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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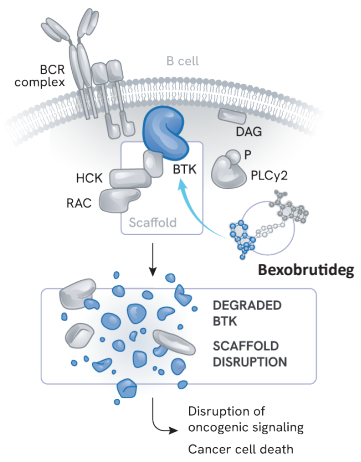
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For information about this clinical trial please scan the QR code

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.

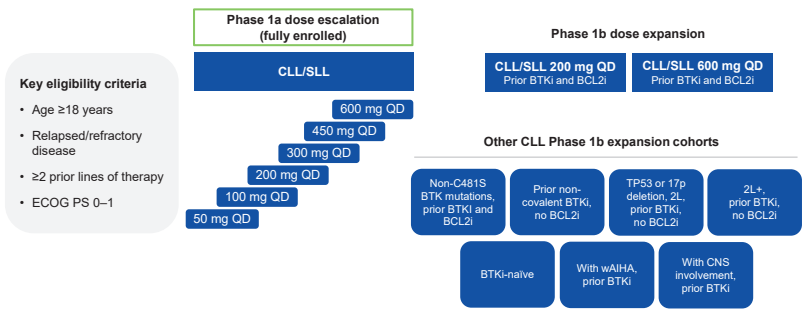
Figure 1. Bexobrutideg Mechanism of Action



Methods

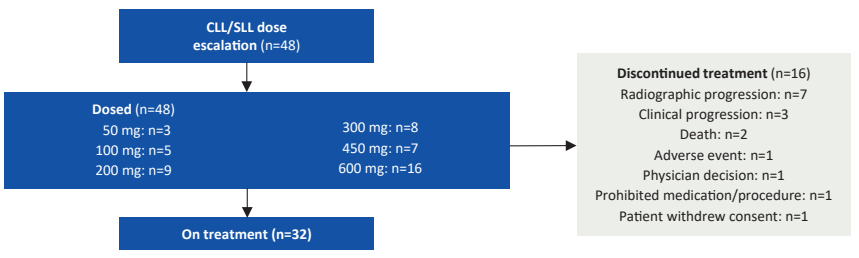
- NX-5948-301 is a Phase 1 clinical trial evaluating the safety and efficacy of bexobrutideg in patients with relapsed/refractory B-cell malignancies, including CLL and NHL, in parallel 3+3 dose-escalation then dose-expansion cohorts (**Figure 2**).
- Key eligibility criteria include ≥2 prior therapy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

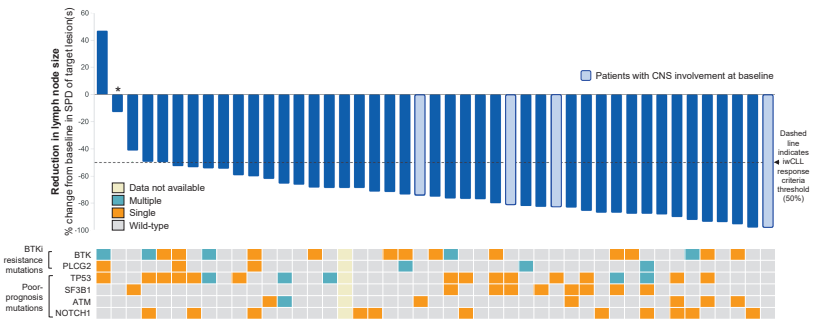
Table 1. Patient Demographics and Baseline Disease Characteristics: Phase 1a

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

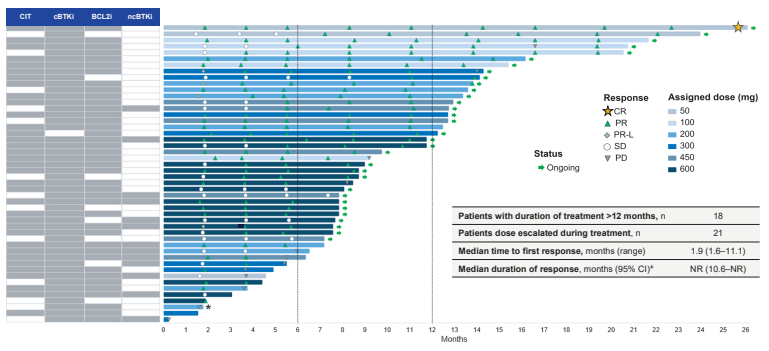
Figure 4. Clinical Activity in Patients with CLL Including Those with Baseline Mutations and CNS Involvement



**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

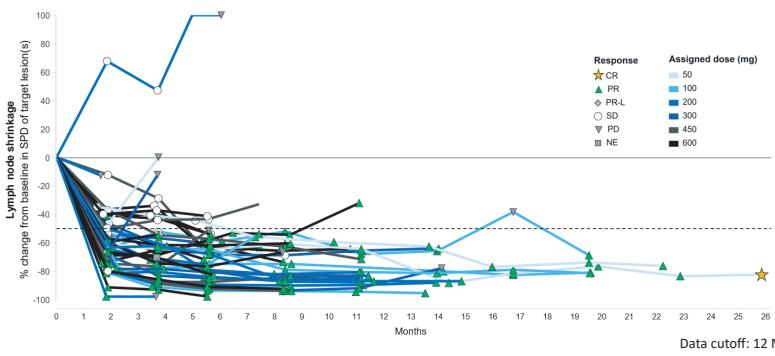
Figure 5. Durable Responses Regardless of Prior Therapy (n=48)



**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

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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.

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

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