Bexobrutideg (NX-5948), a novel Bruton's tyrosine kinase (BTK) degrader, demonstrates rapid and durable clinical responses in relapsed/refractory chronic lymphocytic leukemia (CLL): New and updated findings from an ongoing Phase 1a/b trial

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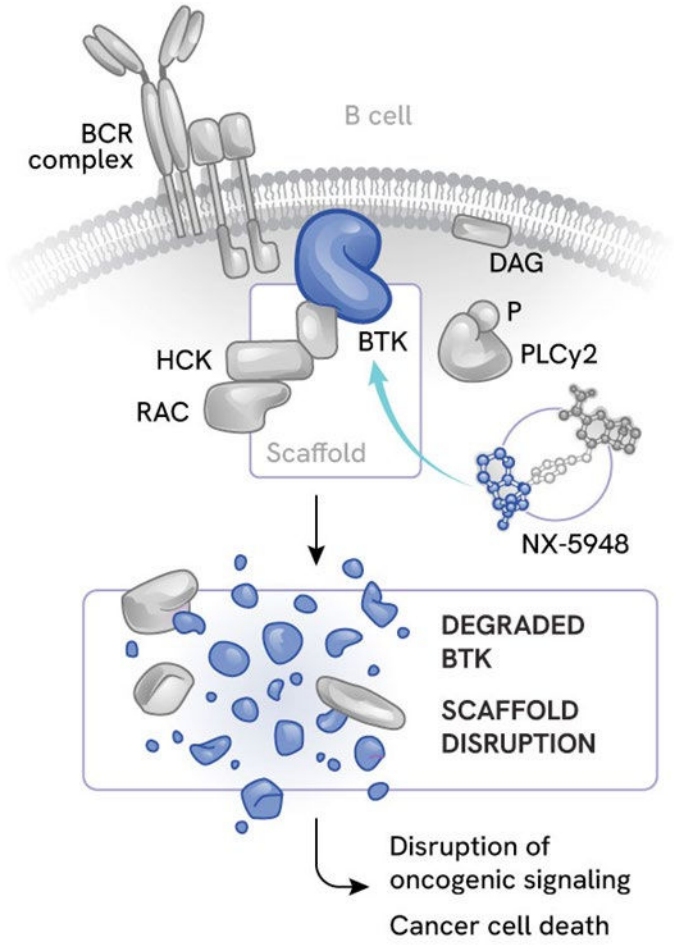
Bexobrutideg (NX-5948) Degrader Properties

A novel BTK degrader distinct from BTK inhibitors



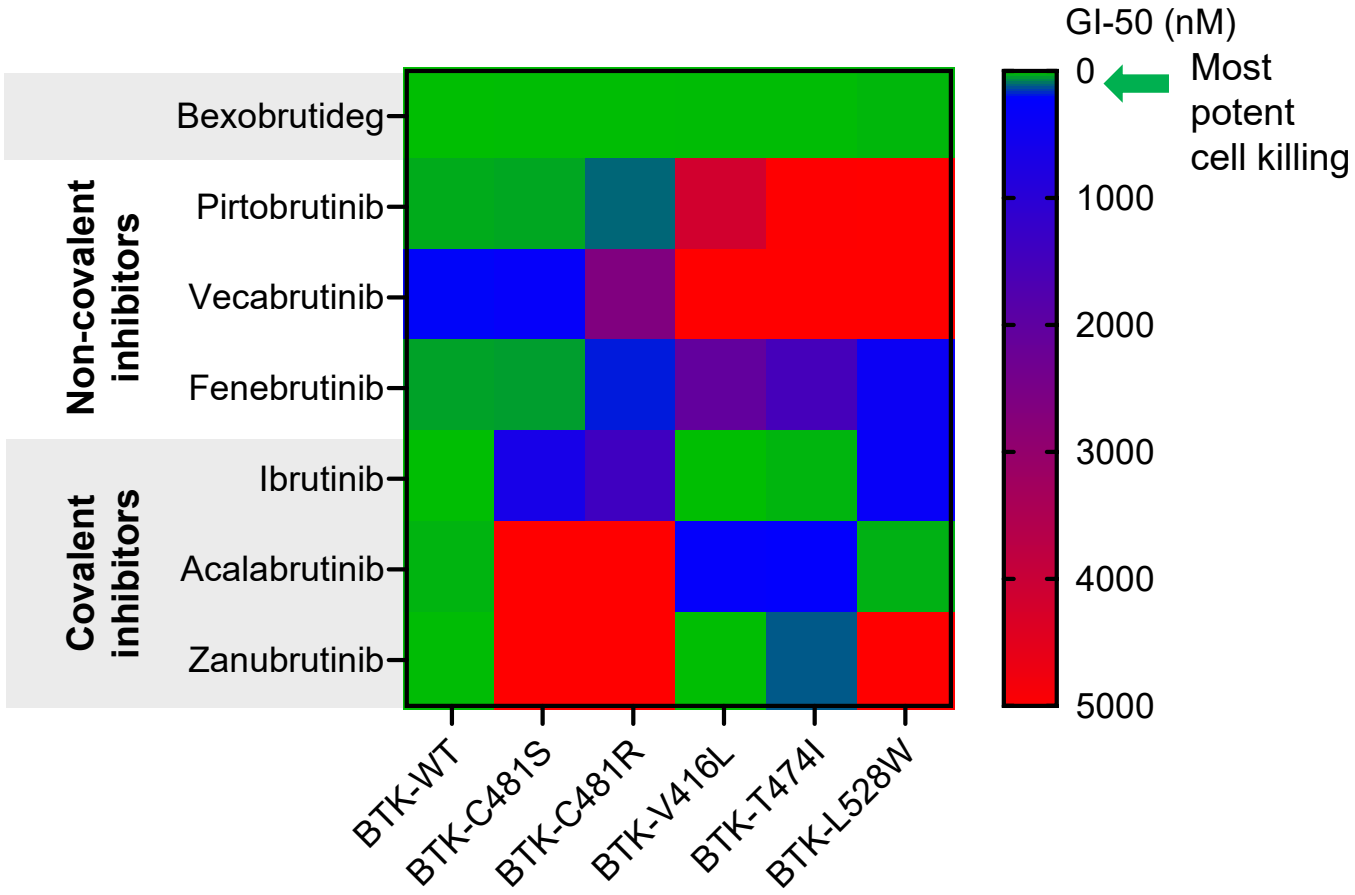
- ✓ Active against wildtype BTK and demonstrated ability to overcome treatment-emergent resistance mutations[1,2]
- ✓ Addresses BTK scaffolding function, unlike current BTK inhibitors[3]
- ✓ Acts catalytically, driving degradation at low free-plasma concentrations
- ✓ Crosses the blood–brain barrier and demonstrated clinical activity in the CNS[4]
- ✓ Demonstrated robust clinical activity in difficult-to-treat B-cell malignancies[5–7]

***BCR**, B-cell receptor; **BTK**, Bruton's tyrosine kinase; **CNS**, central nervous system; **DAG**, diacylglycerol; **HCK**, hematopoietic cell kinase*

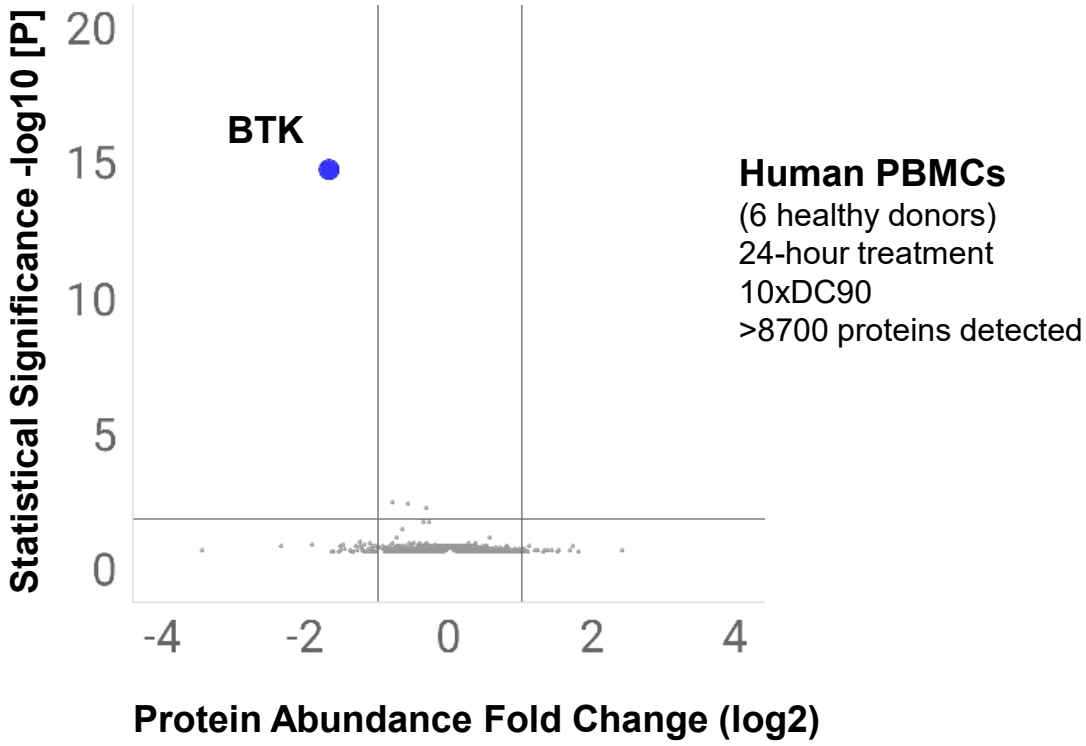
1. Noviski et al. 20th Biennial International Workshop on CLL, Boston, MA, USA. Oct 6–9, 2023; 2. Hansen. Presented at TPD Basel, Switzerland, Sept 19, 2023; 3. Montoya et al. Science 2024;383; eadi5798;
4. Noviski. 8th TPD & Induced Proximity Summit, Boston, MA, USA, Oct 29, 2025; 5. Shah et al. Blood (2024) 144 (Supplement 1): 884*; 6. Danilov et al. Oral presentation at 18th ICML congress, Lugano, Switzerland, Jun 17-21, 2025;*
7. Omer et al. Poster presentation at the EHA Congress 2025, Milan, Italy, Jun 12–15, 2025

Mutation Coverage and Selectivity of Bexobrutideg

Bexobrutideg shows superior cell killing across mutations compared with BTK inhibitors*



Global proteomics using bexobrutideg show selective degradation of BTK at clinically relevant exposures



***BTK**, Bruton's tyrosine kinase; **GI-50**, growth inhibition 50%; **PBMC**, peripheral blood mononuclear cells; **WT**, wildtype*
**In TMD8 cells expression system*

Bexobrutideg Phase 1a/b (NX-5948-301) Trial Design

Phase 1a/b clinical trial in adults with relapsed/refractory B-cell malignancies

Phase 1a dose escalation (fully enrolled)

CLL/SLL

- 600 mg QD
- 450 mg QD
- 300 mg QD
- 200 mg QD
- 100 mg QD
- 50 mg QD

CLL Phase 1b randomized cohort 1 (fully enrolled; 200 vs 600 mg)

- **CLL/SLL 200 mg QD Prior BTKi and BCL2i**
- **CLL/SLL 600 mg QD Prior BTKi and BCL2i**

CLL Phase 1b expansion, other cohorts (ongoing; all 600 mg)

- Non-C481S BTK mutations, prior BTKi and BCL2i
- Prior non-covalent BTKi, no BCL2i
- TP53 or 17p deletion, 2L, prior BTKi, no BCL2i
- 2L+, prior BTKi, no BCL2i
- BTKi-naïve
- With wAIHA, prior BTKi
- With CNS involvement, prior BTKi

WM/NHL

- 600 mg QD
- 450 mg QD
- 300 mg QD
- 200 mg QD
- 100 mg QD
- 50 mg QD

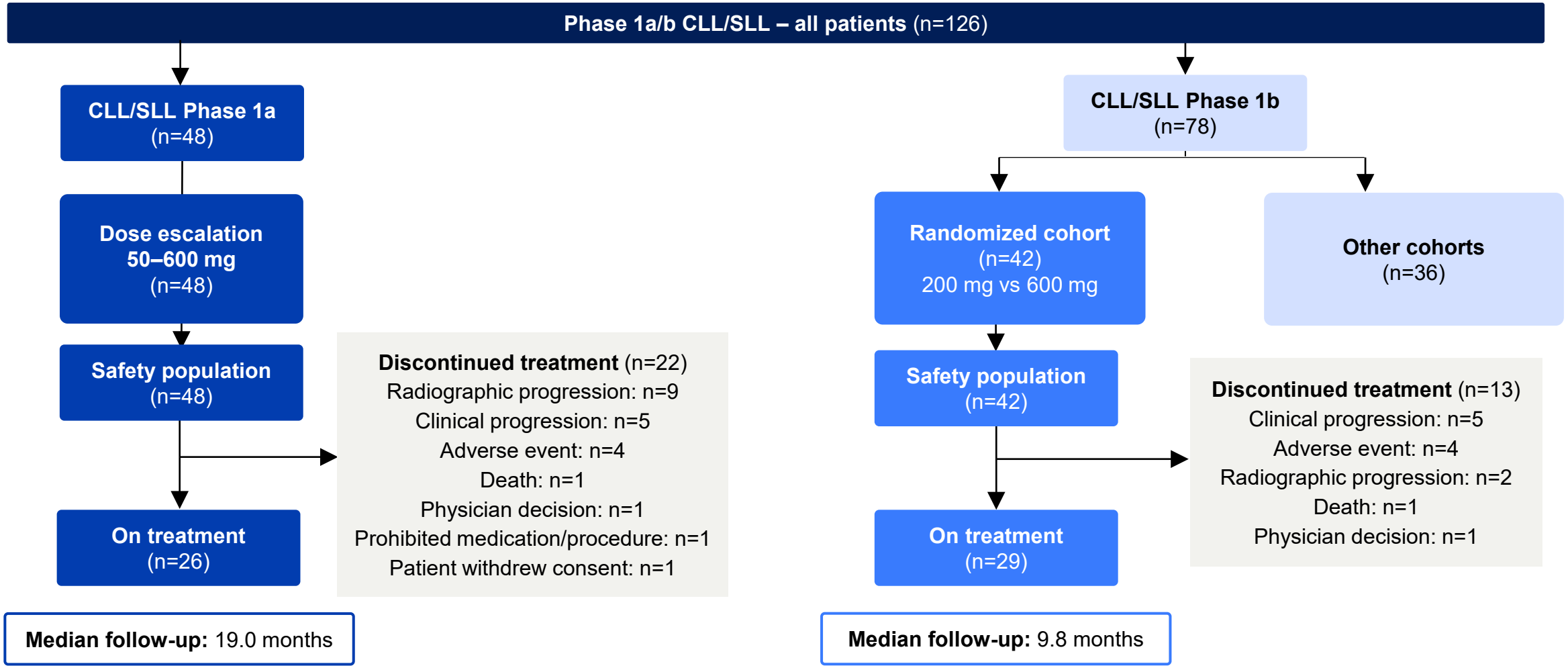
NHL/WM Phase 1b expansion cohorts (600 mg)

- **MZL** Marginal zone lymphoma
- **FL** Follicular lymphoma
- **WM** Waldenström macroglobulinemia
- **MCL** Mantle cell lymphoma
- **DLBCL** Diffuse large B-cell lymphoma
- **PCNSL** Primary CNS lymphoma

__2L+__, second line +; __BCL2i__, B-cell lymphoma 2 inhibitor; __BTKi__, Bruton's tyrosine kinase inhibitor; __CLL__, chronic lymphocytic leukemia; __CNS__, central nervous system; __NHL__, non-Hodgkin's lymphoma; __QD__, once daily; __SLL__, small lymphocytic lymphoma; __wAIHA__, warm autoimmune hemolytic anemia; __WM__, Waldenström macroglobulinemia

NX-5948-301: CLL/SLL Patient Disposition

Multiple study cohorts with distinct doses and median follow-up

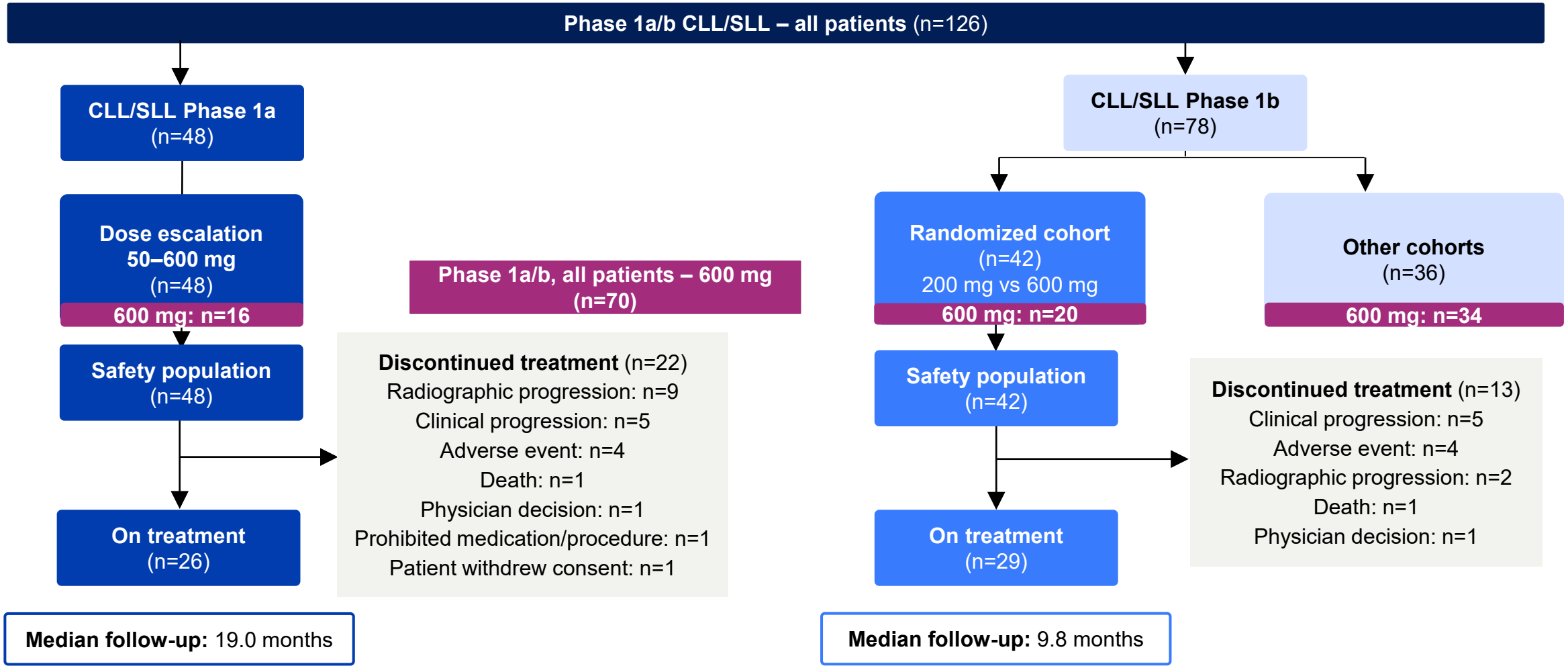


***CLL**, chronic lymphocytic leukemia; **SLL**, small lymphocytic lymphoma*

Data cutoff: 19 Sep 2025

NX-5948-301: CLL/SLL Patient Disposition

Multiple study cohorts with distinct doses and median follow-up



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

Data cutoff: 19 Sep 2025

Demographics in Overall Population (Phase 1a/b)

Population representative of CLL/SLL demographics

Characteristics	Phase 1a/b – all patients (n=126)
Median age, years (range)	69.0 (35–88)
Sex, n (%)	
Female	42 (33.3)
Male	84 (66.7)
Ethnicity, n (%)	
Hispanic or Latino	5 (4.0)
Not Hispanic or Latino	114 (90.5)
Not reported	5 (4.0)
Unknown	2 (1.6)
Race, n (%)	
Black or African American	8 (6.3)
White	110 (87.3)
Not reported	7 (5.6)
Other	1 (0.8)

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

Data cutoff: 19 Sep 2025

Baseline Disease Characteristics in Phase 1a/b and 1a

Multiple prior lines of therapy and a high prevalence of baseline mutations

Characteristics	Phase 1a/b – all patients (n=126)	Phase 1a (n=48)
ECOG PS, n (%)		
0	45 (35.7)	19 (39.6)
1	81 (64.3)	29 (60.4)
CNS involvement, n (%)	5 (4.0)	5 (10.4)
Median prior lines of therapy, n (range)	3.0 (1–17)	4.0 (2–12)
Previous treatments,[a] n (%)		
BTKi	108 (85.7)	47 (97.9)
cBTKi	106 (84.1)	47 (97.9)
ncBTKi	34 (27.0)	13 (27.1)
BCL2i	78 (61.9)	40 (83.3)
BTKi and BCL2i	75 (59.5)	39 (81.3)
CAR-T therapy	9 (7.1)	3 (6.3)
Bispecific antibody	5 (4.0)	1 (2.1)
PI3Ki	26 (20.6)	14 (29.2)
Chemo/chemo-immunotherapies	84 (66.7)	35 (72.9)
Mutation status,[b] n (%)	(n=111)	(n=47)
BTK	44 (39.6)	18 (38.3)
TP53	44 (39.6)	21 (44.7)
PLCG2	9 (8.1)	7 (14.9)
BCL2	8 (7.2)	6 (12.8)

[a]Patients could have received multiple prior treatments; [b]Mutations presented here were centrally sequenced

Data cutoff: 19 Sep 2025

***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; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ncBTKi**, non-covalent BTKi; **PI3Ki**, phosphoinositide 3-kinase inhibitor; **PLCG2**, phospholipase C gamma 2*

Overall Safety Summary in Phase 1a/b 600 mg Group vs All Patients

Tolerable safety profile, consistent between the RP2D 600 mg and overall study population

	Phase 1a/b – all patients (n=126)	**Phase 1a/b 600 mg** (n=70)
Any TEAE, n (%)	114 (90.5)	60 (85.7)
Treatment related	95 (75.4)	51 (72.9)
Grade ≥3	62 (49.2)	31 (44.3)
Treatment-related	31 (24.6)	18 (25.7)
SAE	27 (21.4)	10 (14.3)
Treatment-related	7 (5.6)	3 (4.3)
Grade 5[a]	3 (2.4)	1 (1.4)
Treatment-related	0	0
Leading to treatment discontinuation	8 (6.3)	4 (5.7)
Treatment-related	5 (4.0)	2 (2.9)
DLT	0	0
Median duration of treatment, months (range)	7.1 (0.0–32.3)	3.6 (0.0–18.0)

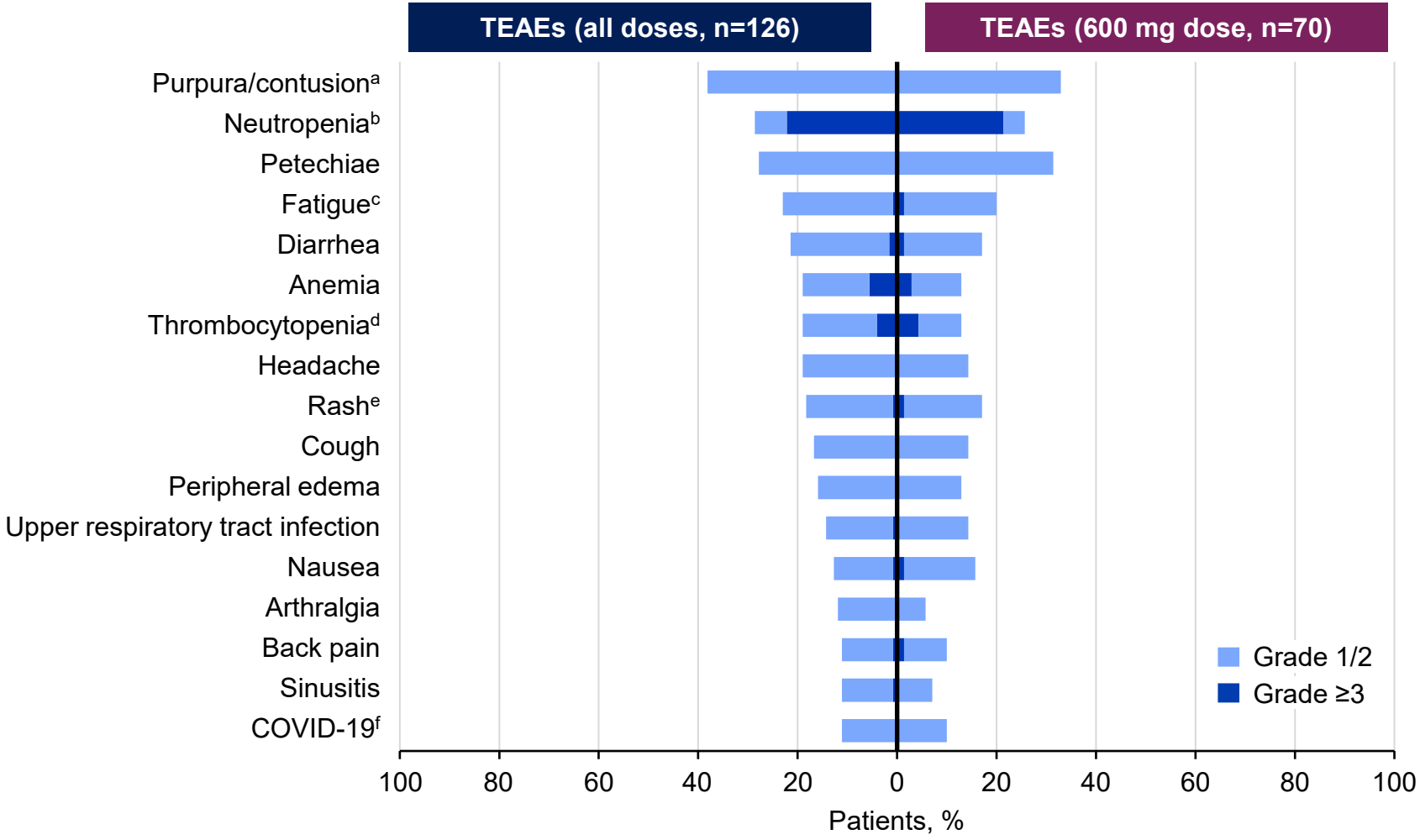
[a]*Grade 5 AEs: pulmonary embolism; death not otherwise specified; pneumonia*

***AE**, adverse event; **DLT**, dose-limiting toxicity; **RP2D**, recommended Phase 2 dose; **SAE**, serious AE; **TEAE**, treatment-emergent AE*

Data cutoff: 19 Sep 2025

TEAEs in ≥10% in Phase 1a/b 600 mg Group vs All Patients

Comparable AE profile for patients at the RP2D 600mg dose and overall population



- Tolerable safety profile consistent with prior disclosures
- No dose-limiting toxicities
- No systemic fungal infections or Grade 4 infections of any kind reported
- Single event of new onset atrial fibrillation consistent with the rate in the age-matched general population
- 3 Grade 5 AEs (death not otherwise specified; pulmonary embolism; pneumonia; all deemed not related to bexobrutideg)

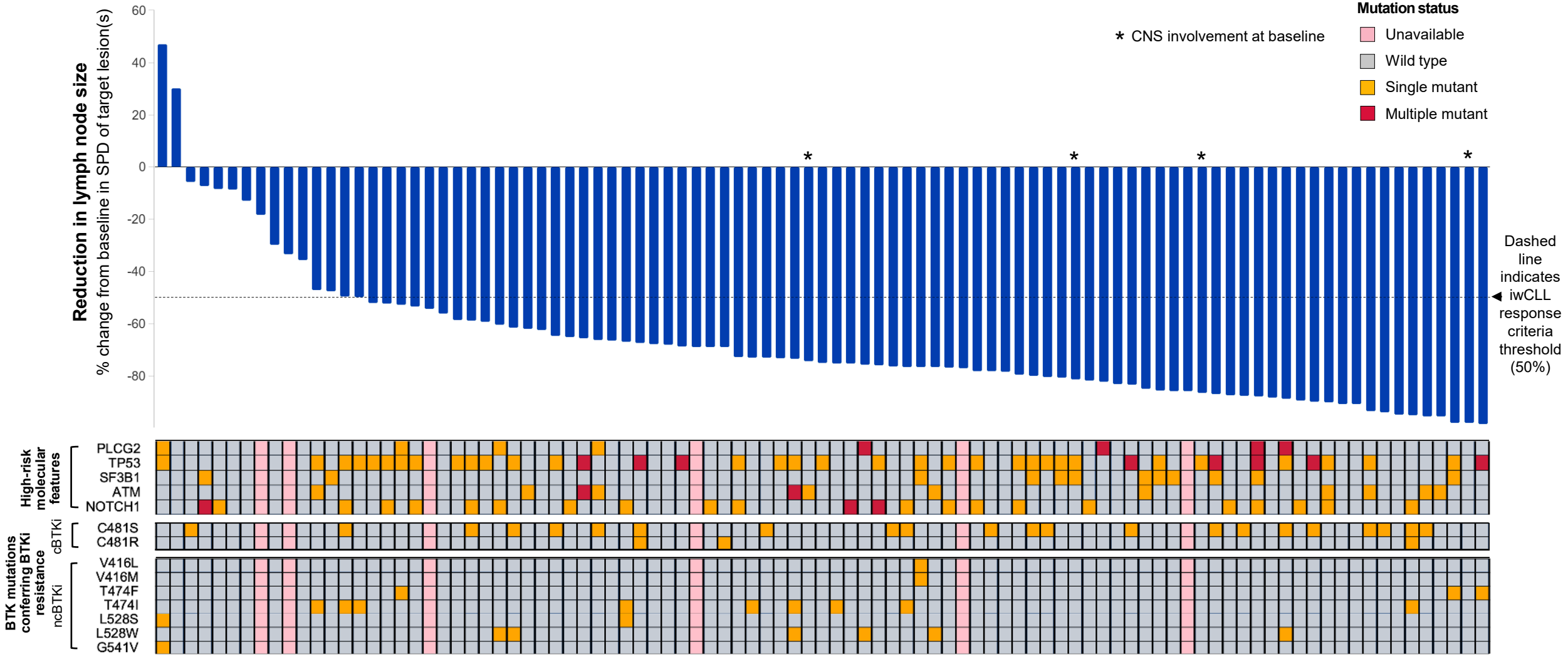
[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [c]Fatigue was transient; [d]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [e]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [f]Aggregate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

***AE**, adverse event; **NOS**, not otherwise specified; **RP2D**, recommended Phase 2 dose; **TEAE**, treatment-emergent adverse event*

Data cutoff: 19 Sep 2025

Reduction in Lymph Node Size in Phase 1a/b Overall Population[a]

Clinical activity across patients with BTK mutations,[b] high-risk molecular features and/or CNS involvement



[a]*Waterfall plot includes patients with measurable lymph node status (n=93); mutations were reported at VAF >5%;* [b]*Patients could have no mutations, a single mutation, or multiple mutations*

***ATM**, ataxia-telangiectasia mutated; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **iwCLL**, International Workshop on CLL; **ncBTKi**, non-covalent BTKi; **NOTCH1**, neurologic locus notch homolog protein 1; **PLCG2**, phospholipase C gamma 2; **SPD**, sum of products diameters*

Data cutoff: 19 Sep 2025

Overall Response Rate in Phase 1a Across All Dose Levels (n=47)

Encouraging ORR and long median duration of response

Response-evaluable patients	Phase 1a (n=47)
Objective response rate (ORR),[a] % (95% CI)	**83.0 (69.2–92.4)**
Disease control rate (DCR),[b] % (95% CI)	95.7 (85.5–99.5)
Best response,[c] n (%)	
Complete response (CR)	2 (4.3)
Nodal partial response (nPR)	1 (2.1)
Partial response (PR/PR-L)	36 (76.6)
Stable disease (SD)	6 (12.8)
Progressive disease (PD)	2 (4.3)
Median follow-up,[d] months (range)	19.0 (13.5–32.3)
Median duration of response, months (95% CI)	20.1 (12.2–NE) (n=39)

[a]Objective response rate includes CR + nPR + PR + PR-L; [b]Disease control rate includes CR + nPR + PR/PR-L + SD; [c]Percentages are based on the number of patients dosed who had at least one post-baseline disease assessment or documented clinical PD; [d]Time from treatment start to data cutoff

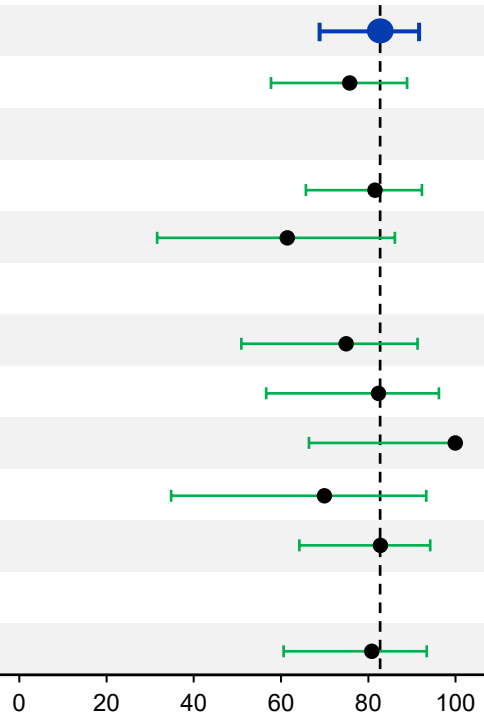
***CI**, confidence interval; **CR**, complete response; **DCR**, disease control rate; **NE**, not evaluable; **nPR**, nodal partial response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **PR-L**, partial response with lymphocytosis; **SD**, stable disease*

Data cutoff: 19 Sep 2025

Overall Response Rate by Subgroup in Phase 1a (n=47)

Clinically meaningful response rate observed across difficult-to-treat subgroups

Subgroup	Number of patients with a response/total number[a]	Objective response rate, % (95% CI)
ORR in Phase 1a population	39/47	83 (69–92)
Discontinued due to PD on any prior BTKi	25/33	76 (58−89)
Prior therapy		
Prior BCL2i and BTKi	31/38	82 (66−92)
Prior non-covalent BTKi	8/13	62 (32−86)
Mutations		
TP53 mutation	15/20	75 (51−91)
Any baseline BTK mutation	14/17	82 (57−96)
C481 BTK mutation	9/9	100 (66−100)
L528/T474/V416/G541 BTK mutation	7/10	70 (35−93)
Wild-type BTK	24/29	83 (64−94)
Prior lines of systemic therapies received		
≥4 prior lines	21/26	81 (61−93)



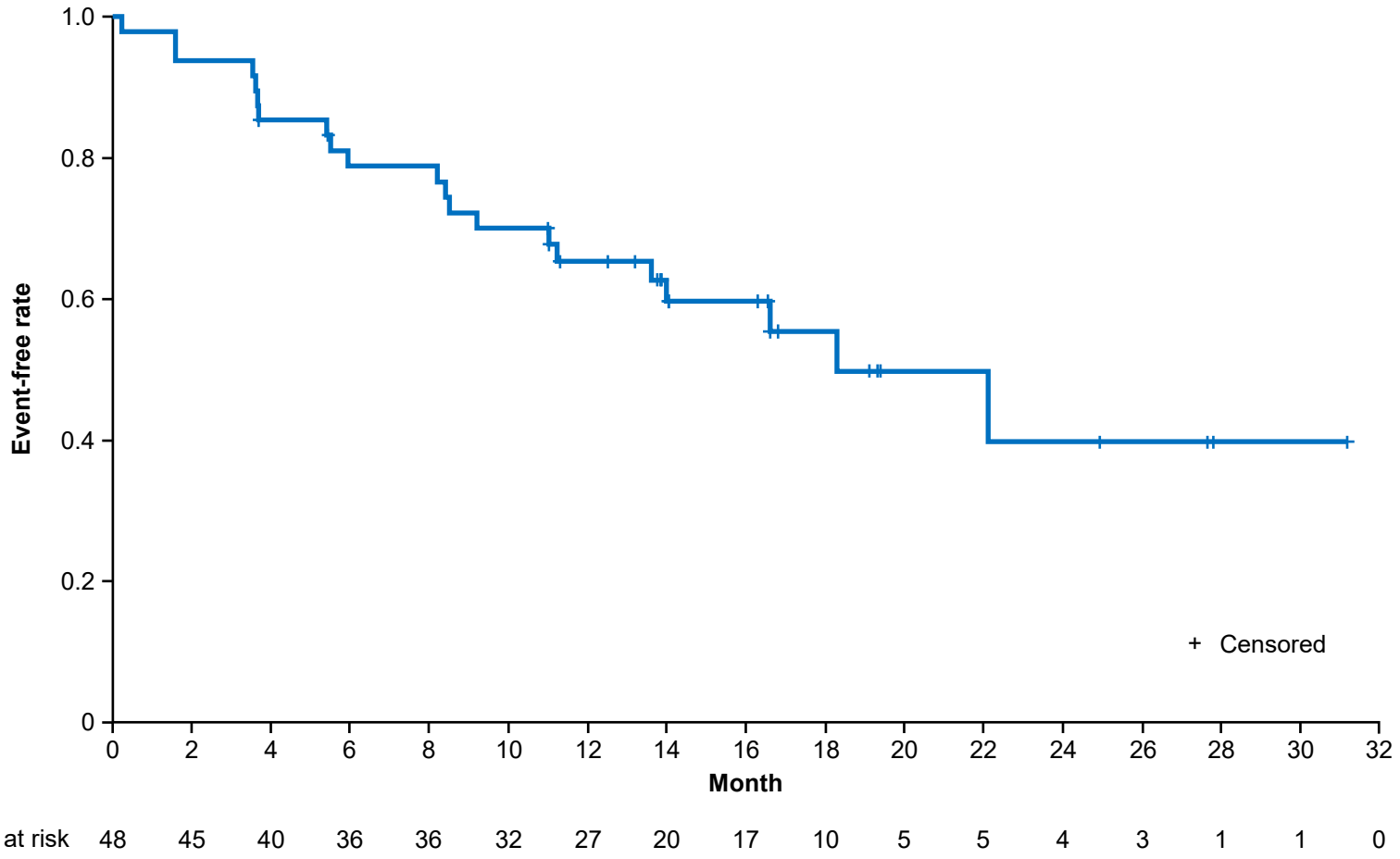
[a]*Total number of response-evaluable patients*

***BCL2i**, B-cell lymphoma 2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CI**, confidence interval; **ORR**, objective response rate; **PD**, progressive disease*

Data cutoff: 19 Sep 2025

PFS in Phase 1a Across All Dose Levels (n=48)

Median PFS of 22.1 months in study population with longest follow-up



PFS summary	
	n=48
Median PFS, months (95% CI)	22.1 (11.2–NE)
Median PFS follow-up, months (95% CI)	16.6 (14.0–19.3)

Median for PFS by Kaplan–Meier method; median PFS follow-up is by reverse Kaplan–Meier method; PFS data currently immature

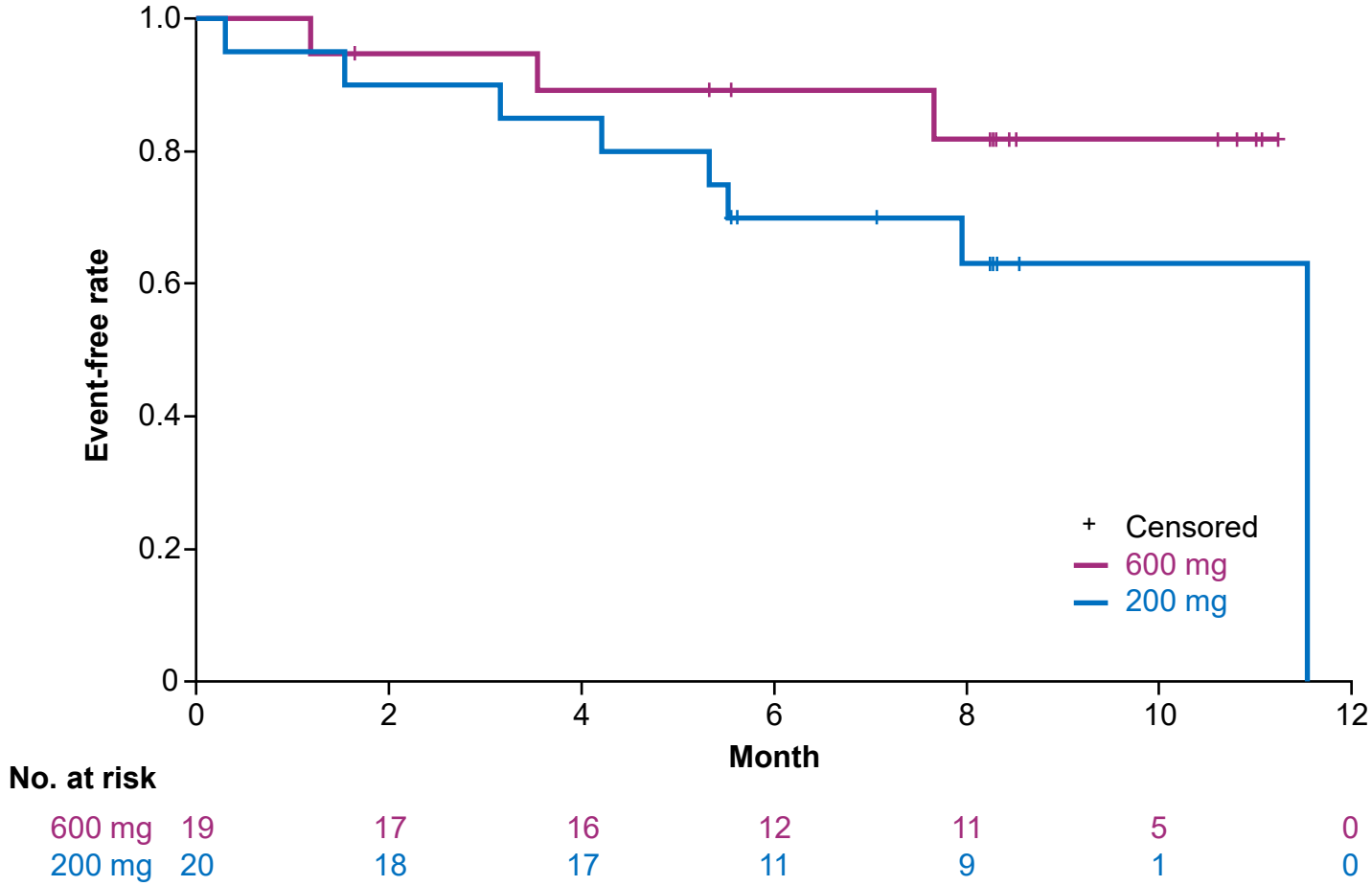
***CI**, confidence interval; **NE**, not evaluable; **PFS**, progression-free survival*

Data cutoff: 19 Sep 2025

Preliminary Efficacy in Phase 1b Randomized Cohort of 200 mg vs 600 mg

Higher ORR and PFS at the RP2D 600 mg dose

Response-evaluable patients	200 mg (n=19)	600 mg (n=18)
Objective response rate,[a] % (95% CI)	73.7 (48.8–90.9)	83.3 (58.6–96.4)
Disease control rate,[b] % (95% CI)	94.7 (74.0–99.9)	100.0 (81.5–100.0)



[a]*Objective response rate includes CR + nPR + PR + PR-L;* [b]*Disease control rate includes CR + nPR + PR/PR-L + SD*
***CI**, confidence interval; **CR**, complete response; **nPR**, nodal partial response; **ORR**, objective response rate; **PFS**, progression-free survival; **PR**, partial response; **PR-L**, partial response with lymphocytosis; **RP2D**, recommended Phase 2 dose*

Data cutoff: 19 Sep 2025

Conclusions

- In this Phase 1a/b trial, bexobrutideg (NX-5948), a novel BTK degrader with high selectivity for BTK, was well tolerated in a heavily pretreated population of patients with relapsed/refractory CLL/SLL:
  - Tolerable safety profile consistent with prior disclosures, and consistent between the RP2D 600 mg and overall trial population
- In the Phase 1a portion of the trial with a median follow-up of 19 months:
  - Bexobrutideg demonstrated an ORR of 83% with a CR rate of 4.3%
  - Median DOR was 20.1 months
  - Median PFS was 22.1 months across all doses (50–600 mg) with data continuing to mature
  - High response rates were observed in the overall population including those in difficult-to-treat subgroups with baseline BTK mutations, high-risk molecular features and CNS involvement
- In the Phase 1b portion of the trial:
  - A randomized cohort, conducted in accordance with Project Optimus, was fully enrolled:
    - ✓ higher ORR and superior PFS were observed at the 600 mg dose, underpinning its selection as the RP2D
  - Non-randomized cohorts in CLL subsets of interest, treated at the RP2D dose, are ongoing
- **Based on the totality and consistency of safety and efficacy findings, including the Phase 1b randomized controlled cohort, the RP2D of 600 mg has been selected. Bexobrutideg will be evaluated in the ongoing pivotal Phase 2 DAYBreak CLL-201 and planned Phase 3 DAYBreak CLL-306 trials**

***BTK**, Bruton's tyrosine kinase**; CLL,** chronic lymphocytic leukemia; **CNS**, central nervous system; **CR**, complete response; **DOR**, duration of response; **ORR**, objective response rate; **RP2D**, recommended Phase 2 dose; **PFS**, progression-free survival; **SLL**, small lymphocytic lymphoma*

Acknowledgments

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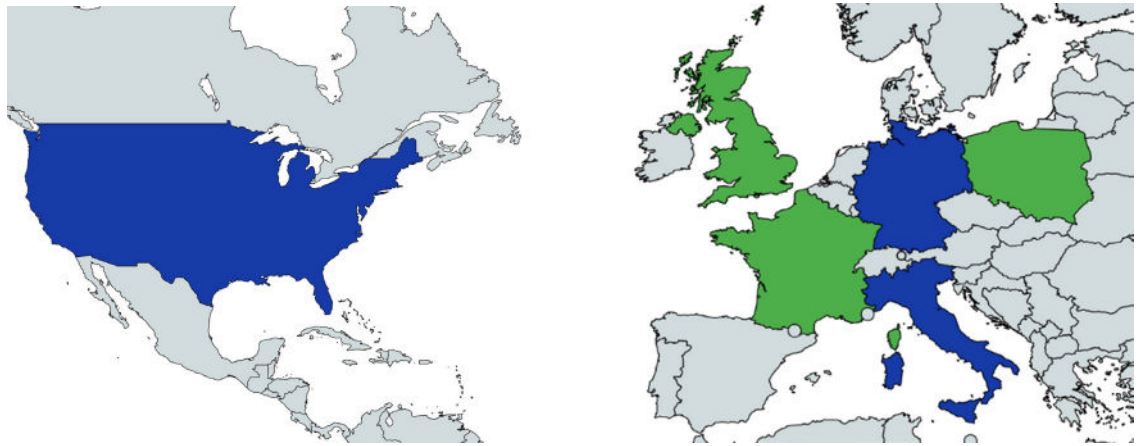
- The authors would also like to thank:
  - All NX-5948-301 investigators and study site staff in France, Italy, the United States, the United Kingdom, the Netherlands, Poland, Spain, and Switzerland for participating in this clinical research
  - Nurix employees developing bexobrutideg and supporting the clinical trial

- Phase 2 clinical trial of bexobrutideg (NX-5948) – DAYBreak CLL-201 is now enrolling globally

DAYBreak CLL-201



- Bexobrutideg (NX-5948) studies are sponsored by Nurix Therapeutics, Inc.