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

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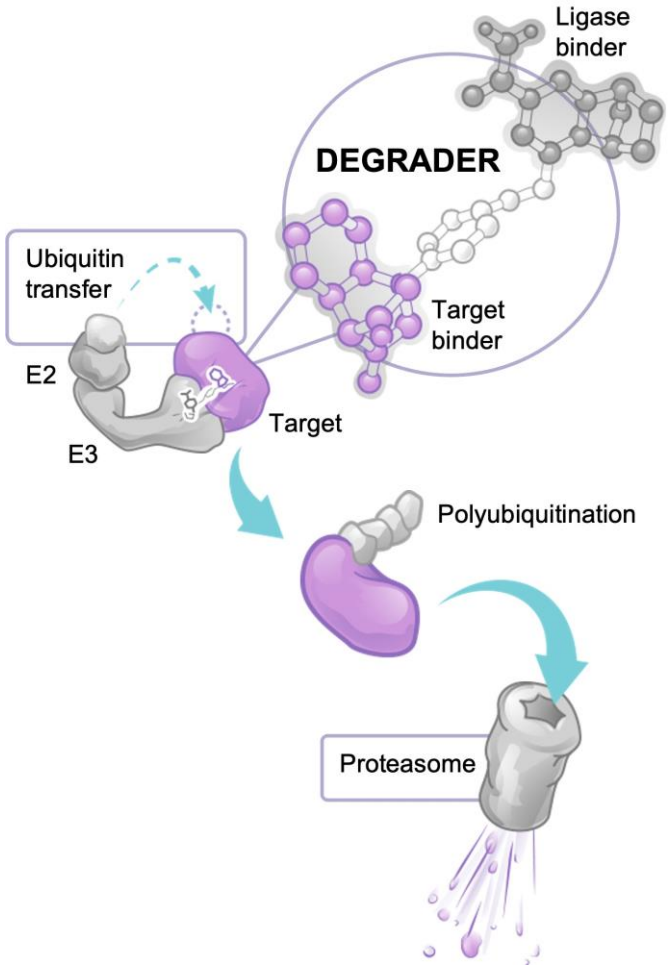
What Is Targeted Protein Degradation?

Harnessing the ubiquitin proteasome system to eliminate disease-causing proteins

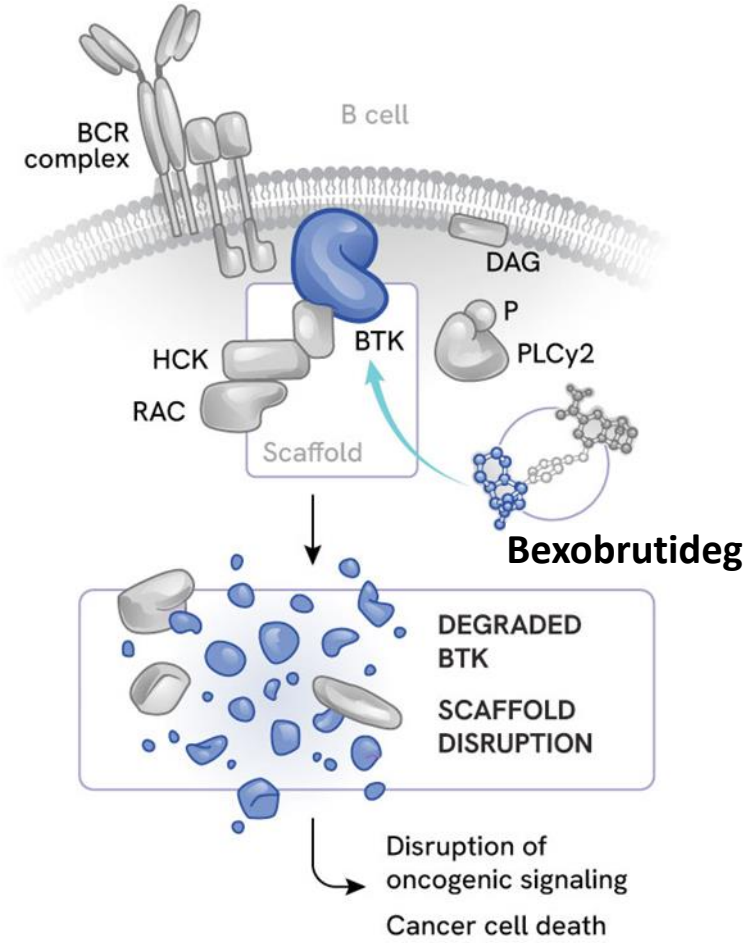


- BTK degraders can overcome treatment emergent resistance mutations
- BTK degraders eliminate BTK scaffolding function
- BTK degraders have the potential to displace inhibitors

***BTK**, Bruton's tyrosine kinase*

Bexobrutideg (NX-5948) – A Small Molecule BTK Degrader that Addresses an Unmet Need in the CLL Treatment Landscape

Bexobrutideg mechanism of action



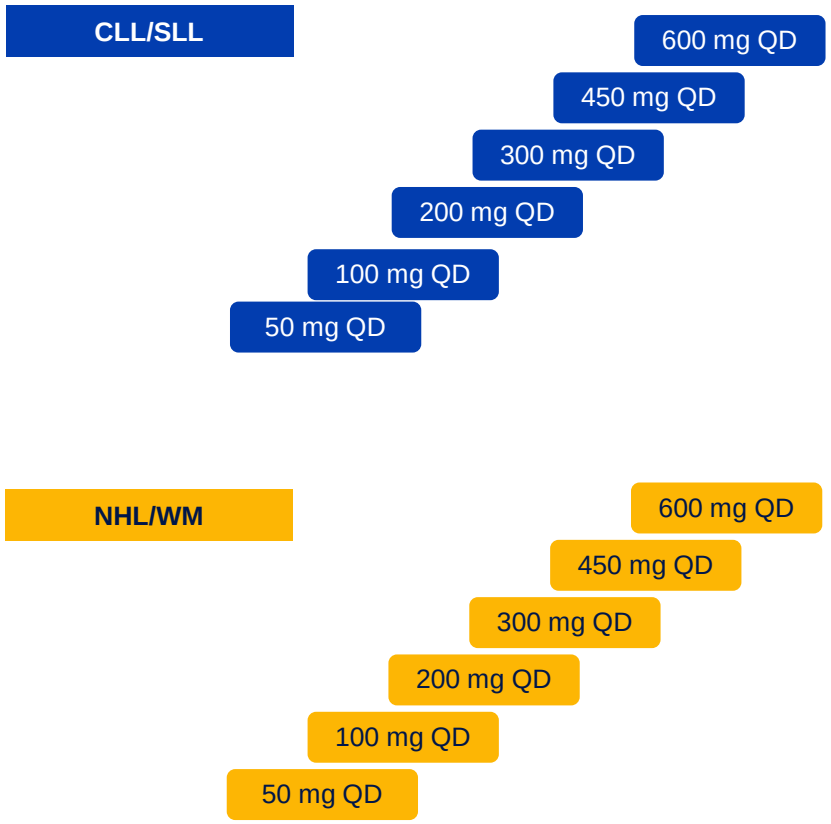
- The current standard of care in CLL focuses on utilizing the inhibitors of two key signaling pathways: BTK and BCL2
- Unmet need still exists in the CLL treatment landscape:
  - Covalent and non-covalent BTKi resistance mutations are found in more than half of patients who progress on BTKi therapies[1,2]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

1. Noviski et al. 20th Biennial International Workshop on CLL, Boston, MA. Oct 6–9, 2023; 2. Molica et al. 66th ASH Annual Meeting, Dec 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 EHA Hybrid Congress; Jun 16, 2024

NX-5948-301 Trial Design

Phase 1a dose escalation (fully enrolled)



Phase 1b CLL dose expansion (fully enrolled)*

CLL/SLL 200 mg QD
Prior BTKi and BCL2i

CLL/SLL 600 mg QD
Prior BTKi and BCL2i

Fast Track Designation

NHL/WM Phase 1b expansion cohorts

MZL
Marginal zone lymphoma

WM
Waldenström macroglobulinemia

FL
Follicular lymphoma

Fast Track Designation

MCL
Mantle cell lymphoma

DLBCL
Diffuse large B-cell lymphoma

PCNSL
Primary CNS Lymphoma

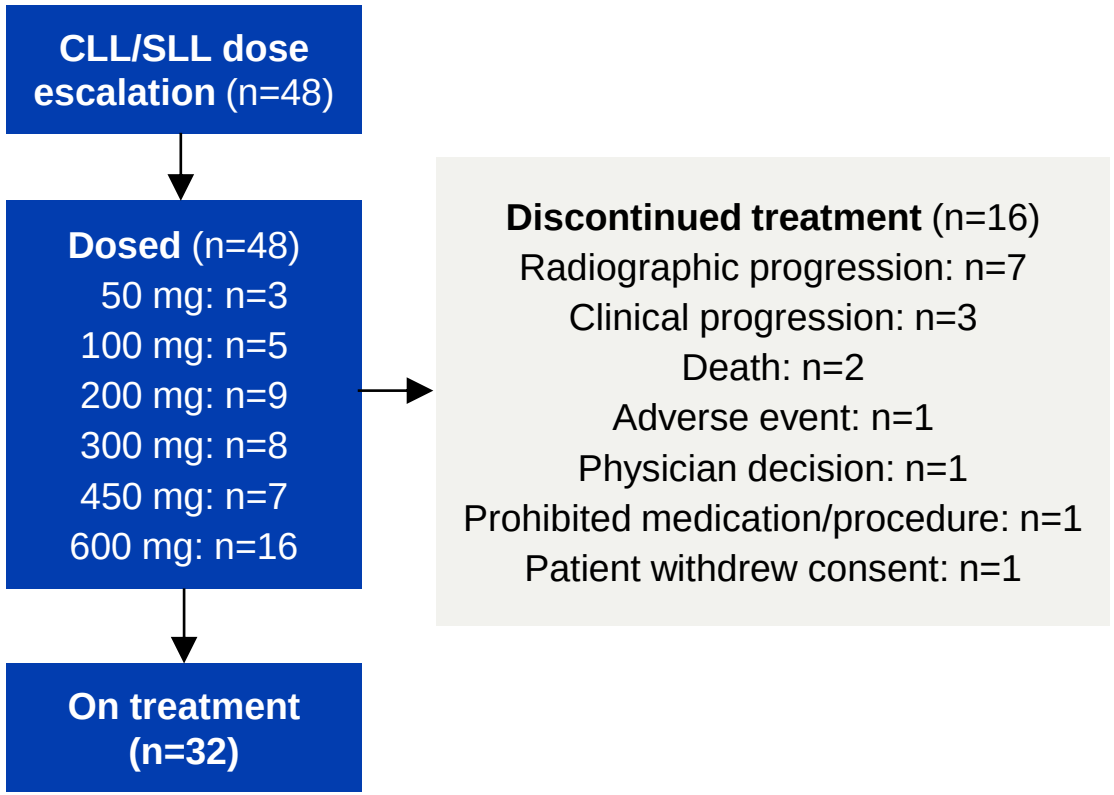
**Additional CLL Phase 1b expansion cohorts are currently enrolling*

***BCL2i**, BCL-2 inhibitor; **BTKi**, BTK inhibitor; **CLL**, chronic lymphocytic leukemia; **NHL**, non-Hodgkin lymphoma; **QD**, once daily; **SLL**, small lymphocytic lymphoma*

CLL Patient Disposition and Demographics

Phase 1a

Patient disposition



Patient demographics

Characteristics	Patients (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	3 (6.3)

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

Data cutoff: 12 Mar 2025

Multiple Prior Lines of Therapy and High Prevalence of Baseline Mutations

Baseline disease characteristics: Phase 1a

Characteristics	Patients with CLL/SLL (n=48)
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)
Chemo/chemo-immunotherapies (CIT)	35 (72.9)
CAR-T therapy	3 (6.3)
Bispecific antibody	3 (6.3)
PI3Ki	14 (29.2)
Mutation status[c], n (%)	(n=47)
BTK	18 (38.3)
TP53	21 (44.7)
PLCG2	7 (14.9)
BCL2	6 (12.8)

[a]Patients could have received multiple prior treatments; [b]All patients who received ncBTKi have also previously received cBTKi; [c]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*

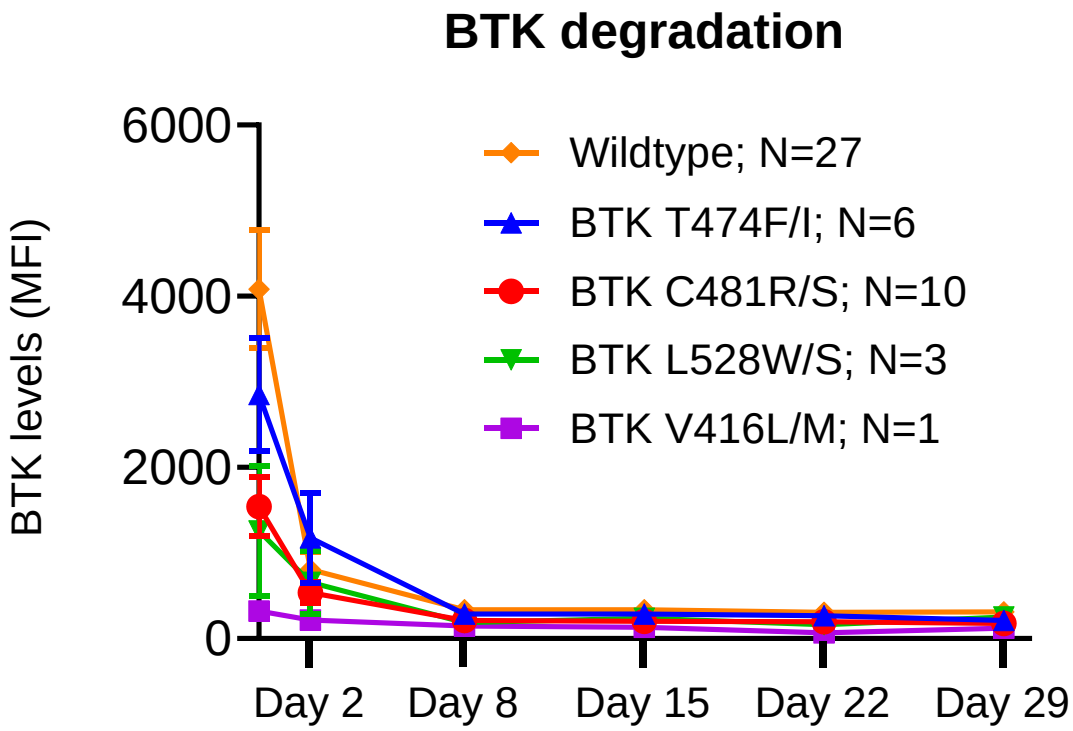
Data cutoff: 12 Mar 2025

Bexobrutideg Degrades Gatekeeper, Kinase-Proficient and Kinase-Dead BTK Mutations

Phase 1a

	Patients with CLL/SLL (n=47)[c]
Baseline mutation status, n (%)	
BTK mutations[1,a,b]	18 (38.3)
C481S	10 (21.3)
C481R	2 (4.3)
L528W	2 (4.3)
L528S	1 (2.1)
T474I	5 (10.6)
T474F	1 (2.1)
V416M	1 (2.1)
V416L	1 (2.1)
G541V	1 (2.1)

[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: 12 Mar 2025

Bexobrutideg Safety Profile in Patients with CLL

TEAEs in ≥10% of patients or Grade ≥3 TEAEs or SAEs in >1 patient: Phase 1a

TEAEs, n (%)	Patients with CLL/SLL (n=48)		
	Any grade	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)

- Tolerable safety profile consistent with prior disclosures
- No dose-limiting toxicities
- 1 related AE leading to treatment discontinuation (Grade 2 hot flushes)
- 1 Grade 5 AE (pulmonary embolism; deemed not related to bexobrutideg)

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

***CLL**, chronic lymphocytic leukemia; **SAE**, serious adverse event; **SLL**, small lymphocytic lymphoma; **TEAE**, treatment-emergent AE*

Data cutoff: 12 Mar 2025

High Overall Response Rate and a Complete Response

Bexobrutideg overall response assessment: Phase 1a

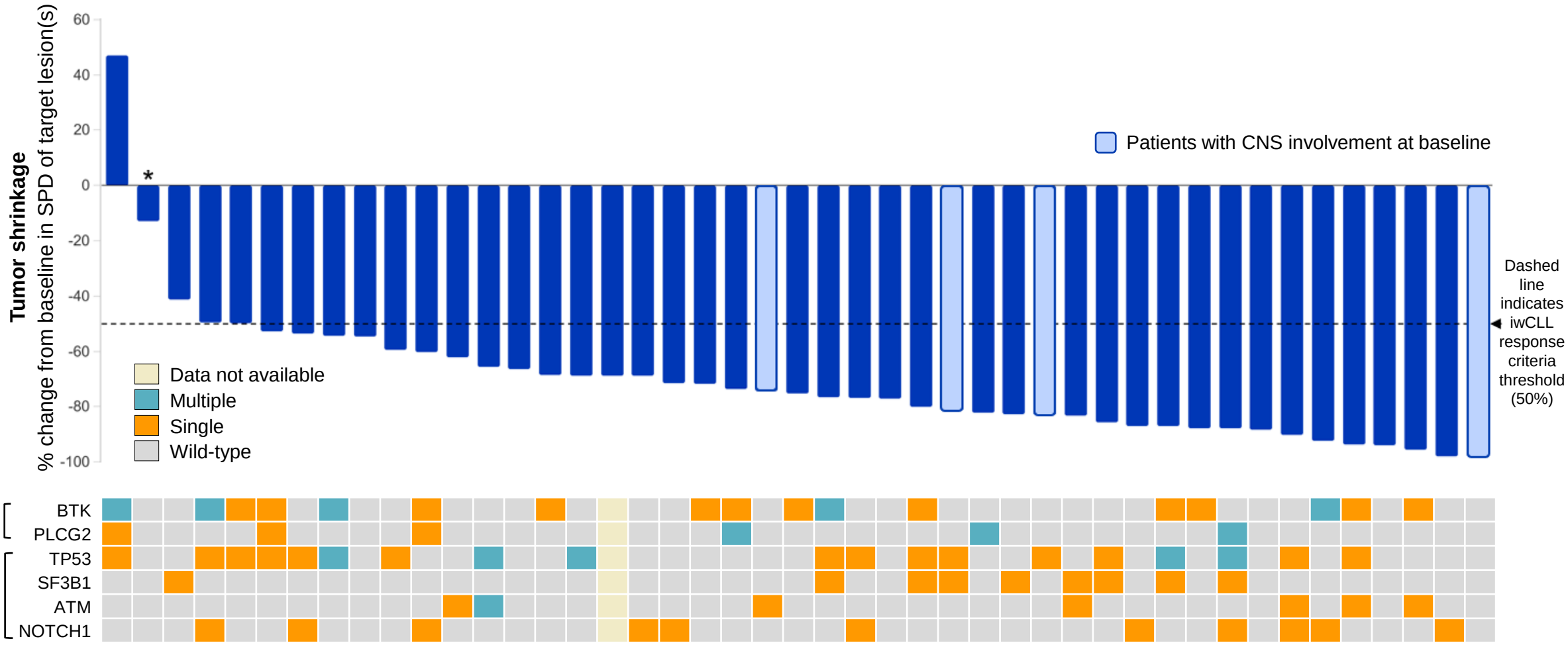
CLL response-evaluable patients[a]	Response analysis (n=47)
Objective response rate (ORR),[b] % (95% CI)	80.9 (66.7–90.9)
Best response, n (%)	
CR	1 (2.1)
PR	37 (78.7)
PR-L	0 (0.0)
SD	7 (14.9)
PD	2 (4.3)
Median follow-up, months[c] (range)[d]	9.0 (1.6–26.1)

[a]Patients who were treated with bexobrutideg having ≥1 post-baseline disease assessment or documented clinical PD
[b]Objective response rate was evaluated using iwCLL criteria and included CR + PR + PR-L
[c]Kaplan-Meier estimate; [d]Observed values

***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: 12 Mar 2025

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



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

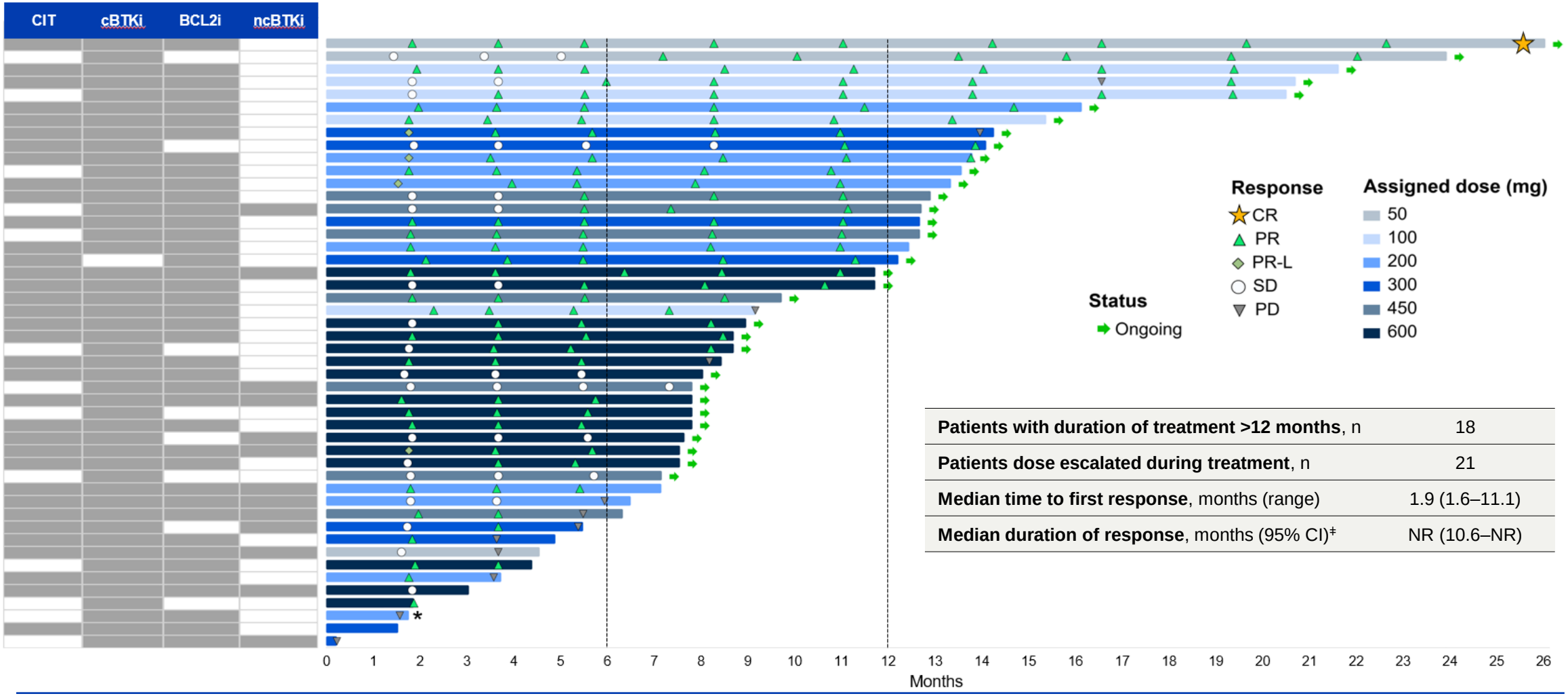
Note: patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL criteria, although they may not be represented in the waterfall plot

***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: 12 Mar 2025

Bexobrutideg Duration of Treatment in Patients with CLL

Durable responses regardless of prior therapy (n=48)



Patients with duration of treatment >12 months, n	18
Patients dose escalated during treatment, n	21
Median time to first response, months (range)	1.9 (1.6–11.1)
Median duration of response, months (95% CI)‡	NR (10.6–NR)

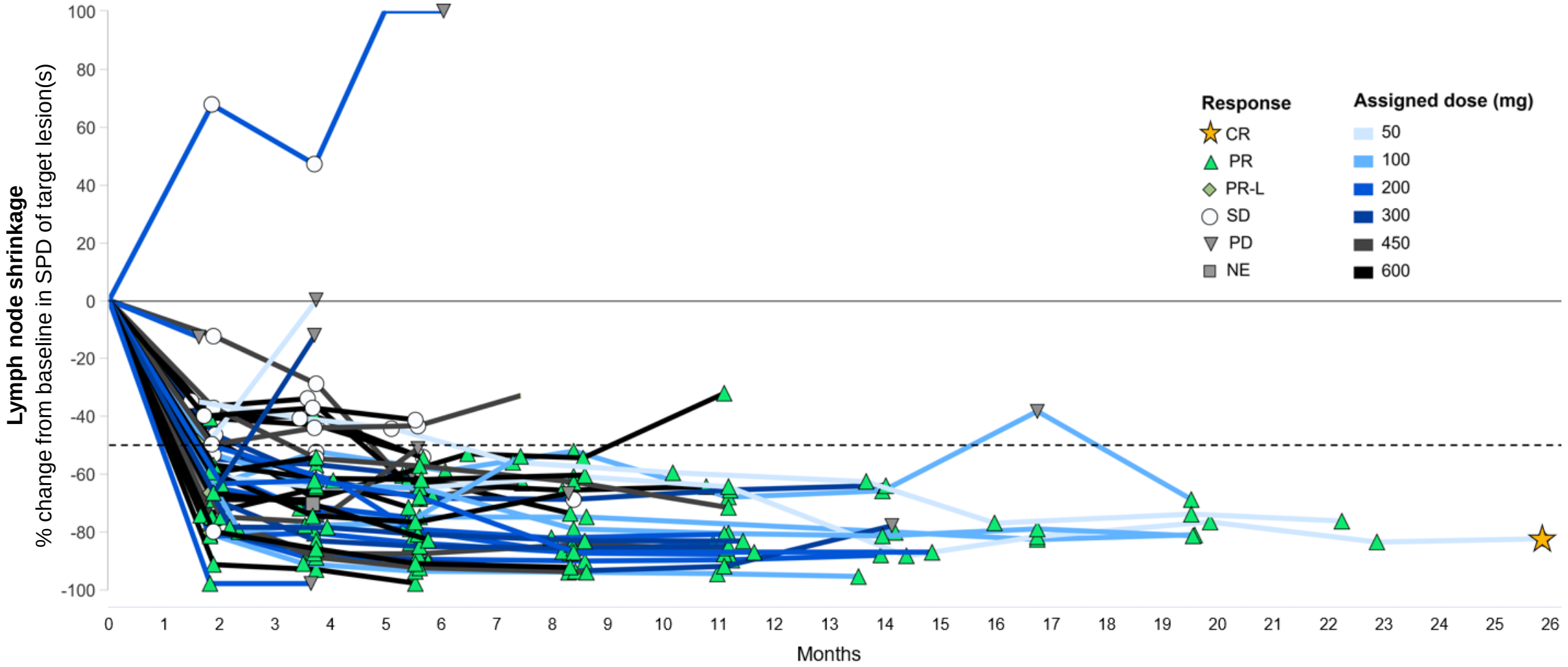
**Patient with Richter's transformation to Hodgkin's on biopsy; ‡Kaplan-Meier estimate*

Data cutoff: 12 Mar 2025

***BCL2i**, BCL2 inhibitor; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CI**, confidence interval; **CIT**, chemo/chemo-immunotherapies; **CR**, complete response; **ncBTKi**, non-covalent BTKi; **NE**, not evaluable; **NR**, not reached; **PD**, progressive disease; **PR**, partial response; **PR-L**, PR with rebound lymphocytosis; **SD**, stable disease*

Rapid and Sustained Decrease in Lymph Node Size in Patients Treated with Bexobrutideg

Percent change from baseline in sum of product diameters in patients with CLL



***CR**, complete response; **NE**, not evaluable; **PD**, progressive disease; **PR**, partial response; **PR-L**, PR with rebound lymphocytosis; **SD**, stable disease; **SPD**, sum of products diameters*

Data cutoff: 12 Mar 2025

Deepening Response Leading to a Complete Response

Case report: patient with CR after 26 months on treatment

Patient demographics and disease characteristics

- 71-year-old Female with CLL
- Initial CLL diagnosis: 2014
- BTK mutation status: no BTK mutations

Prior treatments

1. Bendamustine + Rituximab (Benda-R)
2. Ibrutinib + Venetoclax (Ibr + Ven)

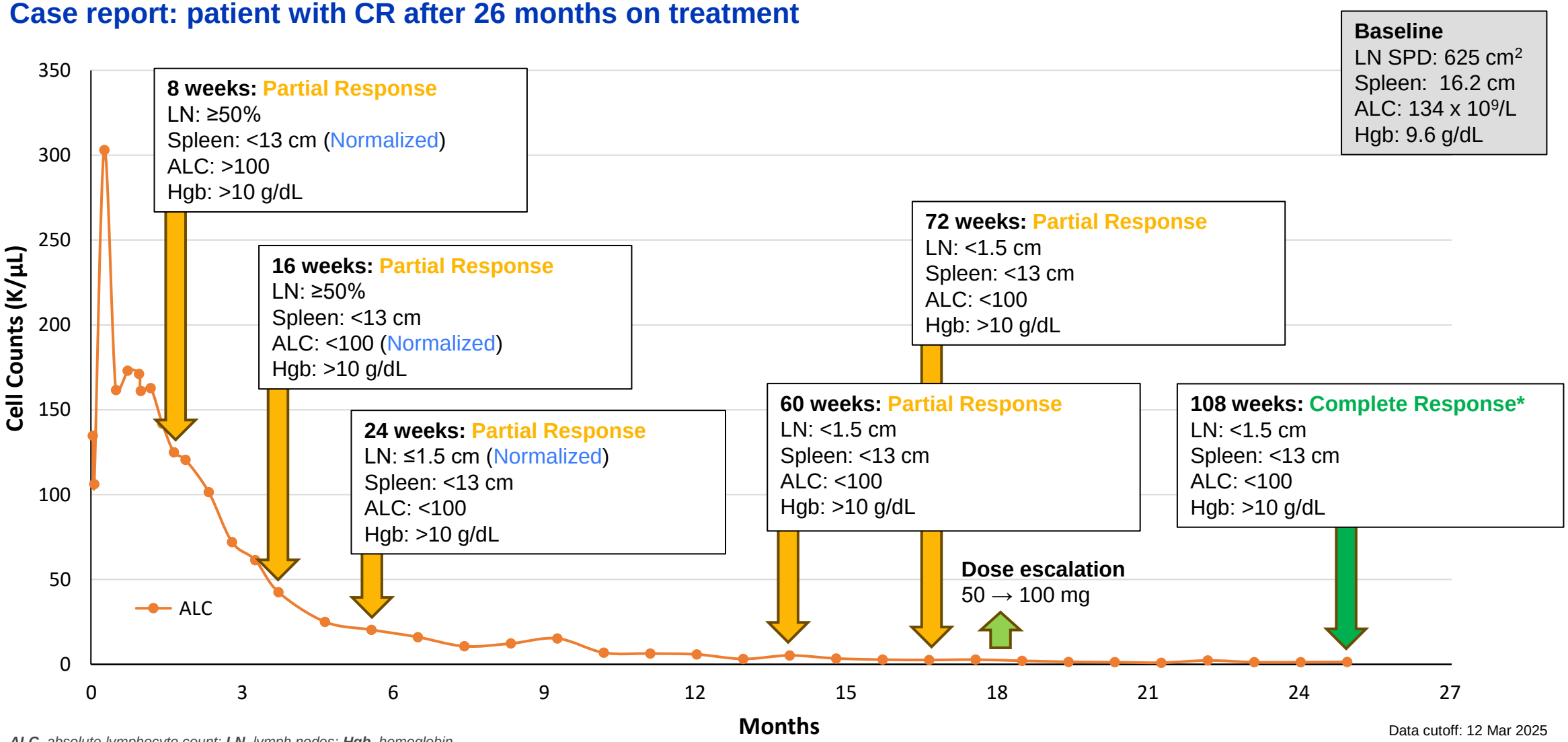
Bexobrutideg treatment

- Starting dose: 50 mg -> 100mg at month 17
- C1D1: 10 Jan 2023
- Current cycle: 28
- All related TEAEs were Grade 1
- Current status: ongoing, Complete Response*

**as assessed by investigator per iwCLL criteria including bone marrow assessment*

Deepening Response Leading to a Complete Response

Case report: patient with CR after 26 months on treatment



Data cutoff: 12 Mar 2025

ALC, *absolute lymphocyte count;* ***LN****, lymph nodes;* ***Hgb****, hemoglobin*

**as assessed by investigator per iwCLL criteria including bone marrow assessment*

Conclusions

- Bexobrutideg (NX-5948) is a novel small molecule that degrades 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
  - 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

Phase 1b dose-expansion cohort enrollment is complete; enrollment is ongoing in additional Phase 1b sub-population cohorts and pivotal trial(s) initiation is planned later in 2025

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  - Nurix employees working on developing bexobrutideg and supporting the clinical trial
- The NX-5948-301 study is sponsored by Nurix Therapeutics, Inc.