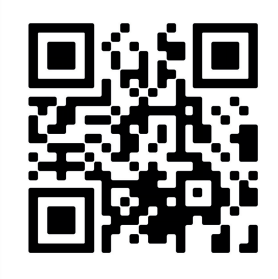


Bexobrutideg (NX-5948), a Novel Bruton’s Tyrosine Kinase (BTK) Degradar, Demonstrates Rapid and Durable Clinical Responses in Relapsed/Refractory CLL: Updated Findings From an Ongoing Phase 1a Study

¹Zulfa Omer, ²Alexey Danilov, ³Francesco Forconi, ⁴Nirav Shah, ⁵Graham P. Collins, ⁶Shuo Ma, ⁷Jane Robertson, ⁸Alvaro Alencar, ⁹Danielle Brander, ¹John C. Byrd, ¹⁰Dima El-Sharkawi, ¹¹Jeffery Smith, ¹²Allison Winter, ¹³Michal Kwiatek, ¹⁴Jonathon Cohen, ¹⁵Prioty Islam, ¹⁶Sarah Injac, ¹⁷Talha Munir

¹University of Cincinnati, Cincinnati, OH, USA; ²City of Hope National Medical Center, Duarte, CA, USA; ³University Hospital Southampton NHS Trust, Southampton, UK; ⁴Medical College of Wisconsin, Milwaukee, WI, USA; ⁵Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, UK; ⁶Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; ⁷The Christie Hospital and Manchester Cancer Research Centre, Division of Cancer Sciences, Manchester, UK; ⁸Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA; ⁹Duke Cancer Institute, Durham, NC, USA; ¹⁰Royal Marsden NHS Foundation Trust, Sutton, UK; ¹¹The Clatterbridge Cancer Centre, Liverpool, UK; ¹²Cleveland Clinic Foundation, Cleveland, OH, USA; ¹³AidPort Hospital, Skórzewo (Poznan), Poland; ¹⁴Emory Winship Cancer Institute, Atlanta, GA, USA; ¹⁵Memorial Sloan Kettering Cancer Center, New York, NY, USA; ¹⁶Nurix Therapeutics, Inc., San Francisco, CA, USA; ¹⁷St. James’s Hospital, Leeds, UK

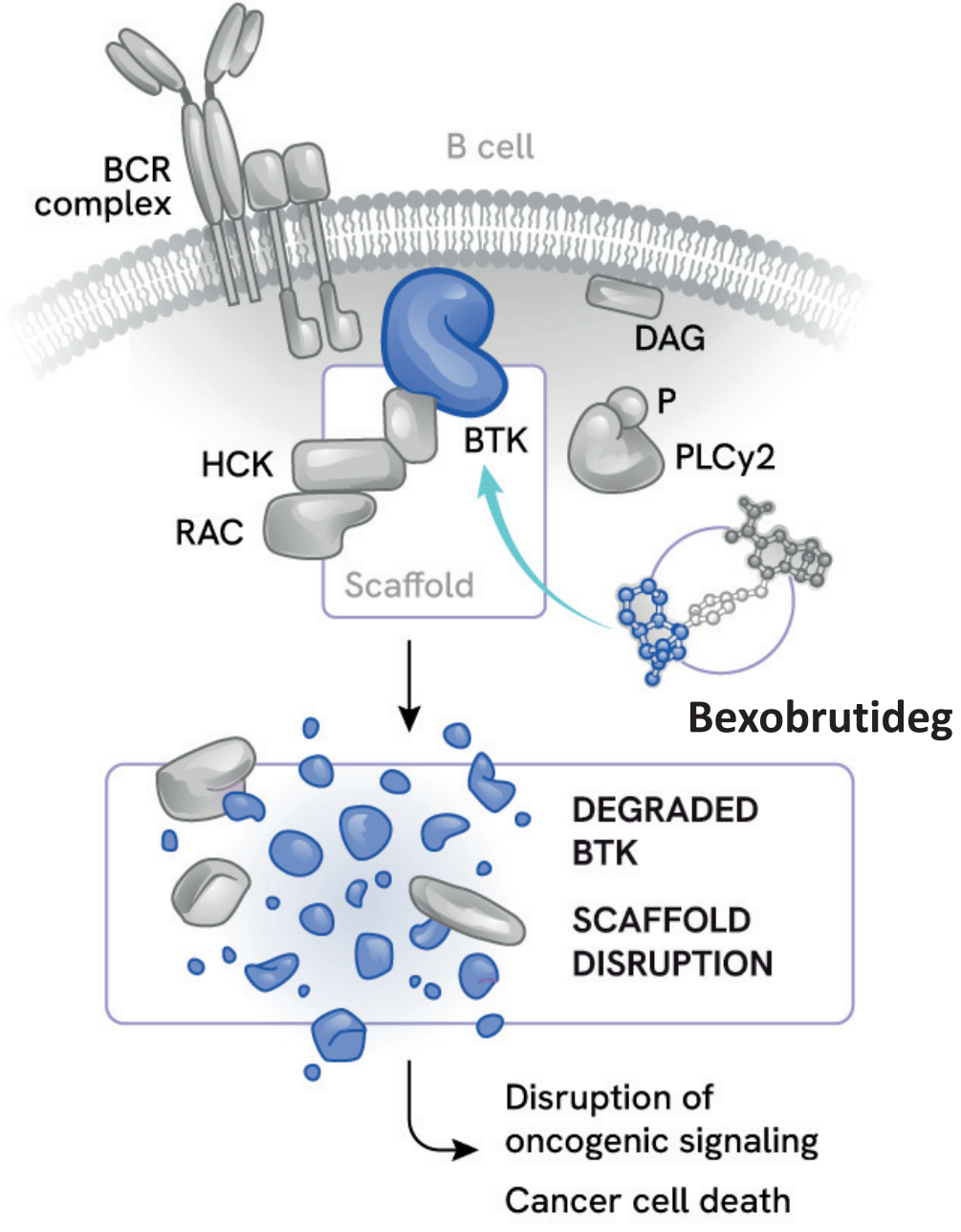
For information about this clinical trial please scan the QR code



Background

- The current standard of care for patients with CLL focuses on utilizing the inhibitors of two key signaling pathways: BTK and BCL2.
- An unmet need still exists in the CLL treatment landscape:
 - Covalent and non-covalent BTKi resistance mutations are found in more than half of patients who progress on BTKi therapies.^{1,2}
 - Some mutations in BTK can maintain intact B-cell receptor signaling through a scaffolding function of BTK.³
 - The number of patients whose disease is BCL2i refractory and double (BTKi/BCL2i) refractory is growing.⁴
- The novel BTK degrader bexobrutideg (NX-5948) is a small molecule degrader that offers an additional treatment modality (**Figure 1**). Bexobrutideg induces specific degradation of wild-type and mutant forms of BTK by ubiquitination via the cereblon E3 ligase complex and subsequent proteasomal degradation. This mechanism allows bexobrutideg to overcome treatment-emergent BTKi resistance mutations⁵ and disrupt BTK scaffolding.^{3,5}
- Here we report updated findings from a Phase 1a trial of bexobrutideg in patients with relapsed/refractory CLL.

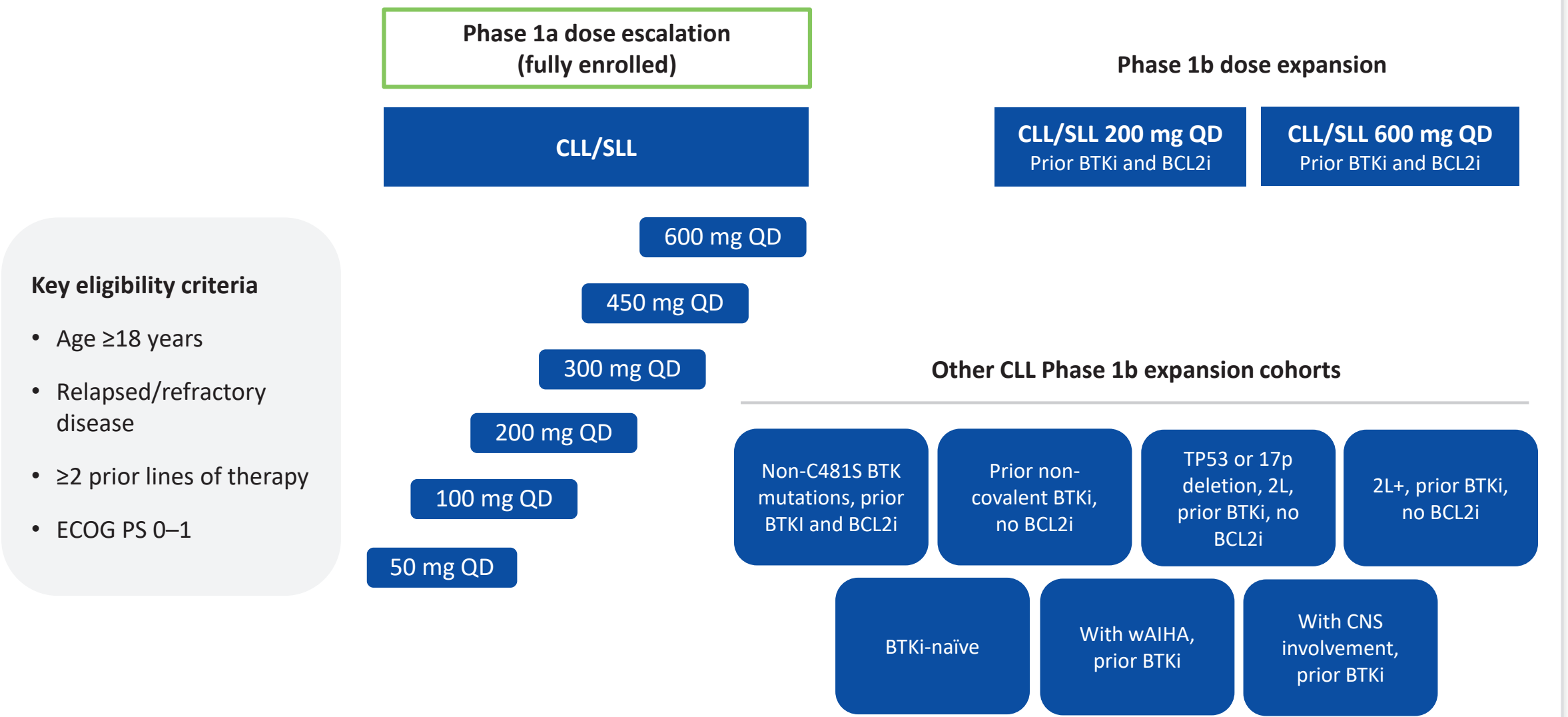
Figure 1. Bexobrutideg Mechanism of Action



Methods

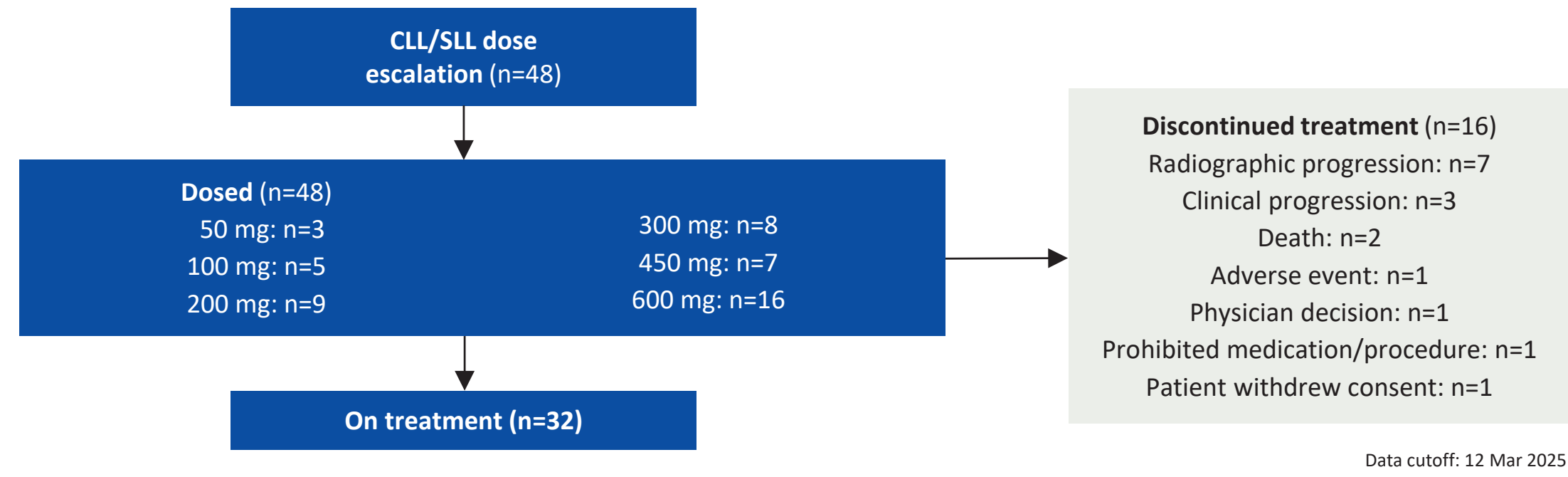
- NX-5948-301 is a Phase 1 clinical trial evaluating the safety and efficacy of bexobrutideg in patients with relapsed/refractory B-cell malignancies, including CLL and NHL, in parallel 3+3 dose-escalation then dose-expansion cohorts (**Figure 2**).
- Key eligibility criteria include ≥2 prior therapy lines and ECOG PS 0–1.
- Objectives:
 - Primary: safety/tolerability and identification of a recommended Phase 2 dose.
 - Secondary: characterization of the pharmacokinetic/pharmacodynamic profile and assessment of preliminary efficacy according to iwCLL criteria.

Figure 2. Trial Design (CLL cohorts)



Results

Figure 3. CLL Patient Disposition – Phase 1a Dose-escalation Cohort



- As of 12 March 2025, 48 patients with CLL/SLL were enrolled in Phase 1 a of the trial and treated at 6 daily oral dose levels (**Figure 3**).
- The CLL population comprised patients with multiple prior lines of therapy and high prevalence of baseline mutations (**Table 1**).
- Bexobrutideg was well tolerated across all doses, consistent with previous reports (**Table 2**).
- There was one treatment-emergent adverse event (TEAE) resulting in drug discontinuation, no dose-limiting toxicities and no new onset atrial fibrillation/flutter.
- In 47 response-evaluable patients with CLL, ORR was 80.9%; best overall responses included: 1 CR, 37 PR, 7 SD, and 2 PD (**Table 3**).
- Clinical activity was observed regardless of TP53 or PLCG2 mutation status, cBTKi or ncBTKi resistance mutations, or CNS involvement (**Figure 4**). Durable responses were observed regardless of prior therapy (**Figure 5**).
- Bexobrutideg resulted in a decrease in lesion size, as measured by the change from baseline in sum of product diameters (**Figure 6**).

Table 1. Patient Demographics and Baseline Disease Characteristics: Phase 1a

Characteristics	Patients with CLL/SLL (n=48)
Median age, years (range)	68.5 (35–88)
Sex, n (%)	
Male	32 (66.7)
Ethnicity, n (%)	
Hispanic or Latino	3 (6.3)
Race, n (%)	
Black or African American	3 (6.3)
White	42 (87.5)
Other	1 (2.1)
ECOG PS, n (%)	
0	19 (39.6)
1	29 (60.4)
CNS involvement, n (%)	5 (10.4)
Median prior lines of therapy (range)	4.0 (2–12)
Previous treatments ^a , n (%)	
BTKi	47 (97.9)
cBTKi	47 (97.9)
ncBTKi ^b	13 (27.1)
BCL2i	40 (83.3)
BTKi and BCL2i	39 (81.3)
CAR-T therapy	3 (6.3)
Bispecific antibody	3 (6.3)
PI3Ki	14 (29.2)
Chemo/chemo-immunotherapies (CIT)	35 (72.9)
Mutation status ^c (n=47), n (%)	
BTK	18 (38.3)
TP53	21 (44.7)
PLCY2	7 (14.9)
BCL2	6 (12.8)

^aPatients could have received multiple prior treatments; ^bAll patients who received ncBTKi also previously received cBTKi; ^cMutations presented here were centrally sequenced

Data cutoff: 12 Mar 2025

Table 2. TEAEs in ≥10% of Patients or Grade ≥3 TEAEs or SAEs in >1 Patient: Phase 1a

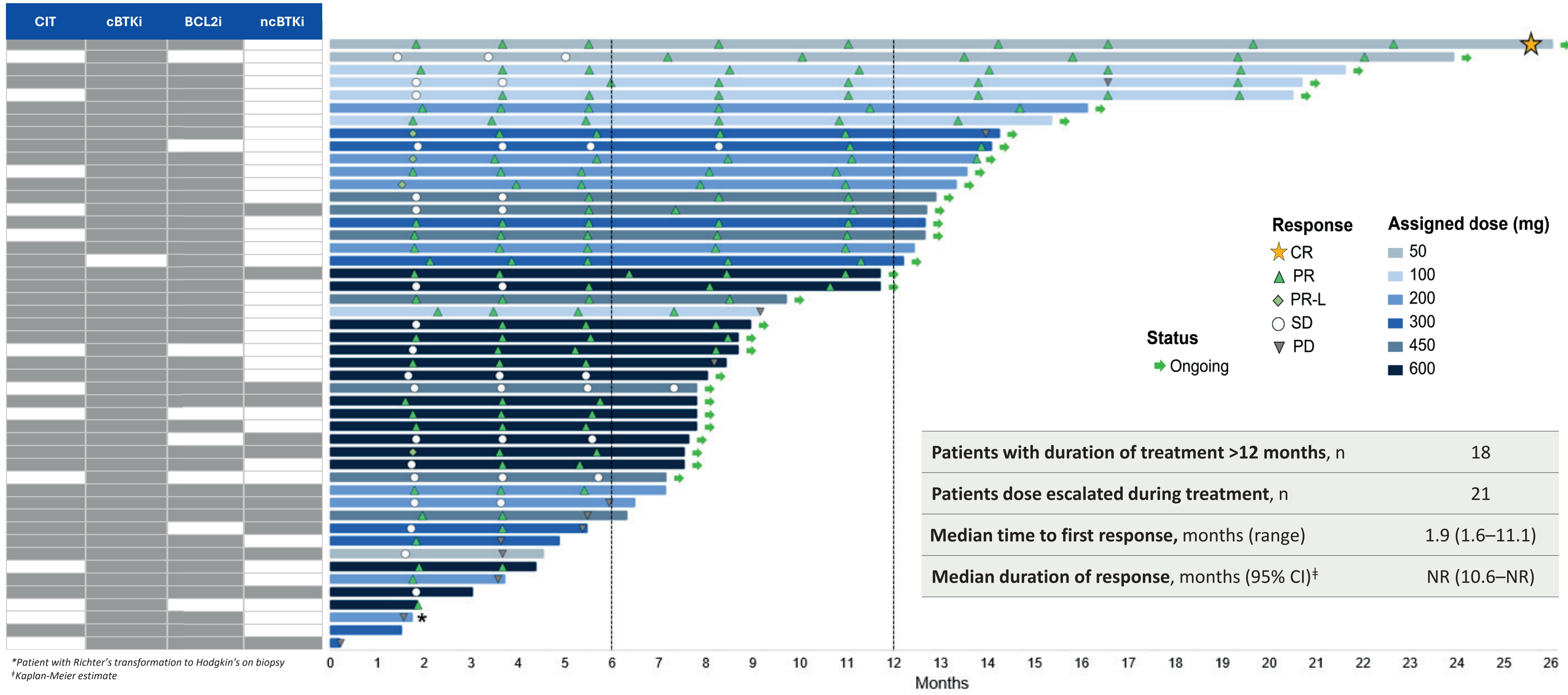
TEAEs, n (%)	Any grade	Patients with CLL/SLL (n=48)	Grade ≥3	SAEs
Purpura/contusion ^a	22 (45.8)			
Diarrhea	15 (31.3)	2 (4.2)		
Fatigue ^b	15 (31.3)			
Neutropenia ^c	14 (29.2)	11 (22.9)		
Rash ^d	13 (27.1)	1 (2.1)		1 (2.1)
Petechiae	12 (25.0)			
Headache	12 (25.0)			
Thrombocytopenia ^e	11 (22.9)	1 (2.1)		
Anemia	9 (18.8)	2 (4.2)		
COVID-19 ^f	9 (18.8)			
Peripheral edema	9 (18.8)			
Cough	8 (16.7)			
Lower respiratory tract infection	7 (14.6)	1 (2.1)		1 (2.1)
Nausea	7 (14.6)			
Pneumonia ^g	6 (12.5)	2 (4.2)		2 (4.2)
Arthralgia	6 (12.5)			
Upper respiratory tract infection	5 (10.4)			
Vomiting	5 (10.4)	1 (2.1)		
Respiratory syncytial virus infection	2 (4.2)	1 (2.1)		2 (4.2)

^aPurpura/contusion includes episodes of contusion or purpura; ^bFatigue was transient; ^cAggregate of 'thrombocytopenia' and 'platelet count decreased'; ^dAggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; ^eAggregate of 'neutrophil count decreased' or 'neutropenia'; ^fAggregate of 'COVID-19' and 'COVID-19 pneumonia'; ^gAggregate of 'pneumonia' and 'pneumonia Klebsiella'

Data cutoff: 12 Mar 2025

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Figure 5. Durable Responses Regardless of Prior Therapy (n=48)

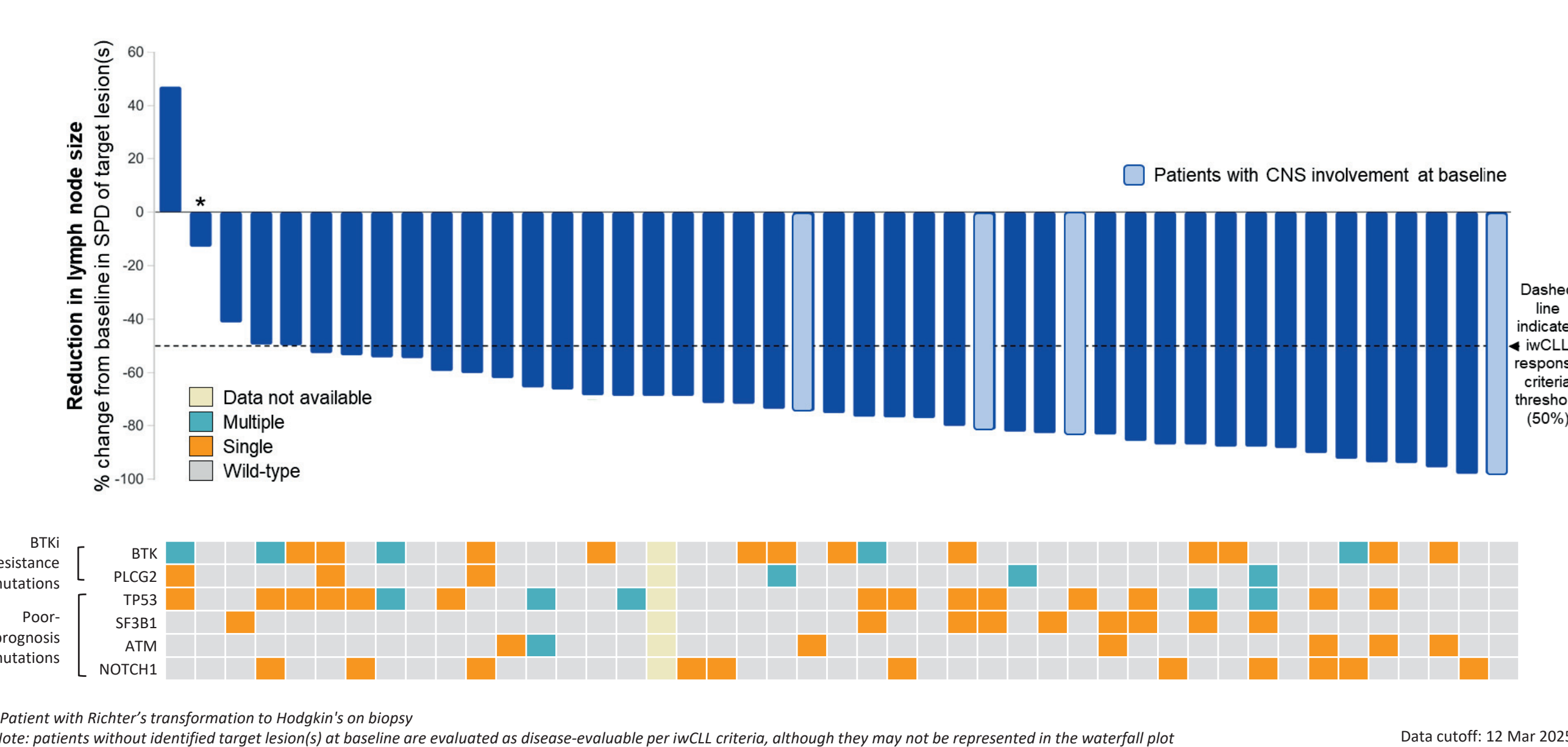


*Patient with Richter's transformation to Hodgkin's on biopsy

*Kaplan-Meier estimate

Data cutoff: 12 Mar 2025

Figure 4. Clinical Activity in Patients with CLL Including Those with Baseline Mutations and CNS Involvement

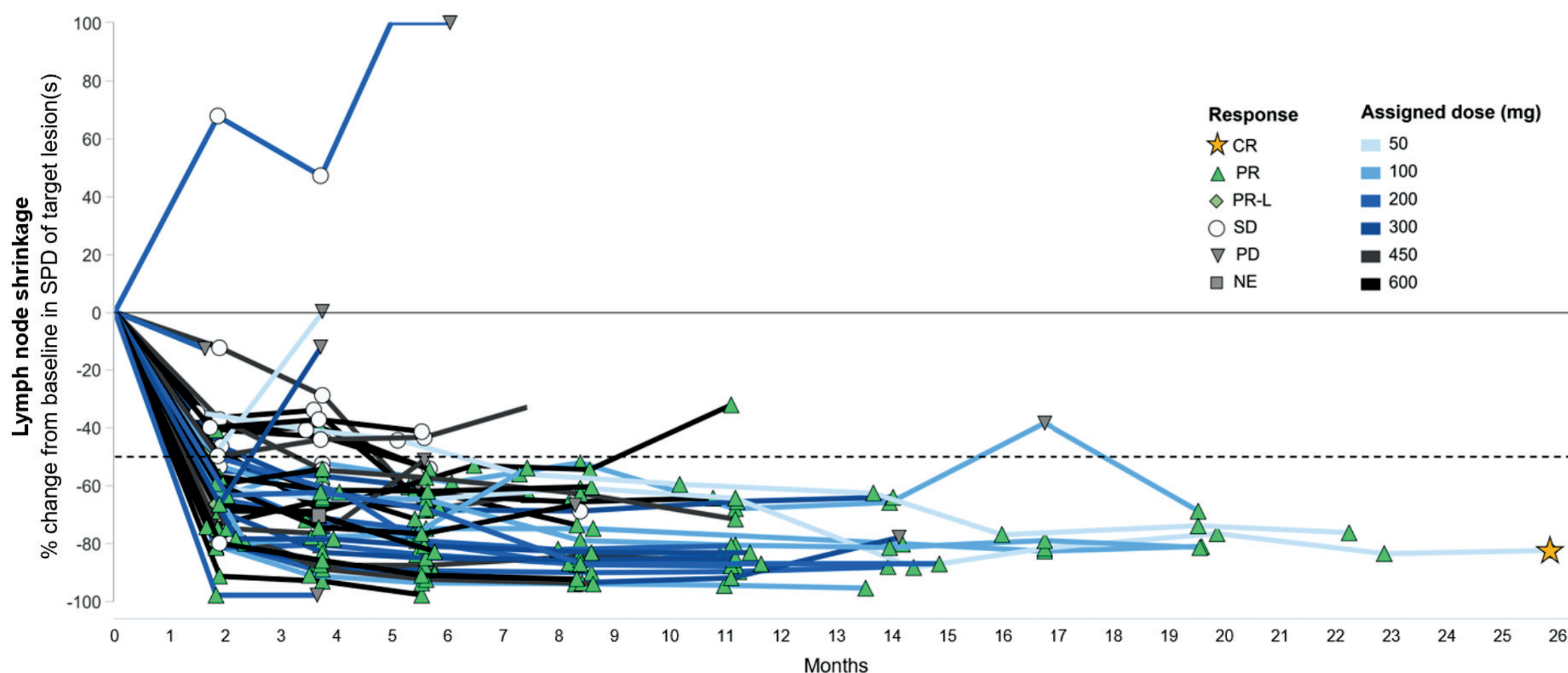


*Patient with Richter's transformation to Hodgkin's on biopsy

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

Data cutoff: 12 Mar 2025

Figure 6. Percent Change from Baseline in Sum of Product Diameters in Patients with CLL



Data cutoff: 12 Mar 2025

Abbreviations

AE, adverse event; ATM, ataxia-telangiectasia mutated; BCL2, B-cell lymphoma 2; BCL2i, BCL2 inhibitor; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; CAR-T, chimeric antigen receptor T-cell; cBTKi, covalent BTKi; CL, confidence interval; CIT, chemo/chemo-immunotherapies; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; iwCLL, International Workshop on CLL; MF, mean fluorescence intensity; ncBTKi, non-covalent BTKi; NE, not evaluable; NHL, non-Hodgkin's lymphoma; NOTCH1, notched homolog protein 1; NR, not reached; ORR, objective response rate; PD, progressive disease; PI3Ki, phosphoinositide 3-kinase inhibitor; PLCG2, phospholipase C gamma 2; PR, partial response; PR-L, partial response with rebound lymphocytosis; QD, once daily; SAE, serious adverse event; SD, stable disease; SLL, small lymphocytic lymphoma; SPD, sum of products diameters; TEAE, treatment emergent AE

Table 3. Bexobrutideg Overall Response Assessment

CLL response-evaluable patients ^a	Response analysis (n=47)
Objective response rate (ORR), ^b % (95% CI)	80.9 (66.7–90.9)
Best response, n (%)	
CR	1 (2.1)
PR	37 (78.7)
PR-L	0 (0.0)
SD	7 (14.9)
PD	2 (4.3)
Median follow-up, months ^c (range) ^d	9.0 (1.6–26.1)

^aPatients who were treated with bexobrutideg having ≥1 post-baseline disease assessment or documented clinical PD

^bObjective response rate was evaluated using iwCLL criteria and included CR + PR + PR-L

^cKaplan-Meier estimate; ^dObserved values

Data cutoff: 12 Mar 2025

Conclusions

- Bexobrutideg (NX-5948) is a novel small molecule that degrades a well-validated CLL target BTK by utilizing the ubiquitin-proteasome pathway.
- In the fully enrolled Phase 1a CLL portion of the NX-5948-301 study as of the 12 March 2025 data cut:
 - Median follow-up was 9.0 months, and most patients were still on treatment.
 - Bexobrutideg was well tolerated, consistent with the overall study population and previous disclosures.
 - Bexobrutideg showed clinical activity in a population of heavily pretreated patients with advanced CLL:
 - Patients had a median of four prior lines of therapy including, among others, prior cBTKi, ncBTKi, and BCL2i treatment.
 - A high number of patients had BTK, PLCG2, and BCL2 mutations, high-risk molecular features and CNS involvement. No patient profile was associated with intrinsic resistance to bexobrutideg.
 - Robust and deepening responses were observed with high ORR (80.9%), including one CR:
 - Responses were rapid with a median time to first response of 1.87 months.
 - Multiple conversions were observed from SD to PR, and one conversion from PR to CR.
 - Of 18 patients treated for more than 12 months, 17 remain on study. One patient is approaching 2.5 years on treatment.

Enrollment is ongoing in additional Phase 1b sub-population cohorts and pivotal trial(s) initiation is planned later in 2025

Acknowledgments

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