Updated efficacy and safety data from an ongoing phase 1a/b trial of the Bruton's tyrosine kinase (BTK) degrader bexobrutideg (NX-5948) in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) across lines of therapy

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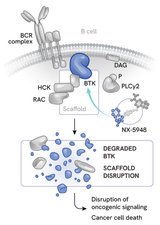
For information about this clinical trial please scan the QR code

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 new and updated efficacy and safety data with bexobrutideg in CLL/SLL from a Phase 1a trial and select Phase 1b cohorts including patients with different prior treatment profiles, in patients with relapsed/refractory disease as well as patients in earlier lines of therapy.

Figure 1. Bexobrutideg Mechanism of Action

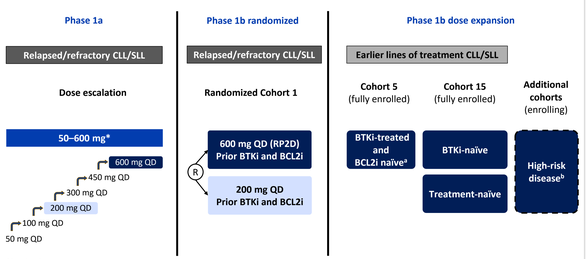


- ✓ Active against not only wild-type BTK but also treatment emergent BTK-inhibitor resistance mutations[1,6]
- ✓ Addresses both BTK scaffolding and kinase functions, unlike current BTK inhibitors[3]
- ✓ Acts catalytically, driving degradation at low free-drug plasma concentrations
- ✓ Crosses the blood–brain barrier and demonstrates clinical activity in the CNS[7]
- ✓ Demonstrates robust clinical activity in difficult-to-treat B-cell malignancies[6–10]

Methods

- NX-5948-301 (NCT05131022) is a Phase 1 first-in-human clinical trial evaluating the safety and efficacy of bexobrutideg in patients with advanced B-cell malignancies (**Figure 2**).
- In CLL/SLL, bexobrutideg is being evaluated in relapsed/refractory patients in the Phase 1a dose-escalation part. The Phase 1b dose-expansion cohorts include heavily pre-treated, earlier-line and treatment-naïve patients:
  - Cohort 5: BCL2i-naïve patients treated with at least 1 line of therapy that included a BTKi.
  - Cohort 15: BTKi-naïve patients, including treatment-naïve patients.
- Key eligibility criteria include age ≥18 years; ECOG PS 0–1; measurable disease per response criteria specific to the malignancy; anticipated life expectancy of at least 12 weeks from the time of screening; adequate organ and bone marrow function.
- Objectives:
  - Phase 1a (dose escalation):
    - Primary: safety/tolerability and identification of a recommended Phase 2 dose (RP2D).
    - Secondary: characterization of the pharmacokinetic/pharmacodynamic profile and assessment of preliminary efficacy according to iwCLL criteria.
  - Phase 1b (dose expansion):
    - Primary: anti-tumor activity and safety/tolerability.
    - Secondary: further characterization of the pharmacokinetic/pharmacodynamic profile and anti-tumor activity.

Figure 2. Trial design – CLL cohorts with BTKi-treated and BCL2i-naïve; BTKi-naïve (including treatment-naïve)

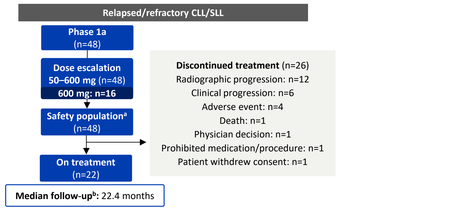


*Starting dose
[a]All patients at 600 mg except one patient on 200 mg dose
[b]Including: non-C481S mutations; prior ncBTKi; TP53 mutations; warm autoimmune hemolytic anemia; CNS involvement with prior BTKi

Results

- As of 1 Jan 2026, 142 CLL/SLL patients have been enrolled: 48 in Phase 1a, with 16 at bexobrutideg 600 mg (**Figure 3**); 42 in Phase 1b Cohort 1; 19 in Phase 1b Cohort 5, with 18 at bexobrutideg 600 mg (**Figure 4**); and 20 in Phase 1b Cohort 15, all treated at bexobrutideg 600 mg (**Figure 4**). The remaining 13 patients have been enrolled in other Phase 1b expansion cohorts (data not presented in this poster).
- The Phase 1a relapsed/refractory CLL population comprised patients with multiple prior lines of therapy and high prevalence of baseline mutations, while Cohorts 5 and 15 comprised patients in earlier lines of treatment with fewer high-risk molecular features/BTK mutations (**Table 1**).

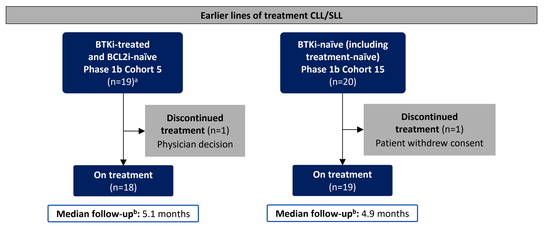
Figure 3. CLL patient disposition: Phase 1a – patients with relapsed/refractory CLL/SLL



[a]Safety and efficacy populations are identical
[b]Time from treatment start to data cutoff

Data cutoff: 1 Jan 2026

Figure 4. CLL patient disposition: Phase 1b – patients in earlier lines of treatment



[a]One patient in Cohort 5 was enrolled at 200 mg prior to selection of 600 mg as the go-forward dose; all other patients at 600 mg;
[b]Time from treatment start to data cutoff

Data cutoff: 1 Jan 2026

Table 1. Patient demographics and baseline disease characteristics: Phase 1a and Phase 1b

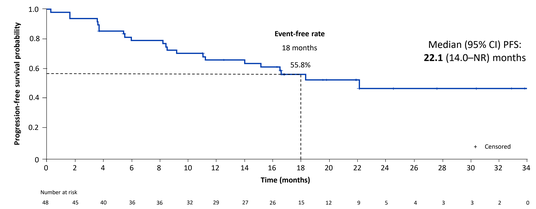
	Relapsed/refractory	Earlier lines of treatment	
Characteristics	**Dose escalation Phase 1a 50–600 mg[a] (n=48)**	**BTKi-treated and BCL2i-naïve Phase 1b Cohort 5 (n=19)**	**BTKi-naïve (including treatment-naïve) Phase 1b Cohort 15 (n=20)**
Median age, years (range)	68.5 (35–88)	71.0 (48.0–79.0)	69.5 (41.0–87.0)
Male, n (%)	32 (66.7)	16 (84.2)	10 (50.0)
White, n (%)	42 (87.5)	18 (94.7)	19 (95.0)
ECOG PS 0/1, n (%)	19 (39.6) / 29 (60.4)	12 (63.2) / 7 (36.8)	5 (25.0) / 15 (75.0)
CNS involvement, n (%)	5 (10.4)	0	0
Median prior lines of therapy, n (range)	4.0 (2–12)	NA	NA
Previous treatments,[b] n (%)			
BTKi	47 (97.9)	19 (100.0)	0
cBTKi / ncBTKi	47 (97.9) / 13 (27.1)	19 (100.0) / 1 (5.3)	0 / 0
BCL2i	40 (83.3)	0	2 (10.0)
BTKi and BCL2i	39 (81.3)	NA	NA
cBTKi, ncBTKi and BCL2i	11 (22.9)	NA	NA
Chemo/chemo-immunotherapies	35 (72.9)	9 (47.4)	8 (40.0)
Mutation status,[c] n (%)	(n=47)	(n=19)	(n=20)
BTK	18 (38.3)	10 (52.6)	0
TP53	21 (44.7)	9 (47.4)	3 (15.0)
PLCG2	7 (14.9)	3 (15.8)	0
BCL2	6 (12.8)	1 (5.3)	0
IGHV (unmutated)	29 (85.3), n=34	14 (93.3), n=15	0 , n=2

[a]Safety and efficacy populations are identical; [b]Patients could have received multiple prior treatments; [c]Patients could have multiple mutations (which are reported at VAF >5%)

Data cutoff: 1 Jan 2026

- In 47 response-evaluable Phase 1a/b relapsed/refractory patients, ORR was 83.0%; best overall responses included: 2 CR, 1 nPR, 36 PR, 6 SD, and 2 PD (**Table 2**). With median study follow-up of 22.4 months, median PFS was 22.1 months (**Figure 5**).
- With shorter follow-up, promising response rates were observed in BCL2i-naïve, BTKi-naïve and treatment-naïve patients (**Table 2**). Responses were ongoing at data cutoff in most BCL2i-naïve, BTKi-naïve and treatment-naïve patients (**data not shown**).
- Clinical activity was observed across patients with BTK mutations, high-risk molecular features and/or CNS involvement in the Phase 1a patients with relapsed/refractory CLL and in the Phase 1b cohorts in patients in earlier lines of treatment (**Figure 6**).
- Rapid and durable responses were observed in most patients (**Figure 7**).

Figure 5. Progression-free survival: Phase 1a relapsed/refractory CLL/SLL (n=48)



Data cutoff: 1 Jan 2026

Table 2. ORR in Phase 1a and Phase 1b (Cohorts 5 and 15)

	Relapsed/refractory CLL/SLL	Earlier lines of treatment CLL/SLL	
	Phase 1a: Dose escalation 50–600 mg* (n=47)	**BTKi-treated and BCL2i-naïve Phase 1b Cohort 5** (n=14)	**BTKi-naïve (including treatment-naïve) Phase 1b Cohort 15** (n=19)
ORR, % (95% CI)[a]	**83.0** (69.2–92.4)	**92.9** (66.1–99.8)	**84.2** (60.4–96.6)
CR	2 (4.3)	0	0
nPR	1 (2.1)	0	0
PR/PR-L	36 (76.6)	13 (92.9)	16 (84.2)
SD	6 (12.8)	0	3 (15.8)
PD	2 (4.3)	0	0
NE	0	1 (7.1)	0
Median follow-up,[b] months (range)	22.4 (16.9–35.7)	5.2 (1.9–7.7)	4.9 (2.9–5.8)

*Starting dose; [a]Objective response rate includes CR + nPR + PR + PR-L; [b]Time from treatment start to data cutoff

Data cutoff: 1 Jan 2026

- Bexobrutideg was well tolerated in patients treated across all doses (n=142), including in 86 patients treated at 600 mg (**Table 3**).
- The most common treatment-emergent AEs included purpura/contusion, neutropenia, and petechiae, with adverse events comparable at 600 mg RP2D and at lower doses (**Figure 8**).
- The tolerable safety profile was consistent with prior disclosures; no dose-limiting toxicities were observed. Three Grade 5 AEs were reported (pneumonia, pulmonary embolism, NOS) all deemed not related to treatment.

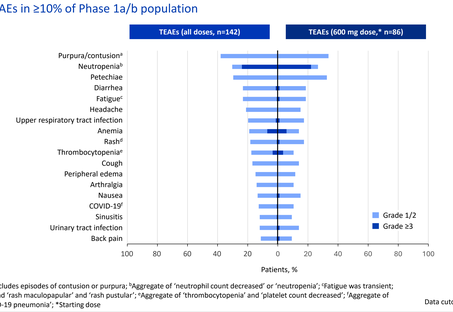
Table 3. Bexobrutideg safety summary: All CLL/SLL patients in Phase 1a/b

n (%)	All patients with CLL/SLL (n=142)	600 mg dose patients* (n=86)	50–450 mg dose patients* (n=56)
Any TEAE	134 (94.4)	79 (91.9)	55 (98.2)
Treatment related	110 (77.5)	65 (75.6)	45 (80.4)
Grade 3+	73 (51.4)	39 (45.3)	34 (60.7)
Treatment related	35 (24.6)	22 (25.6)	13 (23.2)
SAE	33 (23.2)	16 (18.6)	17 (30.4)
Treatment related	9 (6.3)	5 (5.8)	4 (7.1)
Grade 5**	3 (2.1)	1 (1.2)	2 (3.6)
Treatment related	0	0	0
Leading to treatment discontinuation	8 (5.6)	5 (5.8)	3 (5.4)
Treatment related	6 (4.2)	3 (3.5)	3 (5.4)
DLT	0	0	0
Median exposure time, months (range)	7.3 (0.03–35.8)	5.1 (0.03–21.5)	12.5 (0.2–35.7)

*Starting dose; **Grade 5 AEs: pulmonary embolism, death not otherwise specified, and pneumonia

Data cutoff: 1 Jan 2026

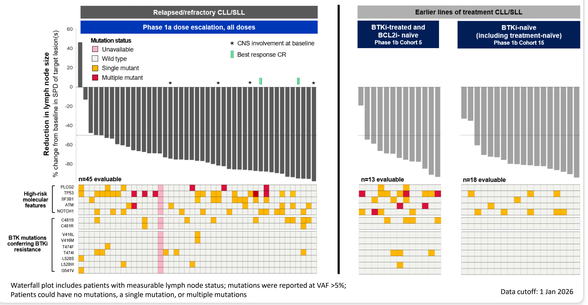
Figure 8. TEAEs in ≥10% of Phase 1a/b population



[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [c]Fatigue was transient; [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'; *Starting dose

Data cutoff: 1 Jan 2026

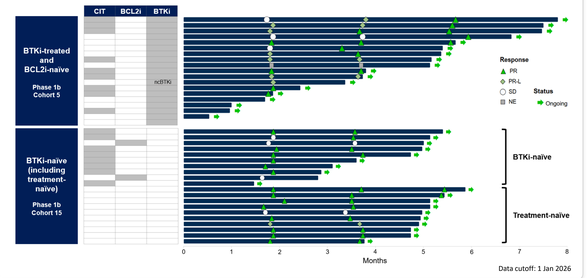
Figure 6. Reduction in lymph node size in patients with CLL/SLL treated with bexobrutideg



Waterfall plot includes patients with measurable lymph node status; mutations were reported at VAF >5%; Patients could have no mutations, a single mutation, or multiple mutations

Data cutoff: 1 Jan 2026

Figure 7. Time on treatment in patients with CLL/SLL receiving earlier lines of treatment



Data cutoff: 1 Jan 2026

Conclusions

- Bexobrutideg is a highly selective, CNS penetrant degrader of both wild-type BTK and BTKi resistance mutations that eliminates both the kinase and scaffolding functions of the BTK protein.
- In the Phase 1a portion of the NX-5948-301 trial, bexobrutideg demonstrated an ORR of 83.0% with a median PFS of 22.1 months across all doses (50–600 mg).
- In the Phase 1b portion of the trial, high ORRs were observed in cohorts of patients with fewer or no prior lines of treatment (despite short follow-up period):
  - 92.9% in patients who were BTKi-treated and BCL2i-naïve (Cohort 5).
  - 84.2% in patients who were BTKi-naïve (including treatment-naïve; Cohort 15).
- Clinical responses were observed across the overall population including those in difficult-to-treat subgroups with baseline BTK mutations, relapsed/refractory disease, high number of prior therapies, high-risk molecular features and CNS involvement.
- Bexobrutideg was well tolerated and had a safety profile that was consistent with prior disclosures, including comparisons between the RP2D 600 mg and overall trial population.
- **Based on the totality and consistency of safety and efficacy findings, bexobrutideg is being evaluated in the ongoing pivotal Phase 2 DAYBreak CLL-201 and planned Phase 3 DAYBreak CLL-306 trials.**

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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; **DLT,** dose-limiting toxicity; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **iwCLL**, International Workshop on CLL; **NA**, not applicable; **ncBTKi**, non-covalent BTKi; **NE**, not evaluable; **NOS,** not otherwise specified; **NOTCH1**, neurologic locus notch homolog protein 1; **nPR**, nodal partial response; **NR**, not reached; **ORR**, objective response rate; **PD,** progressive disease; **PFS,** progression-free survival; **PI3Ki**, phosphoinositide 3-kinase inhibitor; **PLCG2**, phospholipase C gamma 2; **PR**, partial response; **PR-L**, partial response with rebound lymphocytosis; **QD**, once daily; **RP2D**, recommended phase 2 dose; **SAE**, serious adverse event; **SD**, stable disease; **SLL**, small lymphocytic lymphoma; **SPD**, sum of products diameters; **TEAE**, treatment-emergent AE

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