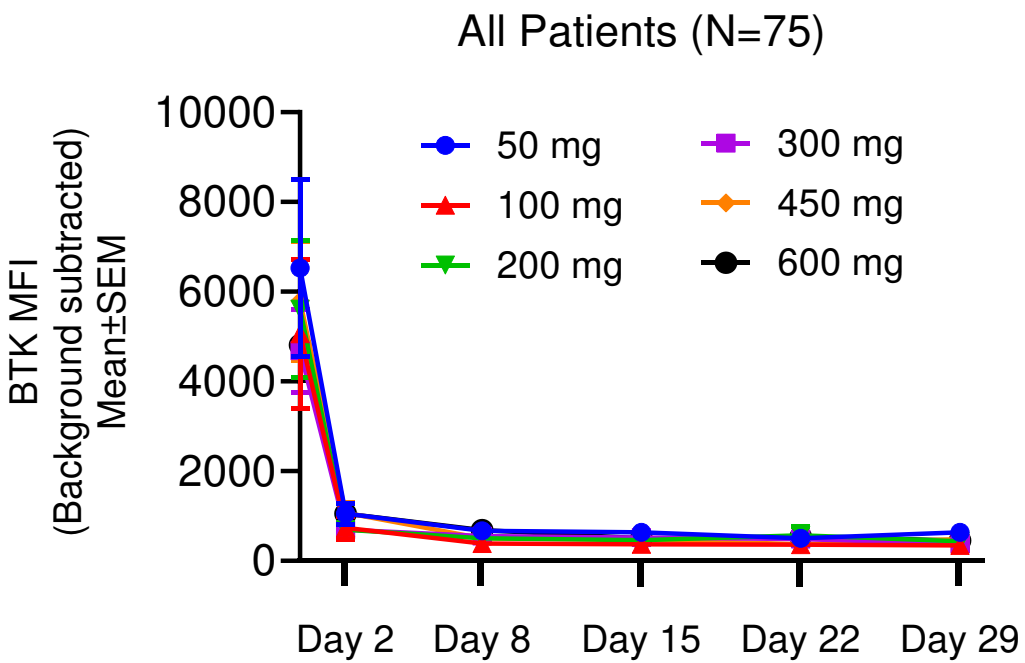
AE, adverse event; **CLL**, chronic lymphocytic leukemia; **DLT**, dose-limiting toxicity; **NHL**, non-Hodgkin's lymphoma; **SAE**, serious adverse event; **TEAE**, treatment emergent adverse event; **TLS**, tumor lysis syndrome

Data cutoff: 17 Apr 2024

[1]Linton K, et al. Oral presentation at European Hematology Association Hybrid Congress; 16 June 2024

NX-5948 BTK Degradation

Robust, rapid and sustained degradation independent of BTK mutation status



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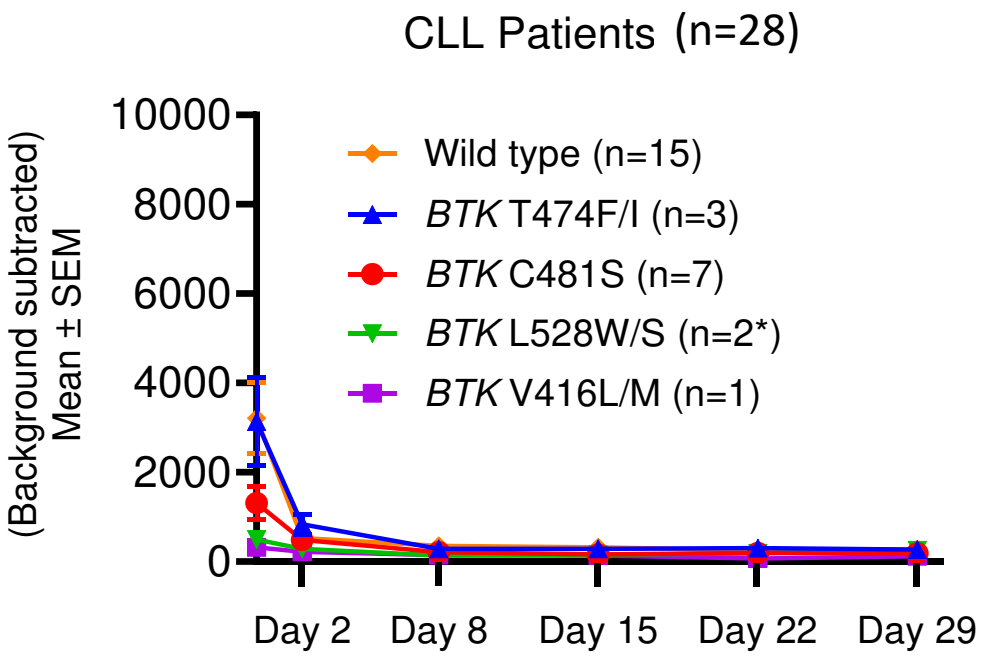


**One patient has BTK L528S and G541V*

Data cutoff: 17 Apr 2024

NX-5948 is potent and acts rapidly in degrading BTK as evidenced by >80% degraded by Day 15 administration

[a]BTK measured in patient B-cells whole blood using flow cytometry assay

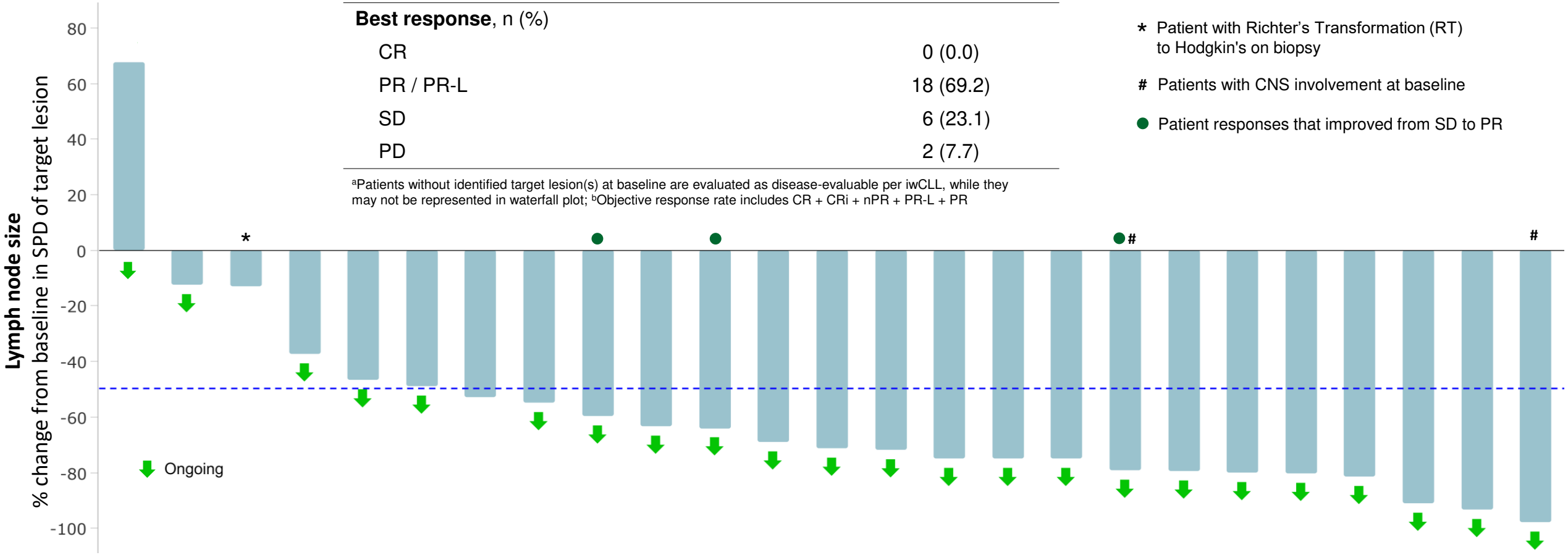
BTK, Bruton's tyrosine kinase; **MFI,** mean fluorescence intensity; **SEM**, standard error of the mean

NX-5948 Efficacy (Response-Evaluable Patients with CLL)

ORR assessment includes patients whose responses deepened over time

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

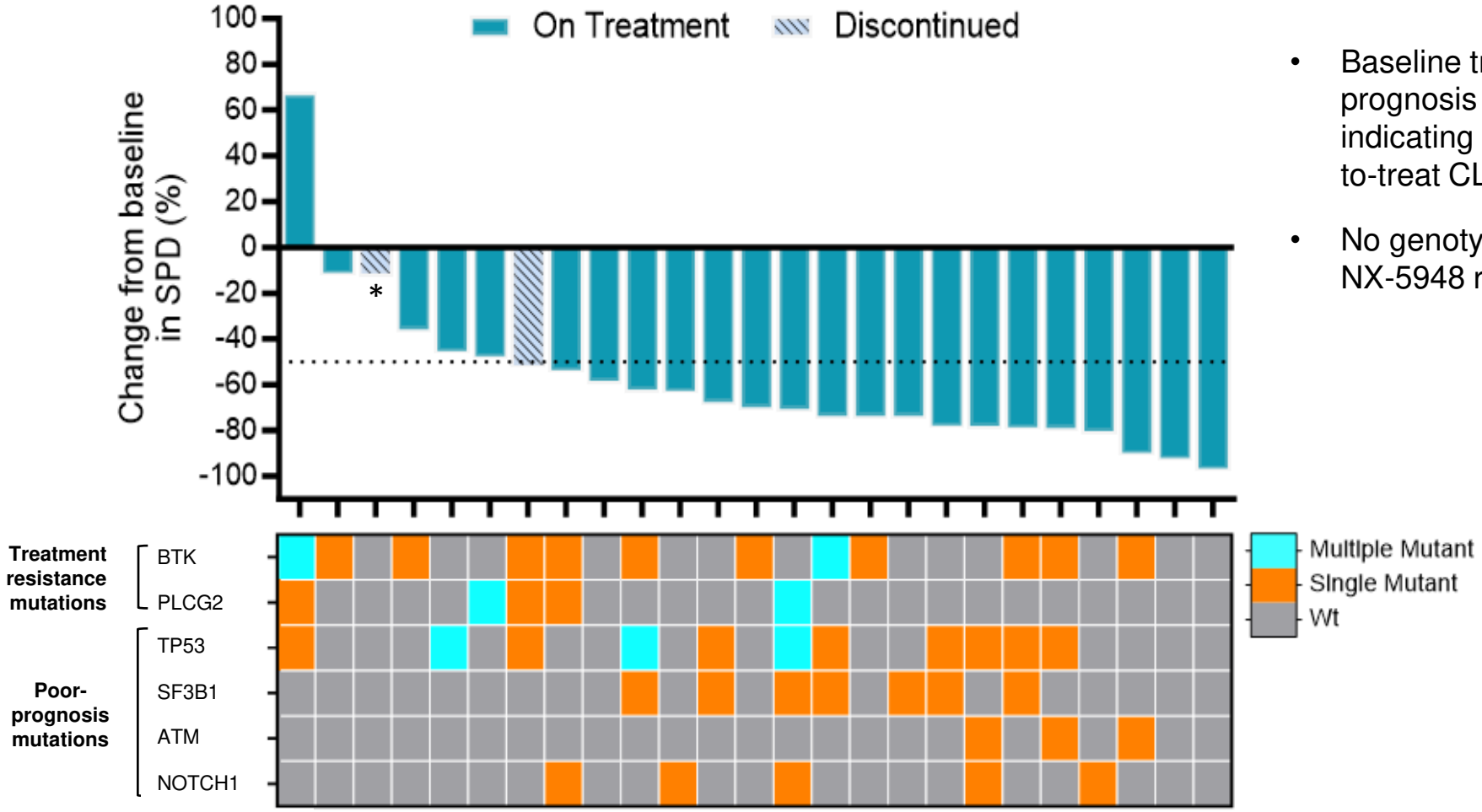
● Patient responses that improved from SD to PR

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

Data cutoff: 17 April 2024

Clinical Activity in Patients with Baseline Mutations

No genotypic profile linked to intrinsic NX-5948 resistance



- 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

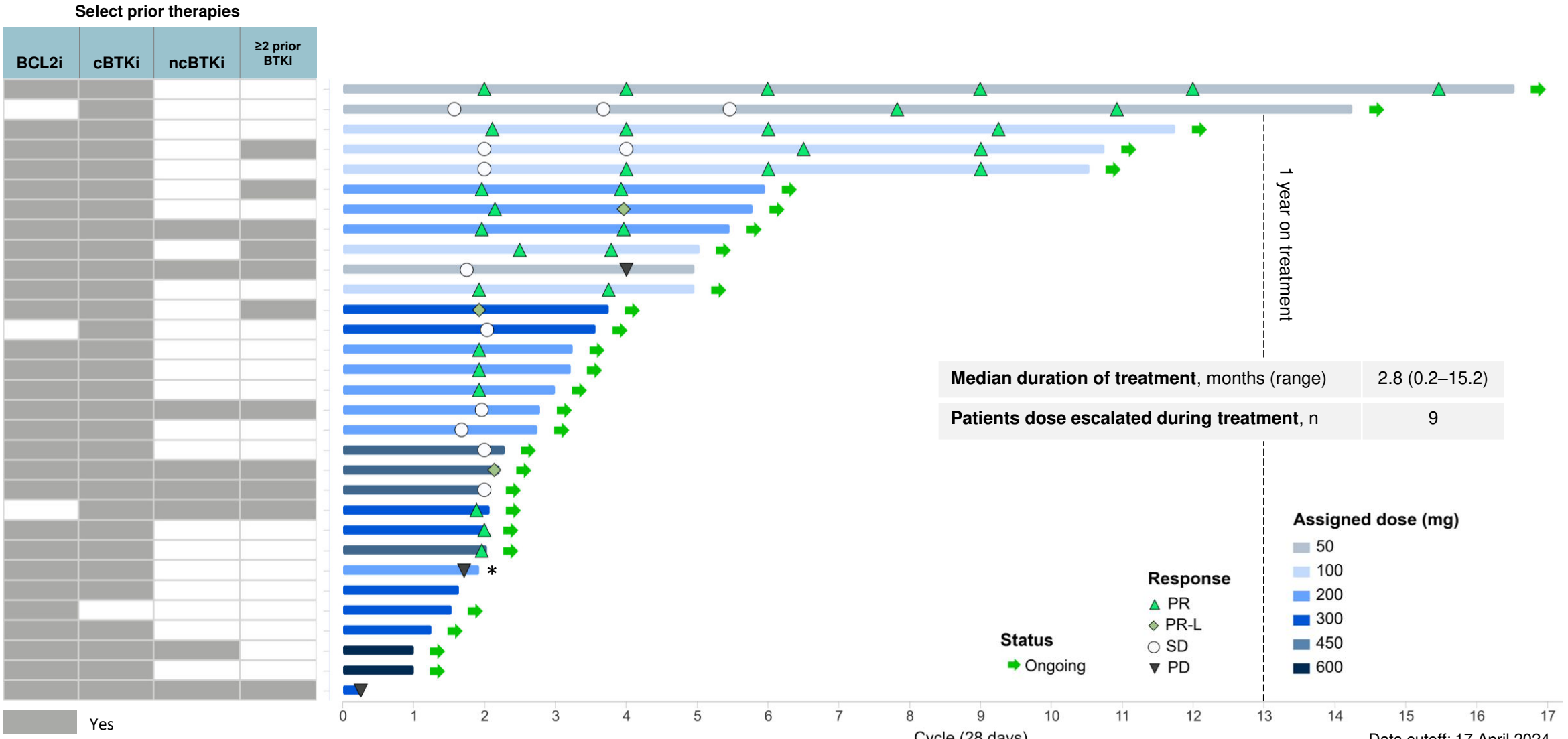
*Patient with Richter's transformation to Hodgkin's on biopsy

Data cutoff: 17 April 2024

Linton K, et al. Oral presentation at European Hematology Association Hybrid Congress; 16 June 2024

NX-5948 Duration of Treatment

Durable responses, including responses beyond one year in heavily pretreated patients with CLL



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

Data cutoff: 17 April 2024

Linton K, et al. Oral presentation at European Hematology Association Hybrid Congress; 16 June 2024

Case Study 1: Patient with CLL and CNS Involvement

Age, Race, M/F	59, White, M
Diagnosis	CLL, High Risk, Stage C
Initial diagnosis	May 2015
Recent progression	03 Oct 2022 (with CNS relapse)
Dose	100 mg/day →300 mg/day
C1D1	27-Jun-23
Status	On treatment
Current cycle	12

Relevant medical history

- Anxiety: 2015-ongoing
- Depression: 2015-ongoing
- Previous Hepatitis B infection: 2015 (on anti-viral prophylaxis but no evidence of recurrent disease)
- Recurrent lung infection: 2015-ongoing
- Face numbness: Unknown-ongoing
- Constipation: 21Jun23-ongoing

Prior systemic therapies

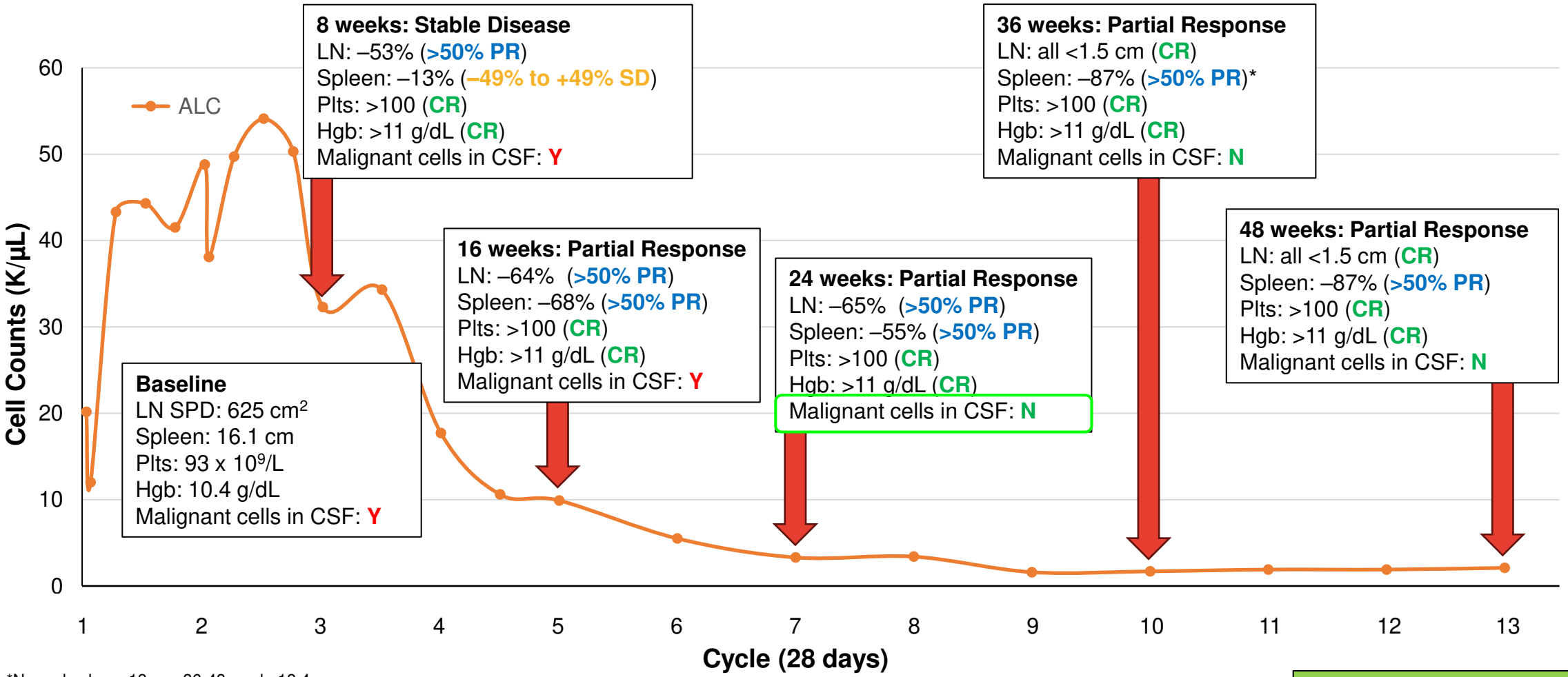
- Idelalisib: 2015-2018
- Venetoclax + Rituximab: 2018-2022
- Acalabrutinib: Oct 2022-Jun 2023

Prior radiotherapy

- None

Case Study 1: Patient with CLL and CNS Involvement

Deepening response over time approaching complete response criteria



*Normal spleen: 13 cm; 36-48 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

Remains on study as of Oct 10

ALC, Absolute lymphocyte count; **CSF**, cerebrospinal fluid; **Hgb**, hemoglobin; **LN**, lymph nodes; **Plts**, platelets

Data cutoff: 10 June 2024

Case Study 2: CLL Patient Exposed to CIT, cBTKi, BCL2i, and PI3Ki

Age, M/F	66, M
Diagnosis	CLL
Initial diagnosis	2008
Prior progression	9 Aug 2019
Dose	200 mg daily
Status	On treatment
Current 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

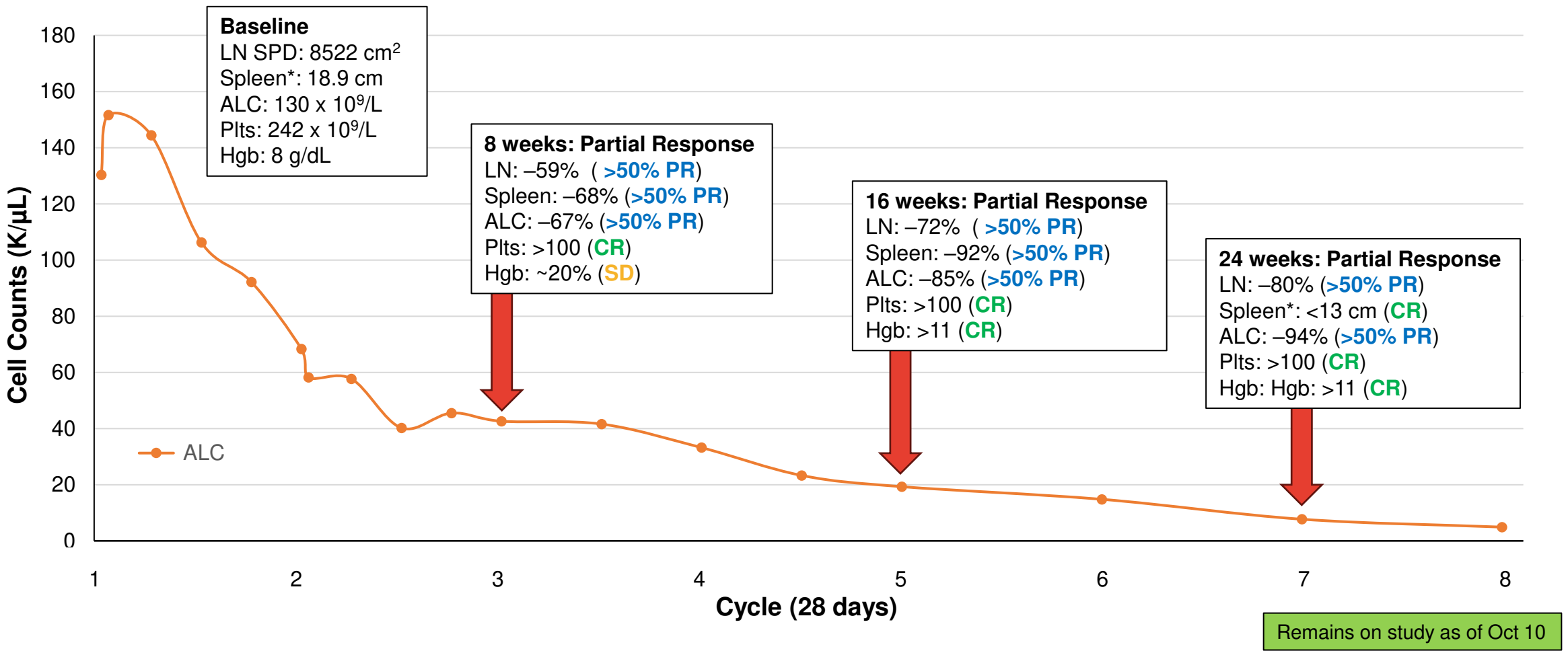
- Bulky disease (1 target lymph node >5cm longest diameter, 6 total)
- Splenomegaly

* From medical records; ** Central lab

Data cutoff: 10 June 2024

Case Study 2: CLL Patient Exposed to CIT, cBTKi, BCL2i, and PI3Ki

Early clinical activity deepening over time



Initial lymphocytosis consistent with BTK targeted MOA.*Normal spleen= <13 cm 24 wk: 12.8 cm

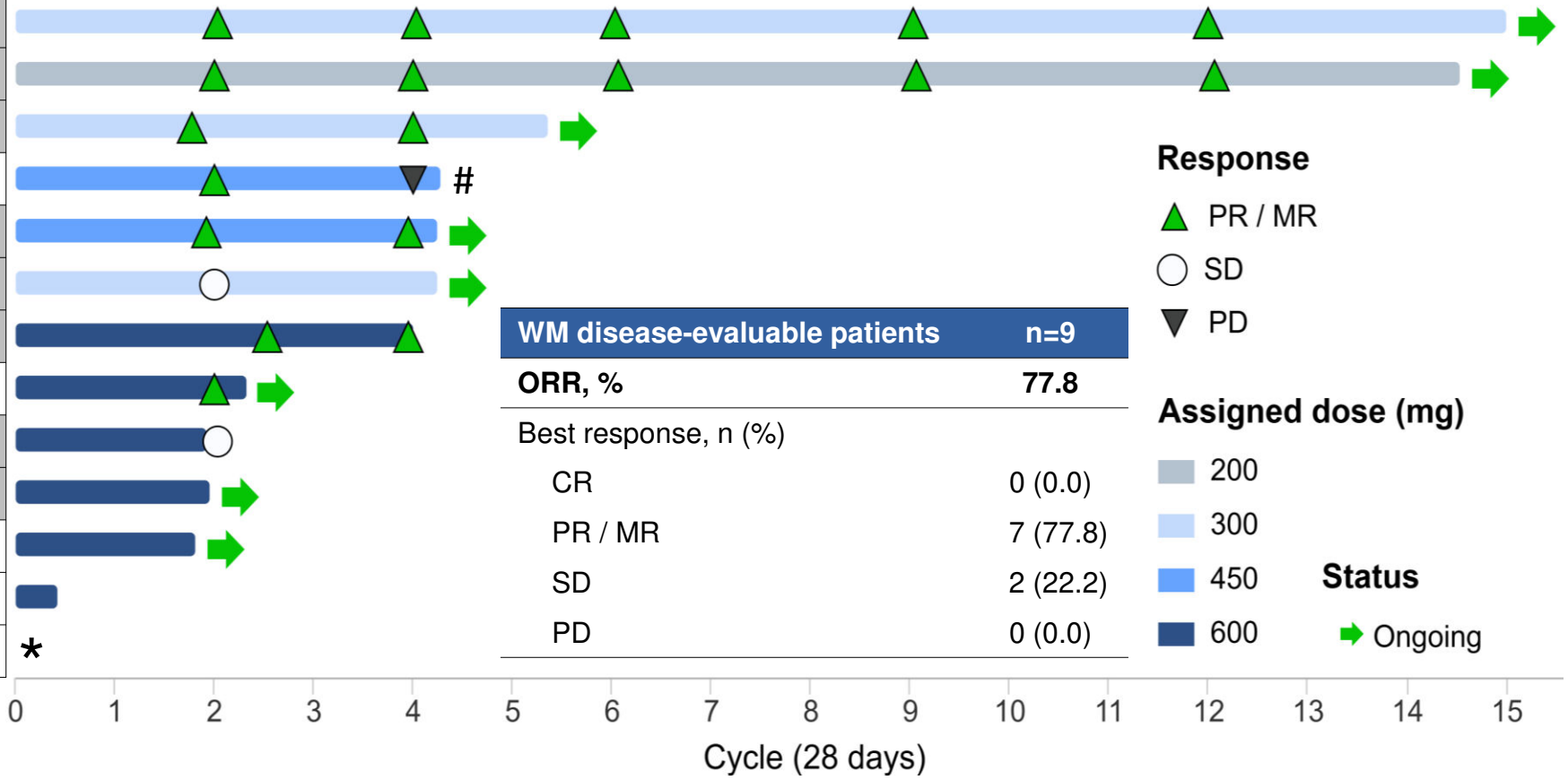
The overall response assessments are from the investigators while the individual parameter response assessment criteria are calculated per iwCLL from the data entered

ALC, Absolute lymphocyte count; **Hgb**, hemoglobin; **LN**, lymph nodes; **Plts**, platelets

NX-5948 Duration of Treatment in Patients with Waldenstrom's Macroglobulinemia

Durable responses, over 1 year, seen in pretreated patients with at least 2 prior therapies (BTKi and chemo-immunotherapy)

Select prior therapies			Select mutations	
BTKi	BCL2i	Pirto	CXCR4	MYD88



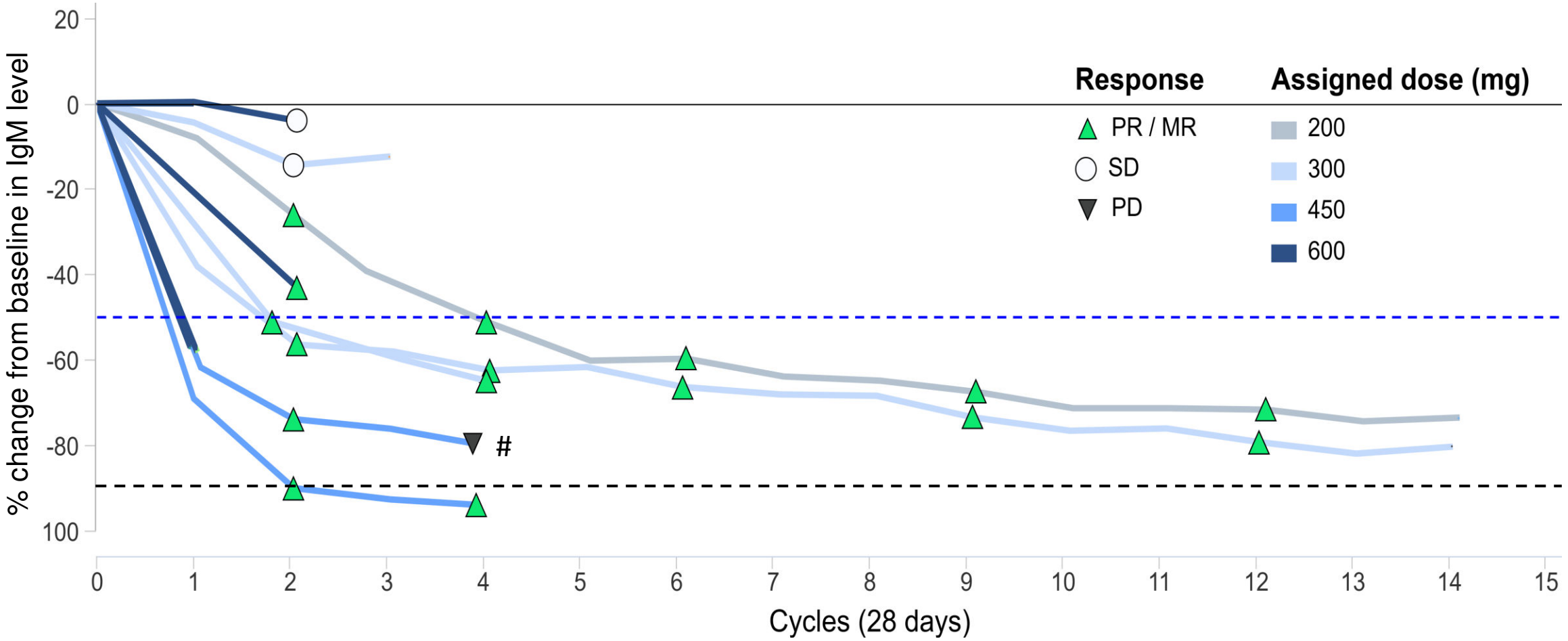
WM disease-evaluable patients	n=9
ORR, %	**77.8**
Best response, n (%)	
CR	0 (0.0)
PR / MR	7 (77.8)
SD	2 (22.2)
PD	0 (0.0)

*Ineligible, identified post 1st dose
#Transformed to DLBCL

Data cutoff: 10 Oct 2024

Steady Decrease in IgM Levels in Patients Treated with NX-5948

Percent change in IgM levels from baseline in patients with Waldenström's macroglobulinemia[1]



#Transformed to DLBCL

[1]Response criteria used: Owen RG, Kyle RA, Stone MJ, et al. VIth International Workshop on Waldenström macroglobulinemia. Response assessment in Waldenström macroglobulinemia: update from the VIth International Workshop. Br J Haematol 2013;160:171–6

Data cutoff: 10 Oct 2024

O'Connor P. Oral presentation at 12th International Workshop on Waldenstrom's Macroglobulinemia meeting; 19 October 2024

Conclusions

- NX-5948 is a novel BTK degrader that utilizes the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in B-cell malignancies

- In an ongoing Phase 1 clinical trial (n=79), NX-5948 has demonstrated a tolerable safety profile as of the April 17, 2024 data cut:
  - Safety profile for CLL and WM consistent with safety profile for overall population

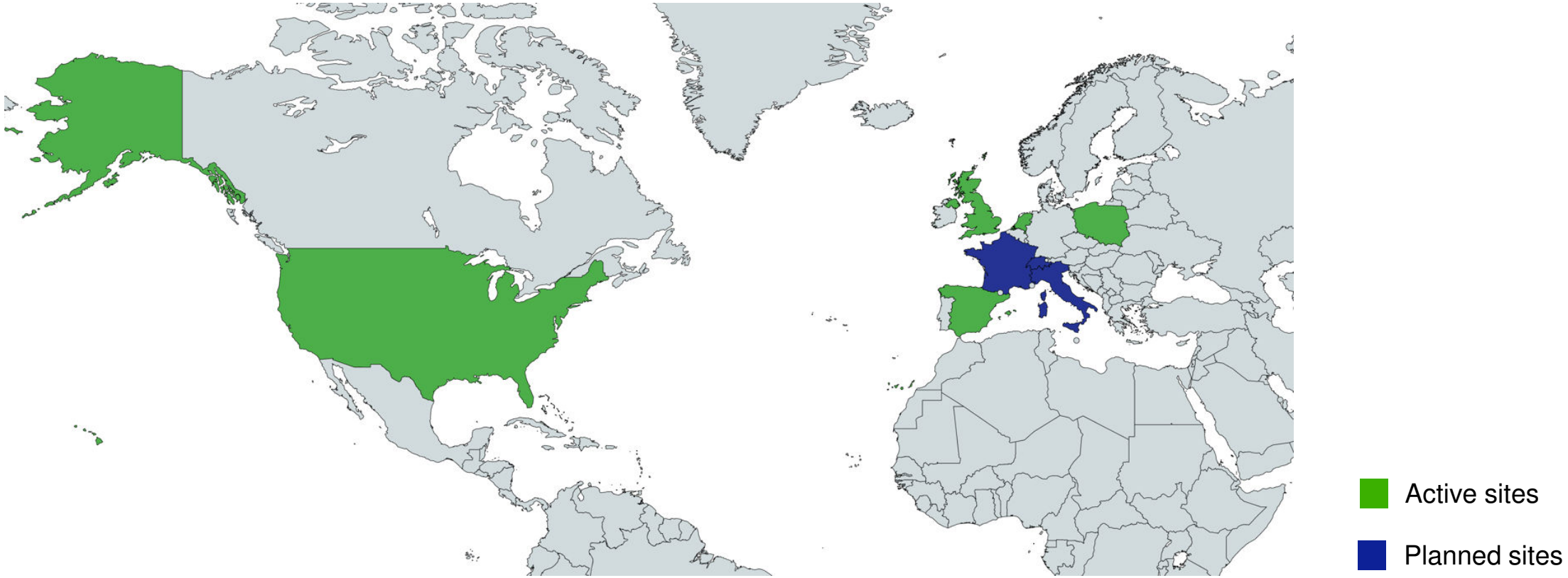
- In CLL (n=31): Deep and durable clinical responses were observed in a difficult-to-treat patient population as of the April 17, 2024 data cut :
  - Heavily pretreated patient population with unfavorable genetic mutations associated with poor prognosis and BTK inhibitor resistance mutations
  - Robust 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

- In WM (n=13): Clinical responses as of the October 10, 2024 data cut in previously treated patients (prior chemo-immunotherapy and BTK inhibitor), including patients with MYD88 and CXCR4 mutations:
  - ORR 77.8% (7/9 efficacy evaluable patients were responders)
  - Steady reduction in IgM levels starting from 2nd treatment cycle (8 weeks) in 8/9 efficacy evaluable patients
    - One patient with 90%+ reduction in IgM level

Acknowledgments and Next Steps

- We would like to acknowledge all the patients and their families, as well as investigators for participating in the NX-5948 study

- The study plans to enroll into Phase 1b worldwide (USA, UK, Netherlands, Poland, Spain, Italy, France, Switzerland)



- Further disclosures/data updates are planned in 2025