NX-5948: BTK Degrader with Activity in Lymphoid Malignancies

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Nurix Pipeline

Advancing 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**				
TPD	**NX-2127**	**BTK-IKZF**	**B-cell malignancies**				
TPE	NX-1607	CBL-B	Immuno-Oncology				
TPD	Multiple	Undisclosed	Undisclosed				
TPD	Multiple	Undisclosed	Undisclosed				GILEAD
TPD	Multiple	Undisclosed	Undisclosed				sanofi
DAC	Multiple	Undisclosed	Oncology				Pfizer

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

DAC: Degrader Antibody Conjugate; **TPD**: Targeted Protein Degradation; **TPE**: Targeted Protein Elevation

Rationale for BTK Degraders in WM

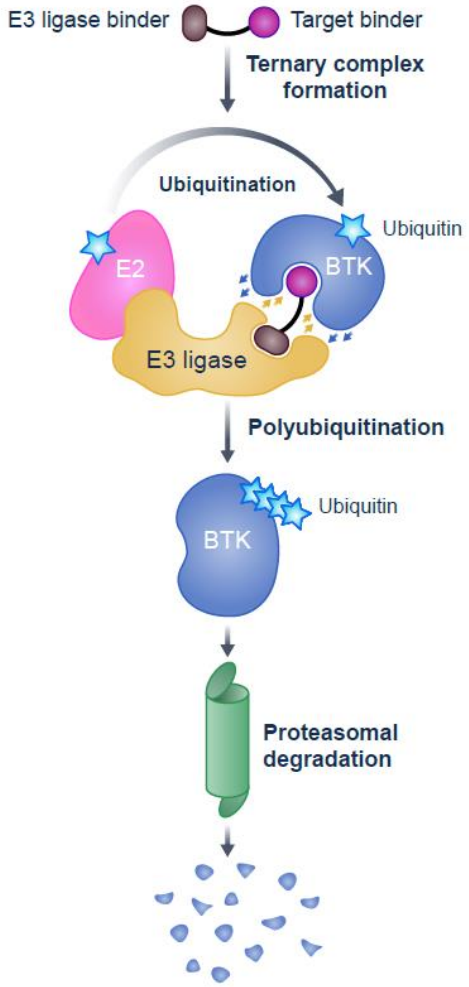
- The BCR signaling pathway mediated by BTK is a key driver in oncogenesis and a validated therapeutic target in WM
- BTK degraders:
  - Can overcome treatment-emergent BTK inhibitor resistance mutations[1]
  - Address BTK scaffolding function – the transduction of BCR signal downstream from BTK in the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

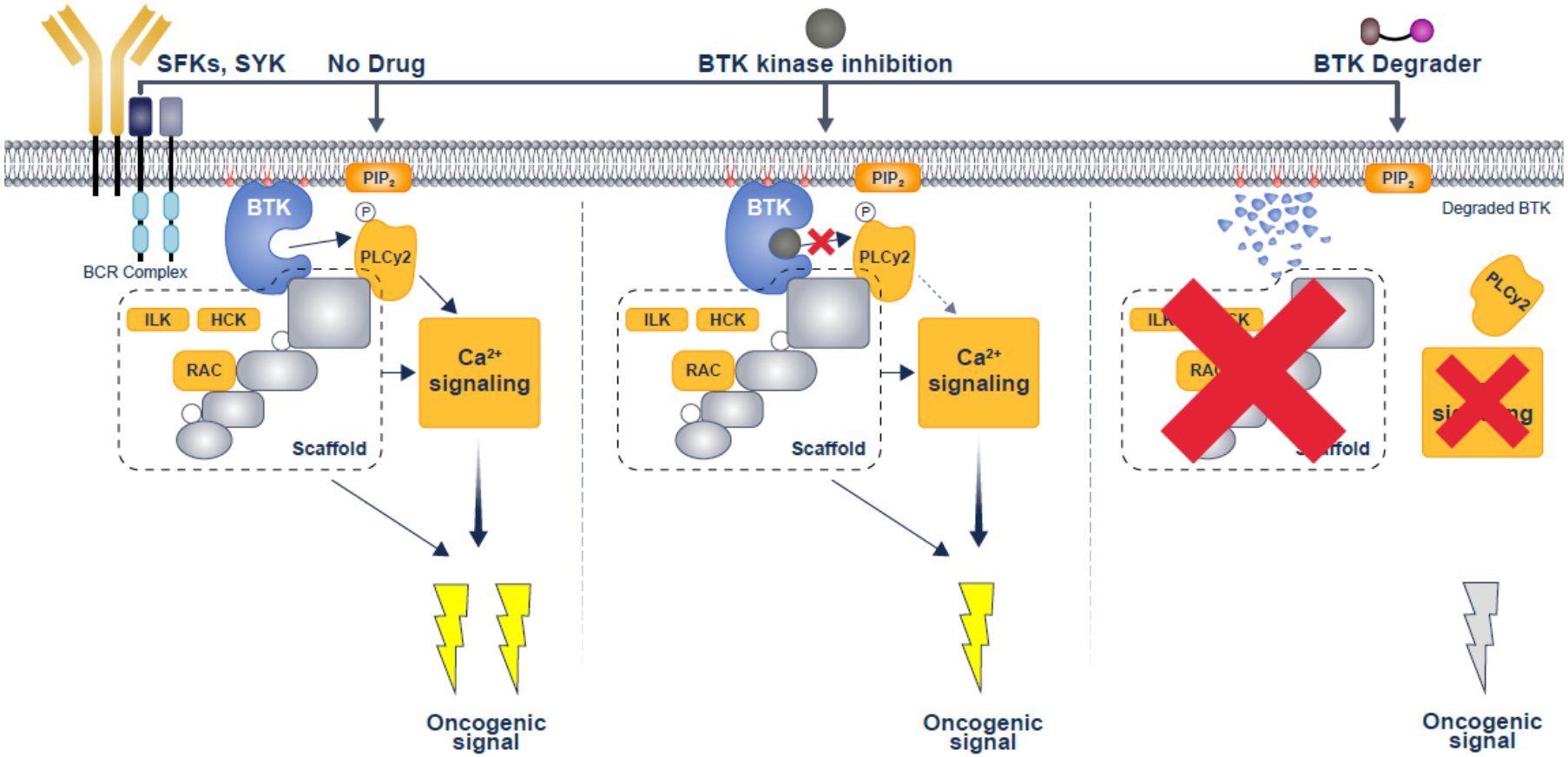
NX-5948 BTK Degrader Mechanism of Action

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

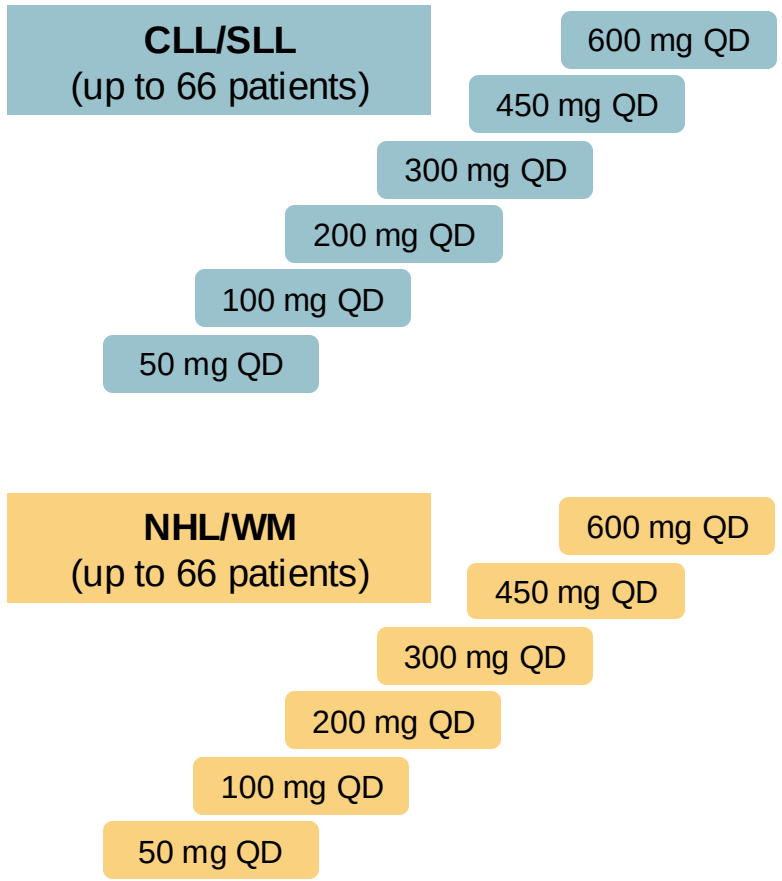
NX-5948-301: Trial Design

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

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

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

NX-5948 Safety Summary (All Patients) by Dose

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

TEAEs, n (%)	**Overall population (N=79)[1]**		
	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

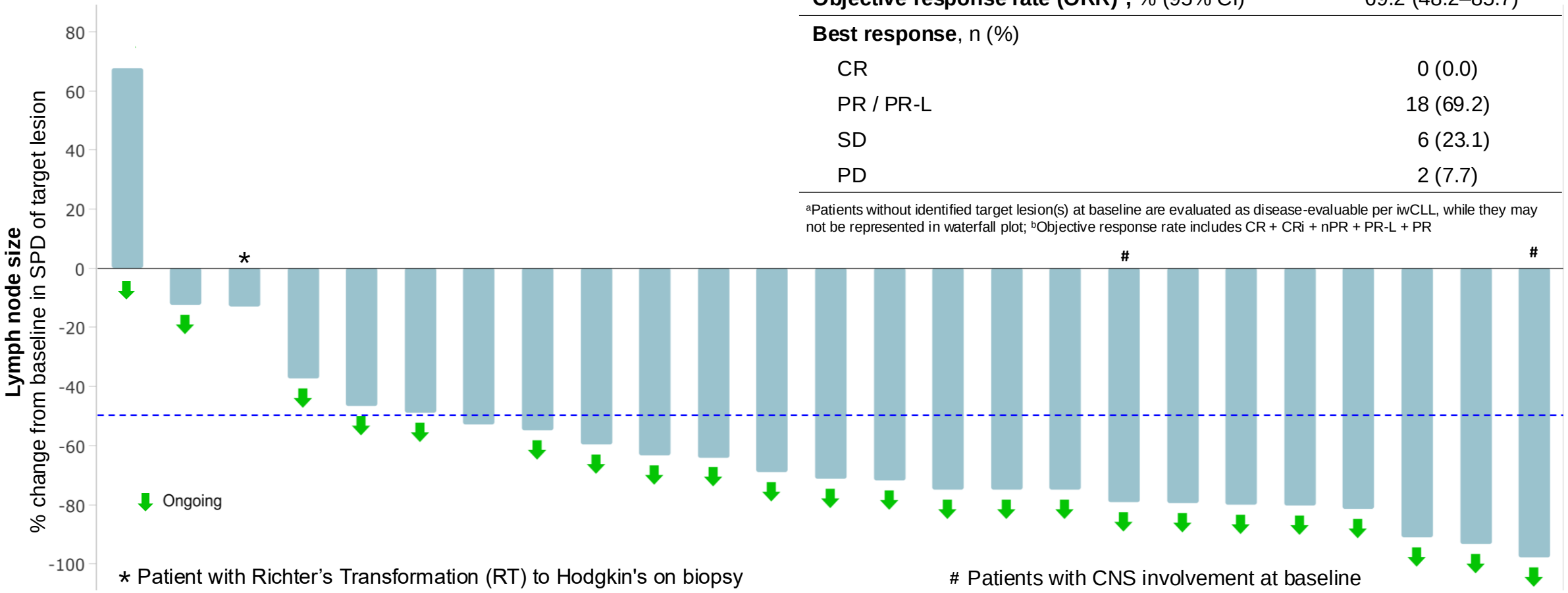
[1]Linton K, et al. HemaSphere 2024;8(S1):S155

NX-5948 Efficacy: Clinical Response in Patients with CLL

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

CLL disease-evaluable patients[a,1]	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



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 Apr 2024

[1]Linton K, et al. HemaSphere 2024;8(S1):S155

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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)

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Baseline Demographics/Disease Characteristics

Elderly population with multiple prior lines of targeted therapies

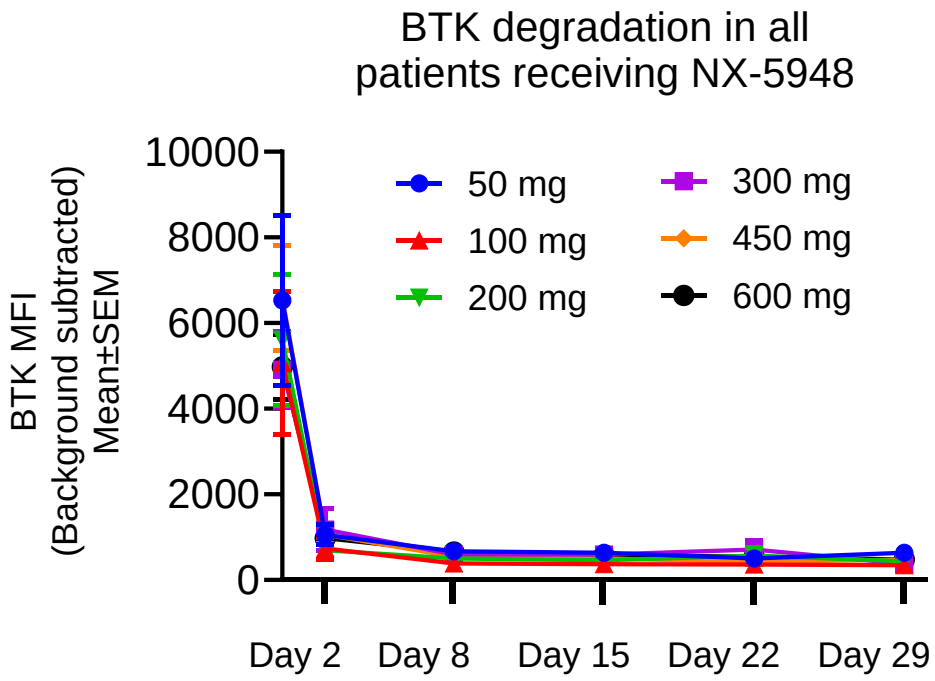
Characteristics	Patients with WM (n=13)
Median age, years (range)	74.0 (64–82)
Male, n (%)	11 (84.6)
ECOG PS, n (%)	
0	3 (23.1)
1	10 (76.9)
CNS involvement, n (%)	0
Median prior lines of therapy (range)	3.0 (2–5)
Previous treatments[a], n (%)	
BTKi	13 (100.0)
Pirtobrutinib	3 (23.1)
BCL2i	1 (7.7)
BTKi and BCL2i	1 (7.7)
CAR-T therapy	0 (0.0)
Bispecific antibody	0 (0.0)
PI3Ki	0 (0.0)
Chemo/chemo-immunotherapies	13 (100.0)
Mutation status*, n (%)	(n=13)
MYD88	8 (61.5)
CXCR4	2 (15.4)

[a]Patients could have received multiple prior treatments
*Mutation status was gathered from historic patient records

BTKi, Bruton's tyrosine kinase inhibitor; **BCL2i**, B-cell lymphoma 2 inhibitor; **CAR-T**, chimeric antigen receptor T-cell; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group (ECOG) performance status; **PI3Ki**, PI3 kinase inhibitor; **WM**, Waldenstrom's macroglobulinemia

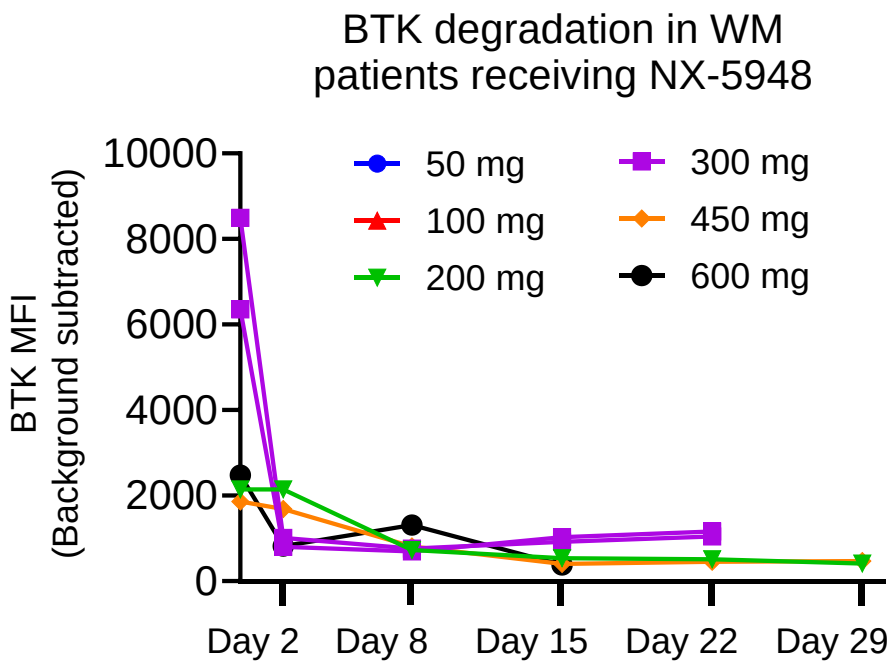
NX-5948 BTK degradation

Robust, rapid and sustained degradation across all indications including WM at all dose levels assessed



Data cutoff: 17 April 2024

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



Data cutoff: 10 June 2024

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

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

NX-5948 Efficacy and Duration of Treatment in Patients with WM

Select prior therapies			Select mutations	
BTKi	BCL2i	Pirto	CXCR4	MYD88
■			■	■
■				■
■				■
■				
■				■
■			■	■
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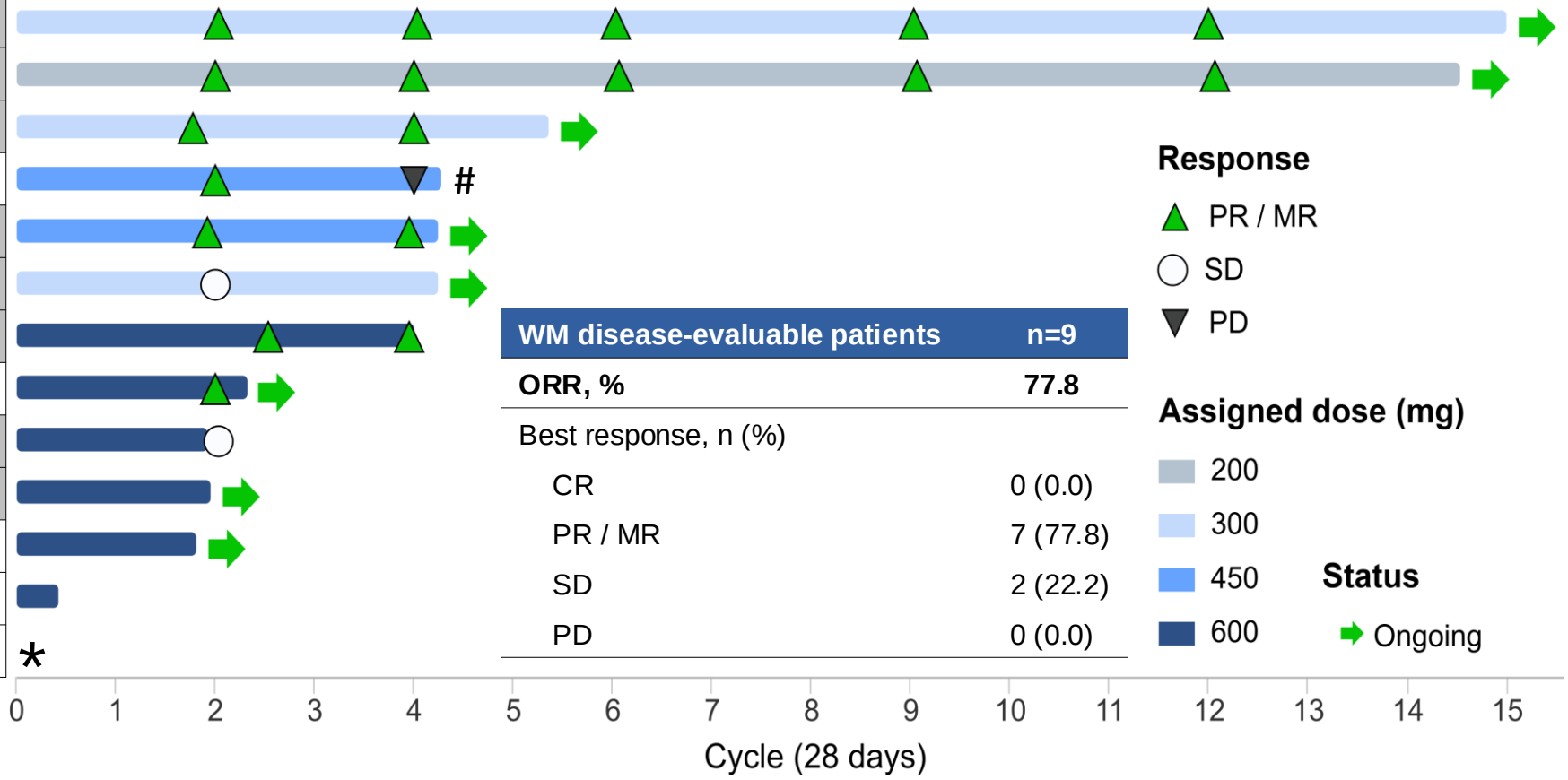


WM disease-evaluable patients	n=9
ORR, %	**77.8**
Best response, n (%)	
CR	0 (0.0)
PR / MR	7 (77.8)
SD	2 (22.2)
PD	0 (0.0)

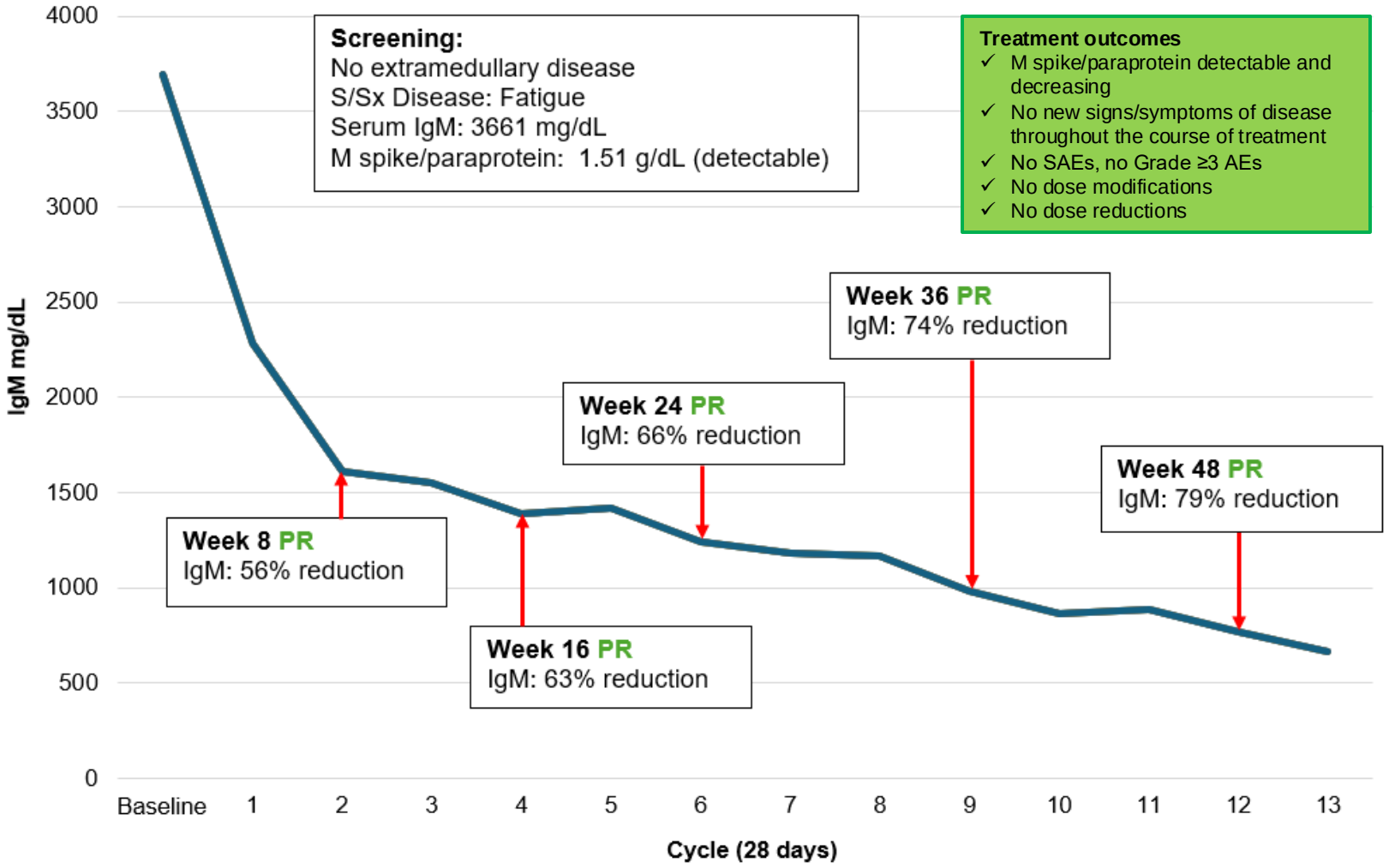
*Ineligible, identified post 1st dose
#Transformed to DLBCL

Clinical Case Study 1

Patient with WM, MYD88 and CXCR4 mutations, and 4 prior lines of therapy treated with NX-5948

Demographics	64, White, F
Relevant mutations	MYD88^{mut} CXCR4^{mut}
NX-5948 dose	300 mg
Status	On treatment (Cycle 16*)
4 prior lines of therapy s/p ASCT with prior BTKi	

1. Bortezomib + rituximab + dexamethasone (Best Response PR)
2. Bendamustine + rituximab (Best Response PD)
3. CHOP, BEAM + autologous stem cell transplantation, **ibrutinib maintenance** (Best Response PR, relapsed after 3 yrs)
4. Bortezomib + rituximab + dexamethasone (Best Response PD)



*1 cycle = 28 days

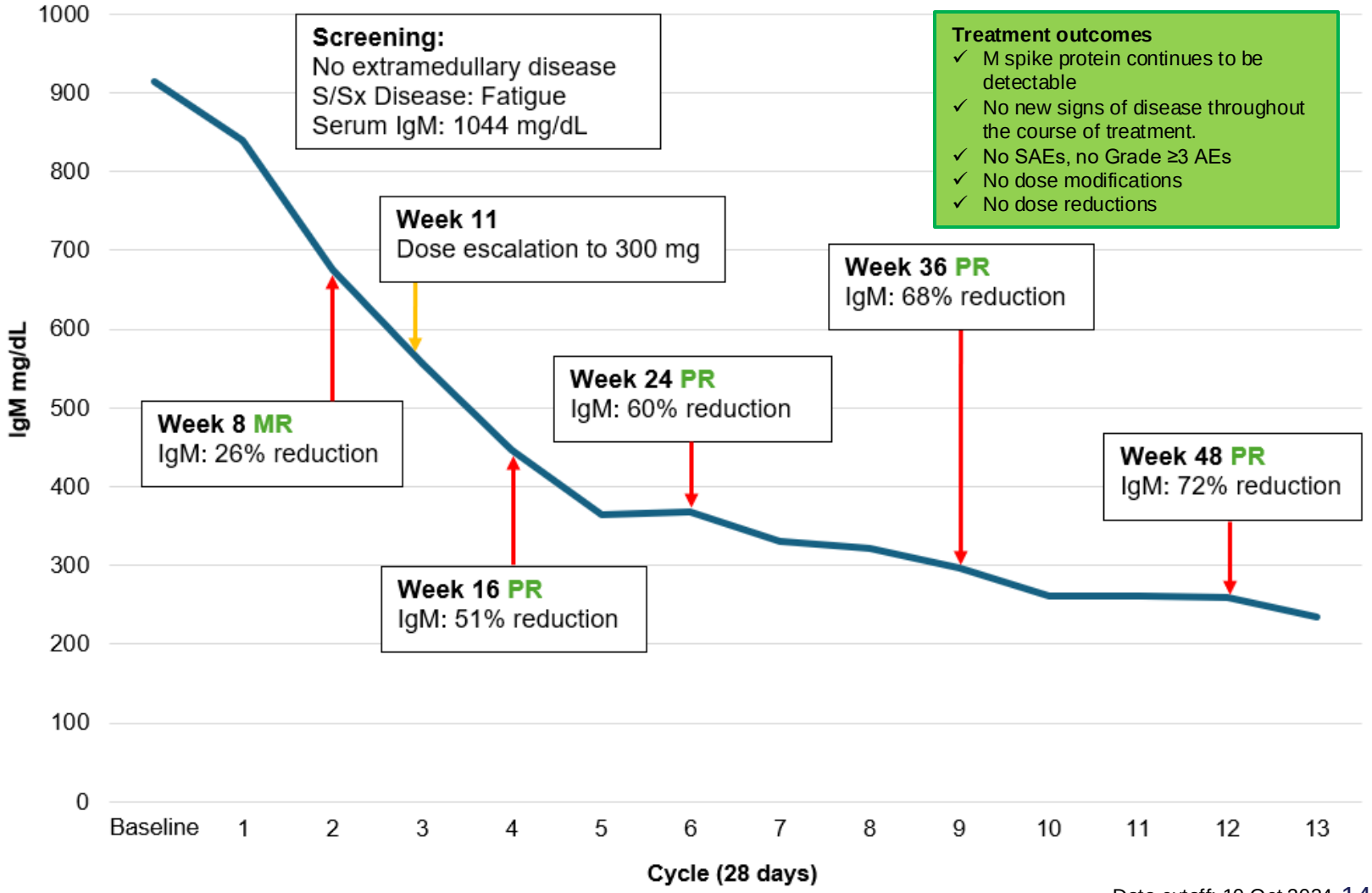
Clinical Case Study 2

Patient with WM, MYD88 mutation, and 3 prior lines of treatment treated with NX-5948

Demographics	66, White, M
Relevant mutations	MYD88^{mut}
NX-5948 dose	200 mg → 300 mg
Status	On treatment (Cycle 15*)
3 prior lines of therapy s/p ASCT with prior BTKi	

1. Bortezomib + rituximab + dexamethasone (Best Response CR)
2. Rituximab + bendamustine, BEAM + autologous stem cell transplantation (Best Response CR)
3. **Zanubrutinib** (Best Response PR, relapsed after 1 yr)

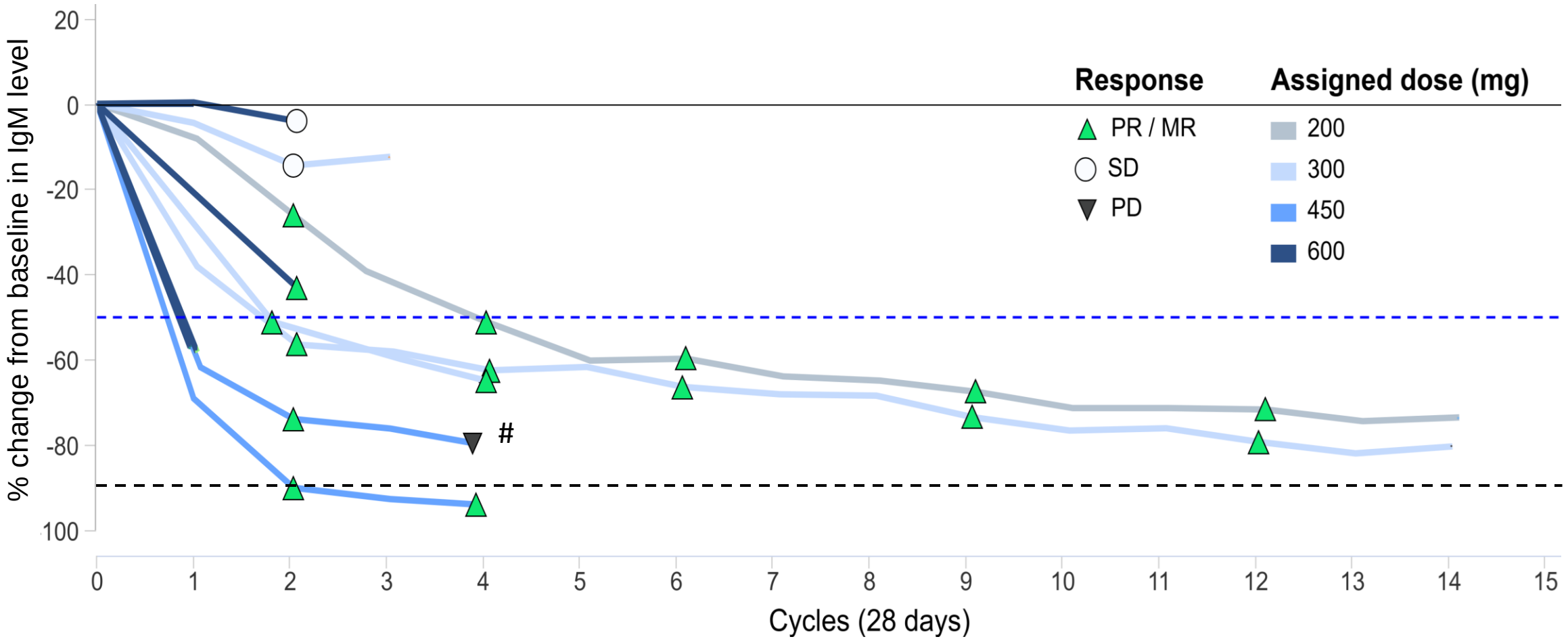
*1 cycle = 28 days



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 WM[1]



#Transformed to DLBCL

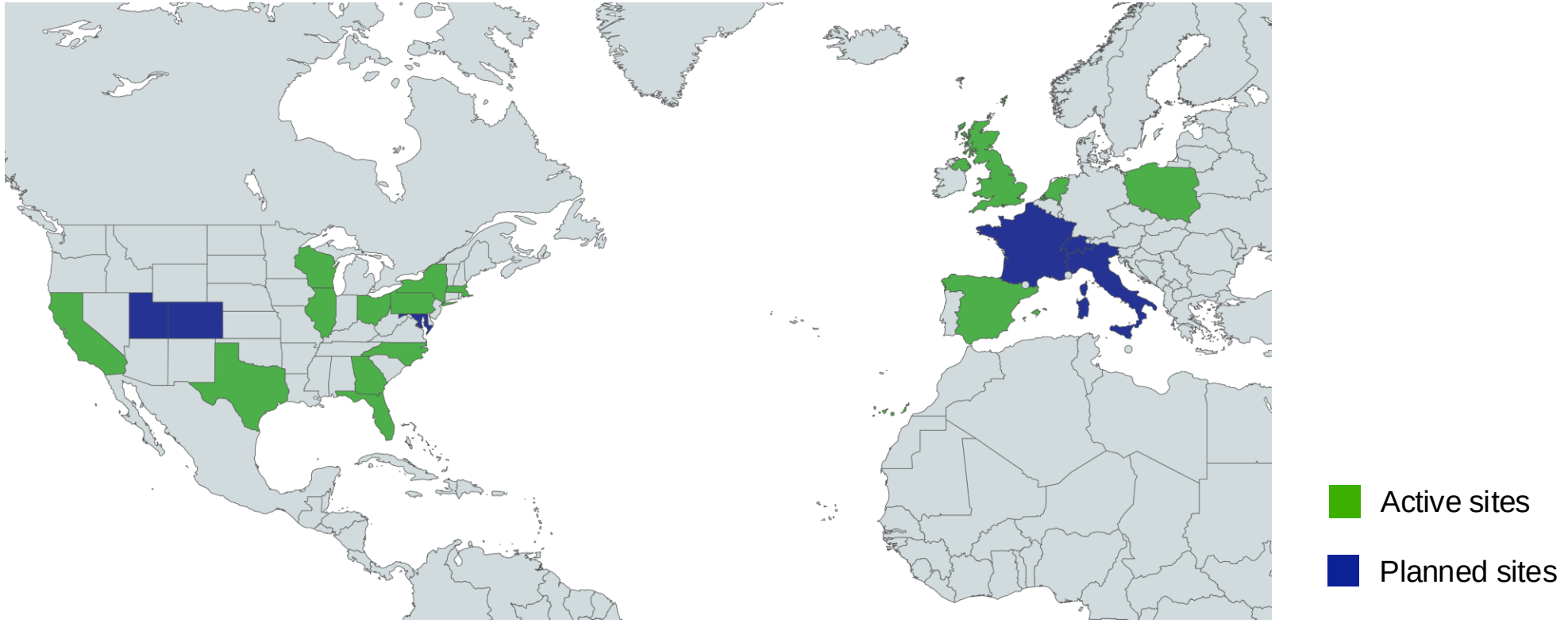
[1]Response criteria used: Owen RG, Kyle RA, Stone MJ, et al. VIth International Workshop on Waldenström macroglobulinaemia. Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. Br J Haematol 2013;160:171–6

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. BTK degraders:
  - Can overcome treatment-emergent resistance mutations
  - Address BTK scaffolding function
  - Show emerging activity in various B-cell malignancies, including WM
  - Have the potential to replace BTK inhibitors in the clinic
- In an ongoing Phase 1 clinical trial, NX-5948 has demonstrated:
  - Tolerable safety profile as of the April 17, 2024 data cut:
    - Safety profile for WM consistent with safety profile for overall population
    - No atrial fibrillation or hypertension; AE were mostly low-grade; purpura/contusion, neutropenia and thrombocytopenia were the most common events
    - 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)
  - Clinical activity as of the October 10, 2024 data cut in previously treated patients with WM (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
- Cohort expansion for the ongoing NX-5948 study is enrolling patients with WM

Acknowledgments and Next Steps

- We would like to acknowledge all the patients and 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)



- The study permits enrollment for Bing-Neel patients in the CNS cohorts
- Further disclosures/data updates are planned in 2025