Initial findings from a first-in-human Phase 1a/b trial of NX-5948, a selective BTK degrader

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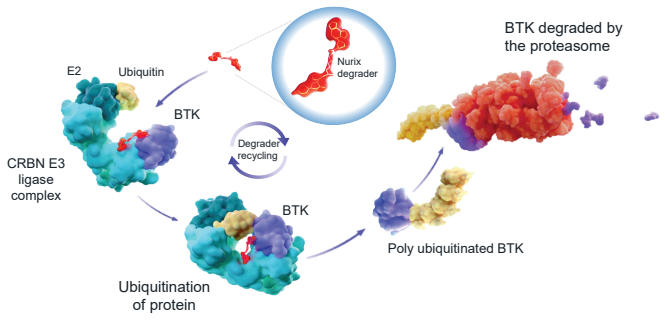
Background

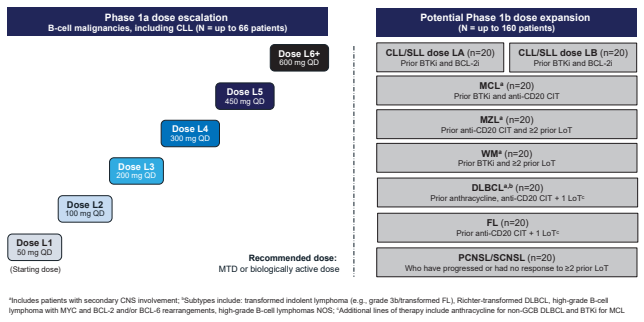
- Bruton's tyrosine kinase inhibitors (BTKis) are widely used in the treatment of patients with B-cell malignancies; however, emergence of *BTK* resistance mutations, as well as the potential growth-promoting, kinase-independent, scaffolding function of BTK, present a need for improved or new approaches.[1]
- NX-5948 is a novel, orally administered small molecule that induces specific protein degradation of wild type and mutant forms of *BTK* by the cereblon E3 ligase (Figure 1).[2,3]
- NX-5948 can cross the blood-brain barrier and degrade BTK intracranially, translating to preclinical efficacy in a mouse brain lymphoma disease model.[3]
- Here we provide the first disclosure safety and efficacy findings from a Phase 1a trial of NX-5948 in patients with relapsed/refractory B-cell malignancies.

Figure 1. NX-5948 mechanism of action



Methods

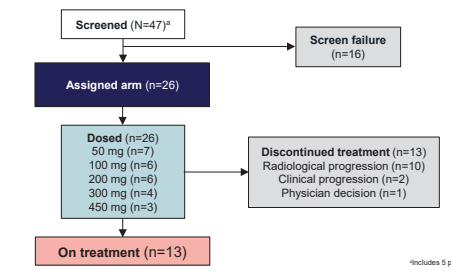
Figure 2. Trial design (ClinicalTrials.gov NCT05131022)



[a]Includes patients with secondary CNS involvement; [b]Subtypes include: transformed indolent lymphoma (e.g., grade 3b/transformed FL), Richter-transformed DLBCL, high-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangements, high-grade B-cell lymphomas NOS; [c]Additional lines of therapy include anthracycline for non-GCB DLBCL and BTKi for MCL

- NX-5948-301 is a Phase 1, first-in-human, dose-escalation and cohort-expansion trial evaluating the safety, tolerability, and clinical activity of NX-5948 in relapsed/refractory CLL/SLL and various subtypes of NHL/WM.
- Key eligibility criteria: ≥2 prior lines of therapy; measurable or other evaluable disease per indication-specific response criteria; ECOG performance status 0–1 (0–2 for patients with PCNSL/SCNSL).
- Phase 1a evaluates safety and tolerability of NX-5948 via a standard 3+3 dose escalation in patients with NHL/WM and a parallel 3+3 dose escalation in patients with CLL. Phase 1b (dose expansion) will include up to seven expansion arms (Figure 2).
- Approximately 226 patients (66 in Phase 1a and 160 in Phase 1b) may be enrolled and treated until confirmed disease progression or unacceptable toxicity.
- Key endpoints include: TEAEs; Grade 3,4,5 TEAEs; SAEs; TEAEs leading to discontinuation; deaths due to TEAEs; all deaths; changes in safety parameters; DLTs; PK parameters; BTK levels; and ORR, CR, time to first response, DOR, PFS and time to next therapy (all responses per disease-specific response criteria).

Figure 3. Patient disposition



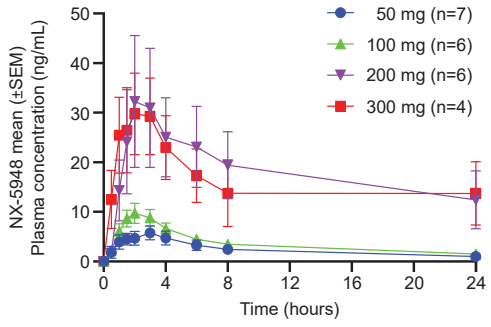
- Patients dosed include:
  - **CLL:** n=7 (26.9%)
  - **DLBCL:** n=7 (26.9%)
  - **MCL:** n=5 (19.2%)
  - **MZL:** n=3 (11.5%)
  - **WM:** n=2 (7.7%)
  - **FL:** n=1 (3.8%)
  - **PCNSL:** n=1 (3.8%)

Data cutoff: 17 Oct 2023

[a]Includes 5 patients at screening but not yet enrolled on study at time of data cutoff

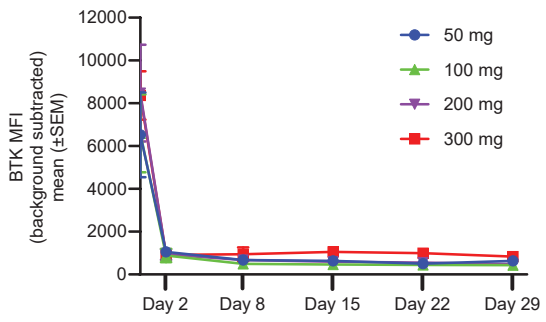
Results

Figure 4. NX-5948 cycle 1, day 1 pharmacokinetics



Data cutoff: 22 Sep 2023

Figure 5. BTK[a] degradation in all patients receiving NX-5948



	Number of patients per day					
Dose (mg)	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29
50	7	7	7	6	5	6
100	6	6	5	6	6	5
200	6	6	6	6	4	3
300	4	4	4	4	4	2

[a]BTK measured in patient B-cells whole blood using flow cytometry assay.

Data cutoff: 22 Sep 2023

- NX-5948 exhibits dose-dependent pharmacokinetics and a half-life of approximately 24 hours, supporting once-daily dosing (Figure 4).
- Rapid, robust, and sustained BTK degradation was observed in all patients, regardless of absolute BTK starting level, tumor type, or NX-5948 dose (Figure 5).

Table 1. Baseline characteristics

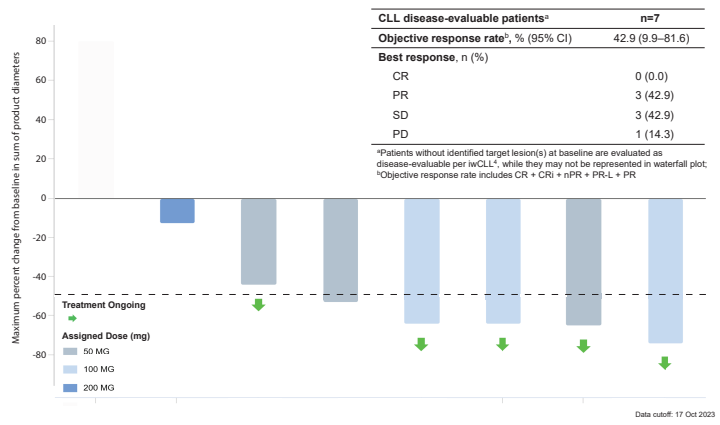
Characteristics	Patients with CLL (n=7)	Patients with NHL/WM (n=19)	Overall population (N=26)
Median age, years (range)	64.0 (53–75)	63.0 (42–79)	63.5 (42–79)
Male, n (%)	5 (71.4)	13 (68.4)	18 (69.2)
Female, n (%)	2 (28.6)	6 (31.6)	8 (30.8)
ECOG PS, n (%)			
0	1 (14.3)	5 (26.3)	6 (23.1)
1	6 (85.7)	14 (73.7)	20 (76.9)
Previous targeted treatments[a], n (%)			
BTKi	7 (100.0)	10 (52.6)	17 (65.4)
Pirtobrutinib	1 (14.3)	2 (10.5)	3 (11.5)
BCL2i	6 (85.7)	3 (15.8)	9 (34.6)
BTKi and BCL2i	6 (85.7)	3 (15.8)	9 (34.6)
CAR-T therapy	0 (0.0)	7 (36.8)	7 (26.9)
Bispecific antibody	0 (0.0)	5 (26.3)	5 (19.2)
PI3Ki	2 (28.6)	2 (10.5)	4 (15.4)
Median prior lines of therapy (range)	3.0 (2–5)	5.0 (2–10)	4.0 (2–10)
Mutation status[b], n (%)	n=6	n=15	n=21
BTK (T474)	1 (16.7)	0 (0.0)	1 (4.8)
PLCG1/2[c]	2 (33.3)	2 (13.3)	4 (19.0)
TP53	2 (33.3)	3 (20.0)	5 (23.8)
BCL2 (G101V and R107-R110dup)	2 (33.3)	0 (0.0)	2 (9.5)

[a]Patients could have received multiple prior treatments; [b]Patients could have multiple mutations, which were tested at baseline by central NGS (≥5% allelic frequency is reported); [c]*PLCG1 (A902V); PLCG2 (K35R, V886A, V105I).*

Data cutoff: 17 Oct 2023

- Median number of prior therapies received in the overall population was 4.0 (range 2–10):
  - In patients with CLL, prior therapies included BTKi (n=7/7) and BCL2i (n=6/7).
  - For patients with NHL/WM, prior therapies included BTKi (n=10/19), bispecific antibody (n=5/19), and CAR-T therapy (n=7/19).
- Patient population included some patients with acquired mutations associated with drug resistance.
- Median duration of treatment for overall patient population was 2.0 (range 0.5–12.6) months, with 13 patients remaining on treatment. Median duration of treatment was 4.6 (range 1.8–9.3) months for CLL, and 1.8 (range 0.5–12.6) months for NHL/WM.

Figure 6. NX-5948 efficacy (patients with CLL)

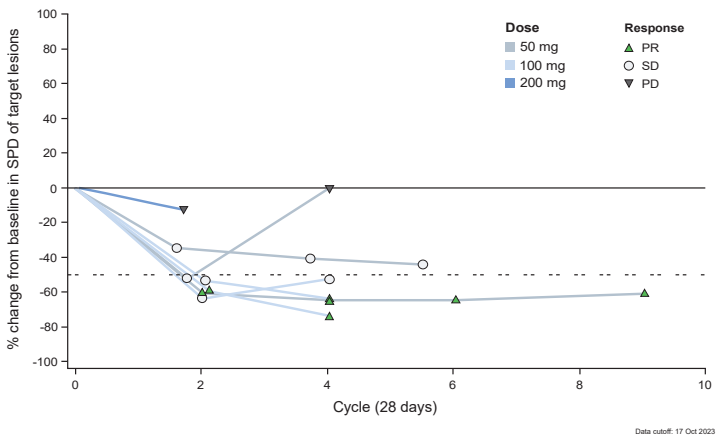


CLL disease-evaluable patients[a]	n=7
Objective response rate[b], % (95% CI)	42.9 (9.9–81.6)
Best response, n (%)	
CR	0 (0.0)
PR	3 (42.9)
SD	3 (42.9)
PD	1 (14.3)

[a]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL[4], while they may not be represented in waterfall plot; [b]Objective response rate includes CR + CRi + nPR + PR-L + PR

Data cutoff: 17 Oct 2023

Figure 7. Change in tumor size (patients with CLL)



Data cutoff: 17 Oct 2023

- An initial decrease in lymph node size (sum of the perpendicular diameters) was observed in all patients regardless of best clinical response, with the majority demonstrating a continued decrease over time.

Table 2. Frequency of any grade TEAEs in ≥15% of patients or grade ≥3 TEAEs in >1 patient or SAEs in >1 patient (N=26)

TEAEs, n (%)	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	12 (46.2)	–	–
Thrombocytopenia[b]	10 (38.5)	2 (7.7)	–
Neutropenia[c]	8 (30.8)	5 (19.2)	–
Anemia	6 (23.1)	1 (3.8)	–
Cough	5 (19.2)	–	–
Headache	5 (19.2)	–	–
Nausea	5 (19.2)	–	–
Rash	4 (15.4)	–	–
COVID-19	3 (11.5)	2 (7.7)	2 (7.7)
Pneumonia	2 (7.7)	2 (7.7)	2 (7.7)

[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [c]Aggregate of neutrophil count decreased or neutropenia

Data cutoff: 17 Oct 2023

Table 3. Frequency of any grade TEAEs in ≥15% of patients (by dose, N=26)

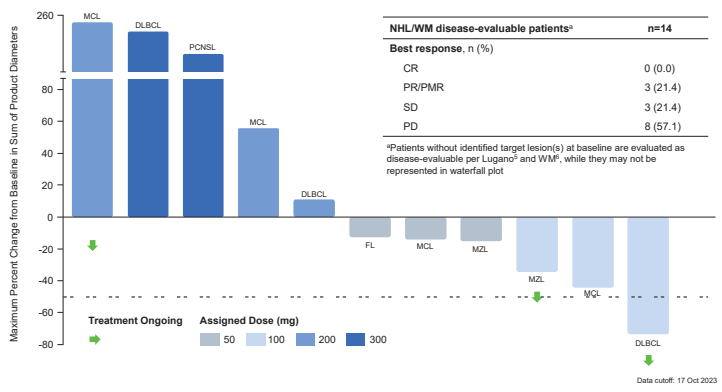
TEAEs, n (%)	50 mg (n=7)	100 mg (n=6)	200 mg (n=6)	300 mg (n=4)	450 mg (n=3)	All doses (n=26)
Purpura/contusion[a]	5 (71.4)	2 (33.3)	1 (16.7)	2 (50.0)	2 (66.7)	12 (46.2)
Thrombocytopenia[b]	2 (28.6)	2 (33.3)	2 (33.3)	3 (75.0)	1 (33.3)	10 (38.5)
Neutropenia[c]	1 (14.3)	2 (33.3)	0 (0.0)	4 (100.0)	0 (0.0)	8 (30.8)
Anemia	2 (28.6)	2 (33.3)	0 (0.0)	1 (25.0)	1 (33.3)	6 (23.1)
Cough	0 (0.0)	2 (33.3)	1 (16.7)	2 (50.0)	0 (0.0)	5 (19.2)
Headache	2 (28.6)	0 (0.0)	2 (33.3)	1 (25.0)	0 (0.0)	5 (19.2)
Nausea	3 (42.9)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	5 (19.2)
Rash	2 (28.6)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (15.4)

[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [c]Aggregate of neutrophil count decreased or neutropenia

Data cutoff: 17 Oct 2023

- The most common all-grade TEAEs were purpura/contusion, thrombocytopenia, and neutropenia. The most common grade ≥3 TEAEs were neutropenia, thrombocytopenia, COVID-19 and pneumonia.
- No atrial fibrillation/flutter or hypertension was reported.
- There were no DLTs and no TEAEs resulting in drug discontinuation. There were 4 NX-5948-related grade ≥3 TEAEs (3 neutropenia, 1 thrombocytopenia) but no related SAEs.

Figure 8. NX-5948 efficacy (patients with NHL/WM)

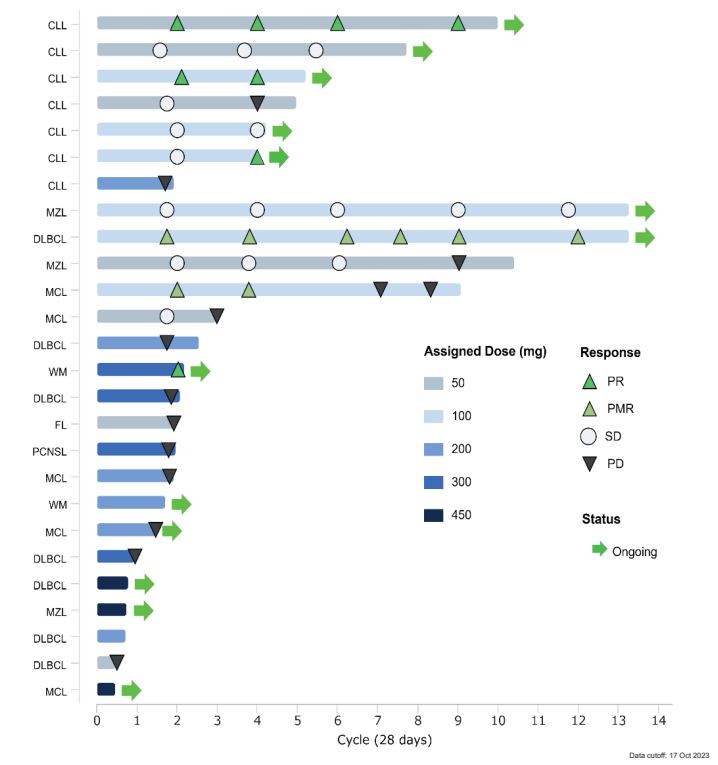


NHL/WM disease-evaluable patients[a]	n=14
Best response, n (%)	
CR	0 (0.0)
PR/PMR	3 (21.4)
SD	3 (21.4)
PD	8 (57.1)

[a]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per Lugano[5] and WM[6], while they may not be represented in waterfall plot

Data cutoff: 17 Oct 2023

Figure 9. Duration of treatment and best response to NX-5948 (all patients)



Data cutoff: 17 Oct 2023

- **CLL** (7 patients, 17 October 2023 cutoff date):
  - PR was observed in 3 patients, who remain on treatment beyond 9 months, 4 months and 3 months, respectively.
  - SD was observed in 3 patients, 1 of whom remains on treatment beyond 7 months, and the other beyond 4 months.
  - 2 patients have discontinued treatment due to PD (1 with transformation to Hodgkin's Disease observed at week 8).
- **NHL/WM** (19 patients, 17 October 2023 cutoff date):
  - PMR was observed in 2 patients, one of whom (DLBCL, 100 mg dose) is ongoing beyond 13 months.
  - PR was observed in 1 patient (WM, 300 mg dose), and is ongoing beyond 2 months.
  - SD was observed in 3 patients, one of whom (MZL, 100 mg dose) is ongoing beyond 13 months.
  - 8 patients with NHL continue to receive treatment.

Conclusions

- NX-5948 pharmacokinetic exposure resulted in rapid, robust, and sustained BTK degradation.
- NX-5948 was well tolerated across doses tested:
  - There were no DLTs and no TEAEs resulting in drug discontinuation.
  - There were 4 NX-5948-related grade ≥3 TEAEs but no related SAEs.
  - There were no atrial fibrillation/flutter or hypertension events.
  - There were no major bleeding or hemorrhage events.
- Treatment with NX-5948 demonstrated clinical activity:

CLL

✓ 6/7 patients showed clinical benefit:
- 3 PR, with 1 ongoing past 9 months.
- 3 SD, with treatment ongoing in 2 patients.
- All patients had some evidence of lymph node reduction.

NHL/WM

✓ Durable responses were seen across indications, with almost half of patients continuing to receive treatment.

- The study is actively enrolling patients in the US, UK and the Netherlands.
- Additional data with higher dose levels and longer treatment duration are expected in 2024.

References

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Abbreviations

BCR, B-cell receptor; **BCL2i**, B-cell lymphoma-2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, Bruton's tyrosine kinase inhibitor; **CAR-T**, chimeric antigen receptor T cells; **CIT**, chemo-immunotherapy; **CLL**, chronic lymphocytic leukemia; **CR**, complete response; **CRBN**, cereblon; **DLBCL**, diffuse large B-cell lymphoma; **DLT**, dose-limiting toxicity; **ECOG**, Eastern Cooperative Oncology Group; **FL**, follicular lymphoma; **GCB**, germinal center B cell; **L**, level; **LoT**, line of therapy; **MCL**, mantle cell lymphoma; **MFI**, mean fluorescence intensity; **MTD**, maximum tolerated dose; **MZL**, marginal zone lymphoma; **NHL**, non-Hodgkin's lymphoma; **NOS**, not otherwise specified; **PCNSL**, primary central nervous system lymphoma; **PD**, progressive disease; **PI3Ki**, PI3 kinase inhibitor; **PMR**, partial metabolic response; **PR**, partial response; **QD**, once daily; **SD**, stable disease; **SEM**, standard error of the mean; **SLL**, small lymphocytic lymphoma; **SPD**, sum of perpendicular diameters; **TEAE**, treatment-emergent adverse event; **VAF**, variant allele frequency; **WM**, Waldenstrom's macroglobulinemia

Acknowledgements

- The authors would like to thank all patients, their caregivers, and their treating physicians for participating in the NX-5948-301 study, which was sponsored by Nurix Therapeutics, Inc.
- Nurix Therapeutics, Inc. also funded the editorial/layout support for this poster, which was provided by Miller Medical Communications.

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Presented at the British Society for Haematology Annual Scientific Meeting, Liverpool, UK, 28–30 April 2024