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

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

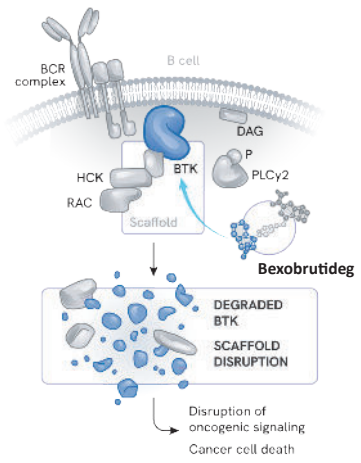
[1]Medical College of Wisconsin, Milwaukee, WI, USA; [2]University of Cincinnati, Cincinnati, OH, USA; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]University Hospital Southampton NHS Trust, Southampton, UK; [5]Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, UK; [6]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [7]The Christie Hospital and Manchester Cancer Research Centre, Division of Cancer Sciences, Manchester, UK; [8]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA; [9]Duke Cancer Institute, Durham, NC, USA; [10]Royal Marsden NHS Foundation Trust, Sutton, UK; [11]The Clatterbridge Cancer Centre, Liverpool, UK; [12]Cleveland Clinic Foundation, Cleveland, OH, USA; [13]AidPort Hospital, Skórzewo (Poznan), Poland; [14]Emory Winship Cancer Institute, Atlanta, GA, USA; [15]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [16]Nurix Therapeutics, Inc., San Francisco, CA, USA; [17]St. 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 mutations[5] and disrupt BTK scaffolding.[3,5]
- Here we report updated findings from a Phase 1a trial of bexobrutideg in patients with relapsed/refractory CLL.

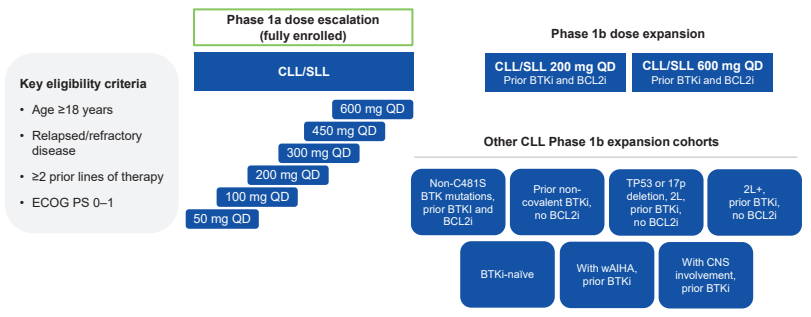
Figure 1. Bexobrutideg Mechanism of Action



Methods

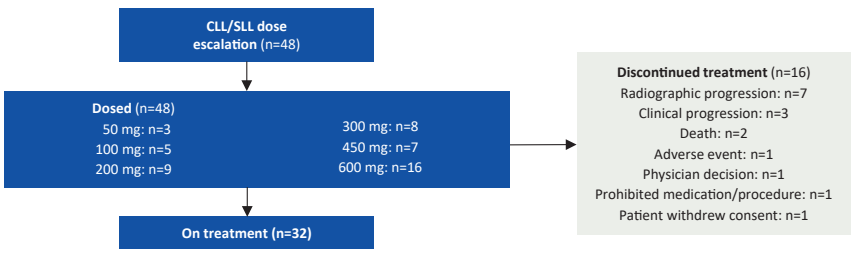
- NX-5948-301 is a Phase 1 clinical trial evaluating the safety and efficacy of bexobrutideg in patients with relapsed/refractory B-cell malignancies, including CLL and NHL, in parallel 3+3 dose-escalation then dose-expansion cohorts (**Figure 2**).
- Key eligibility criteria include ≥2 prior therapy 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



Data cutoff: 12 Mar 2025

- 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**).

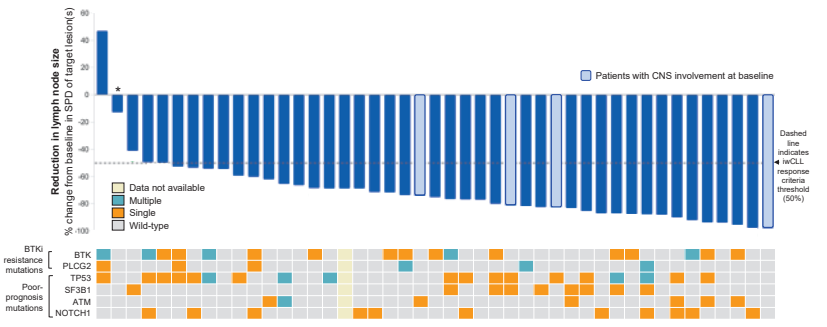
Table 1. Patient Demographics and Baseline Disease Characteristics: Phase 1a

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 (%)	
BTK	18 (38.3)
TP53	21 (44.7)
PLCγ2	7 (14.9)
BCL2	6 (12.8)

[a]*Patients could have received multiple prior treatments;* [b]*All patients who received ncBTKi also previously received cBTKi;* [c]*Mutations presented here were centrally sequenced*

Data cutoff: 12 Mar 2025

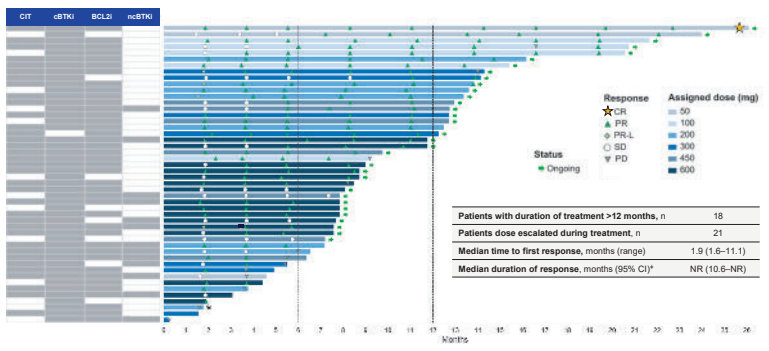
Figure 4. Clinical Activity in Patients with CLL Including Those with Baseline Mutations and CNS Involvement



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

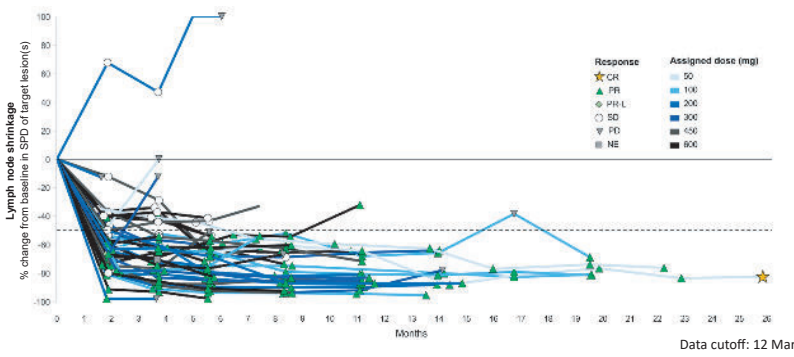


Patients with duration of treatment >12 months, n	18
Patients dose escalated during treatment, n	21
Median time to first response, months (range)	1.9 (1.6–11.1)
Median duration of response, months (95% CI)*	NR (10.6–NR)

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

Data cutoff: 12 Mar 2025

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



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 (%)	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)

[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'*

Data cutoff: 12 Mar 2025

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)

[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 unconfirmed responses*
[c]*Kaplan-Meier estimate;* [d]*Observed 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

Acknowledgements

- The authors are grateful to the patients and their families who enrolled in this trial.
- The authors would also like to thank:
  - All NX-5948-301 investigators and study sites in France, Italy, the United States, the United Kingdom, the Netherlands, Poland, Spain, and Switzerland for participating in this clinical research.
  - Nurix employees working on developing bexobrutideg and supporting the clinical trial.
- The NX-5948-301 study is sponsored by Nurix Therapeutics, Inc.

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; **CI**, 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; **MFI**, mean fluorescence intensity; **ncBTKi**, non-covalent BTKi; **NE**, not evaluable; **NHL**, non-Hodgkin's lymphoma; **NOTCH1**, neurologic locus notch 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

References

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