# Initial Findings From a First-in-Human Phase 1a/b Trial of NX-5948, a Selective Bruton's Tyrosine Kinase Degrader, in Patients with Relapsed/Refractory B-Cell Malignancies

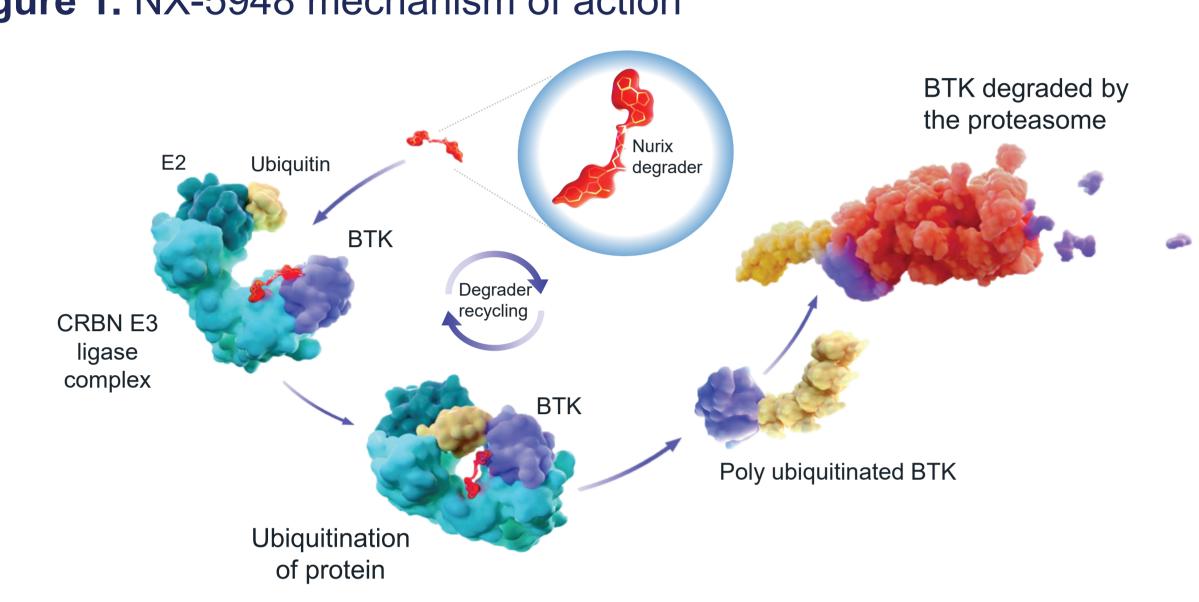
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# Background

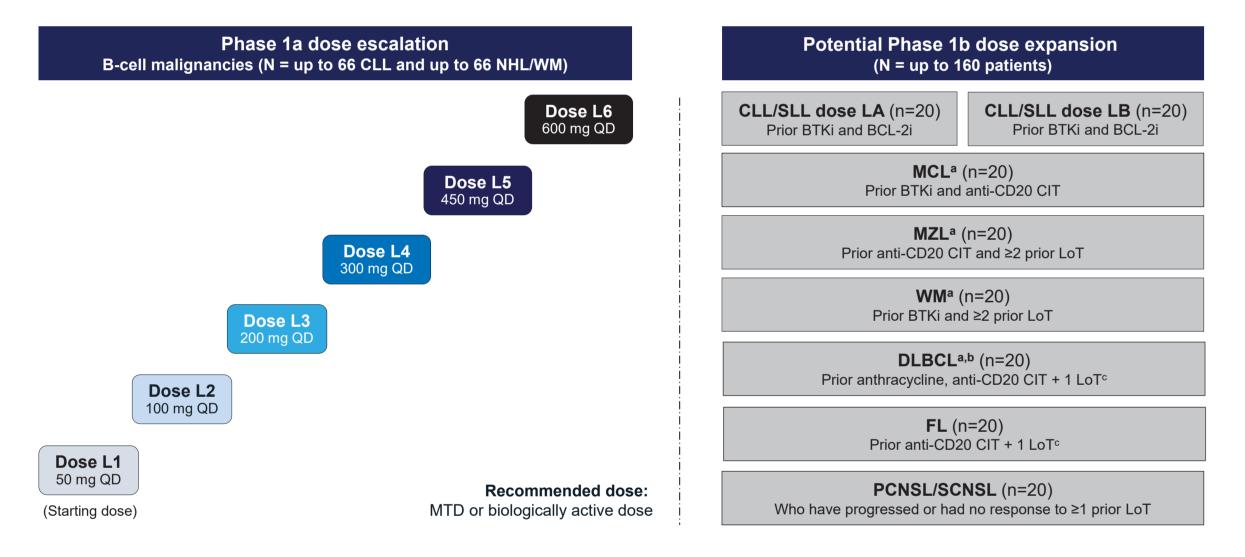
- Bruton's tyrosine kinase inhibitors (BTKis) are widely used in the treatment of patients with B-cell malignancies; however, emergence of BTK resistance mutations, as well as the potential growth-promoting, kinase-independent, scaffolding function of BTK, present a need for improved or new approaches.<sup>1</sup>
- 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).<sup>2,3</sup>
- NX-5948 can cross the blood-brain barrier and degrade BTK intracranially, translating to preclinical efficacy in a mouse brain lymphoma disease model.<sup>3</sup>
- 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



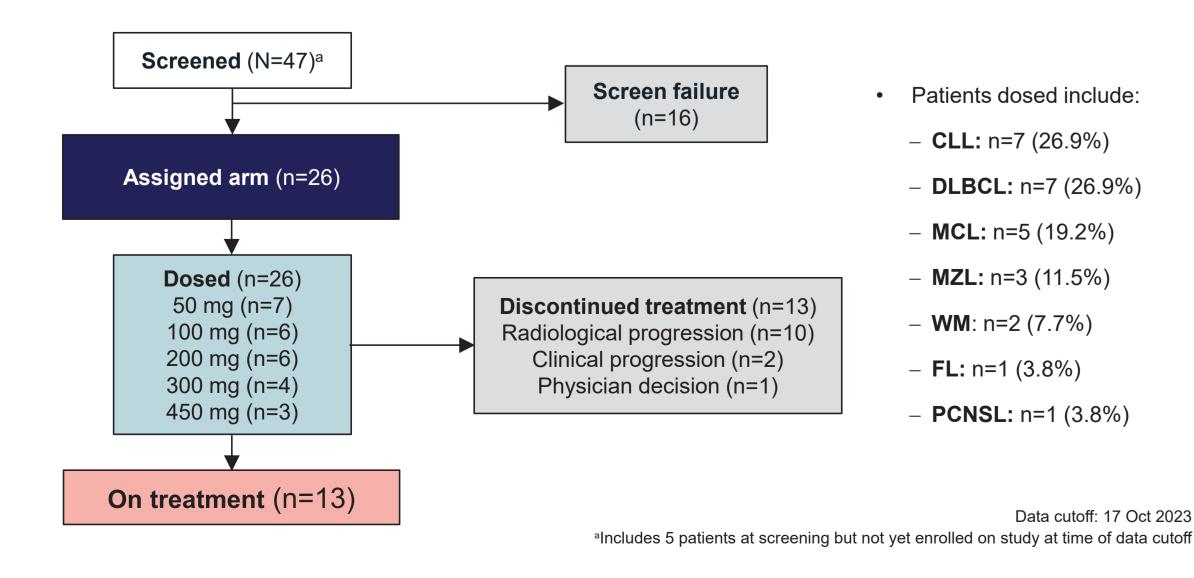
## Methods

Figure 2. Trial design (ClinicalTrials.gov NCT05131022)



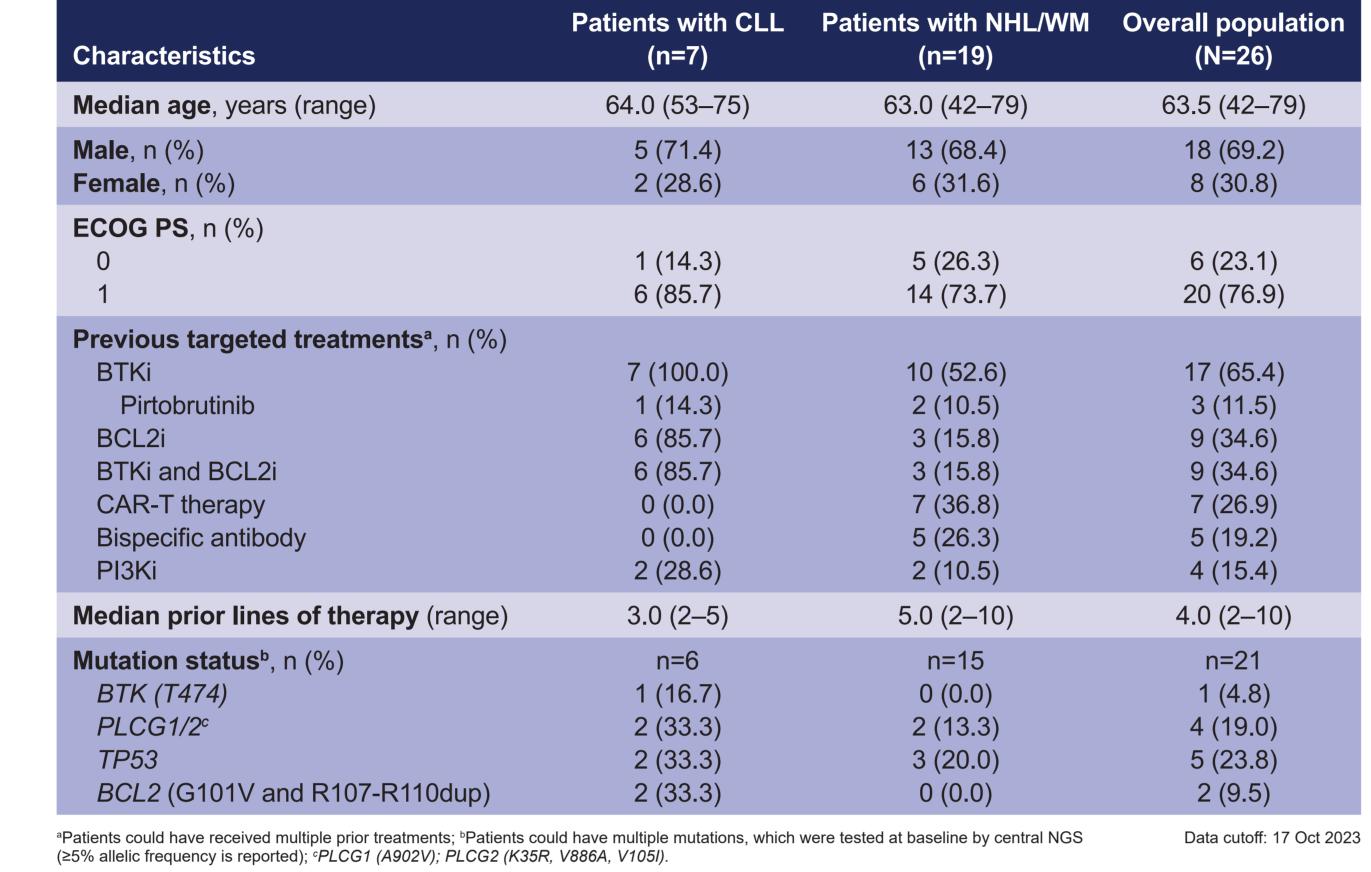
- Includes patients with secondary CNS involvement; bSubtypes include: transformed indolent lymphoma (e.g., grade 3b/transformed FL), Richter-transformed DLBCL, high-grade B-cell lymphomas NOS; Additional lines of therapy include anthracycline for non-GCB DLBCL and BTKi for MCL
- NX-5948-301 is a Phase 1, first-in-human, dose-escalation and arm-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 (≥1 prior line of therapy for patients with PCNSL/SCNSL); 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



## Results

## Table 1. Baseline characteristics



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

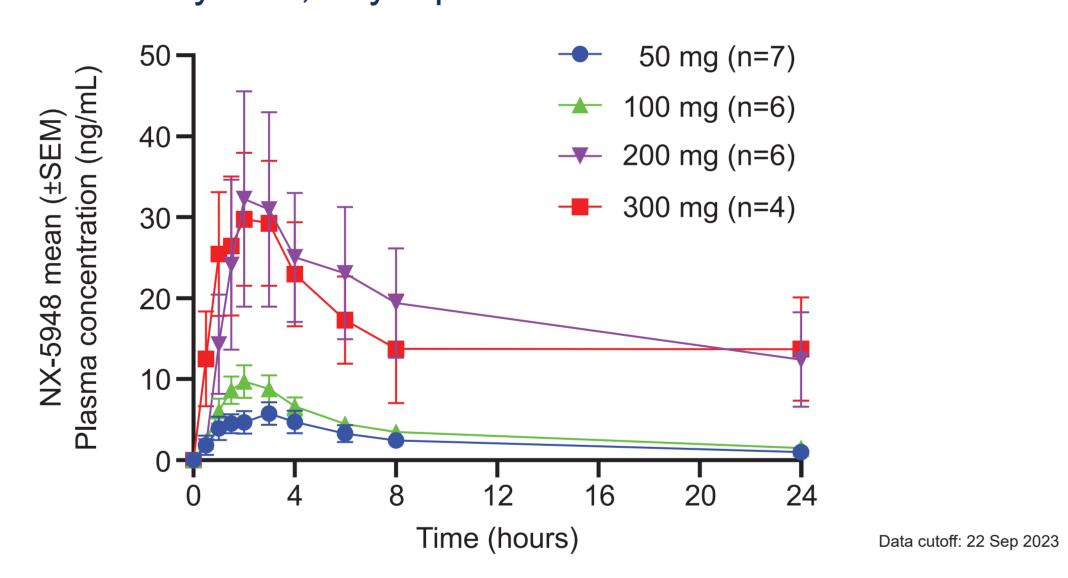
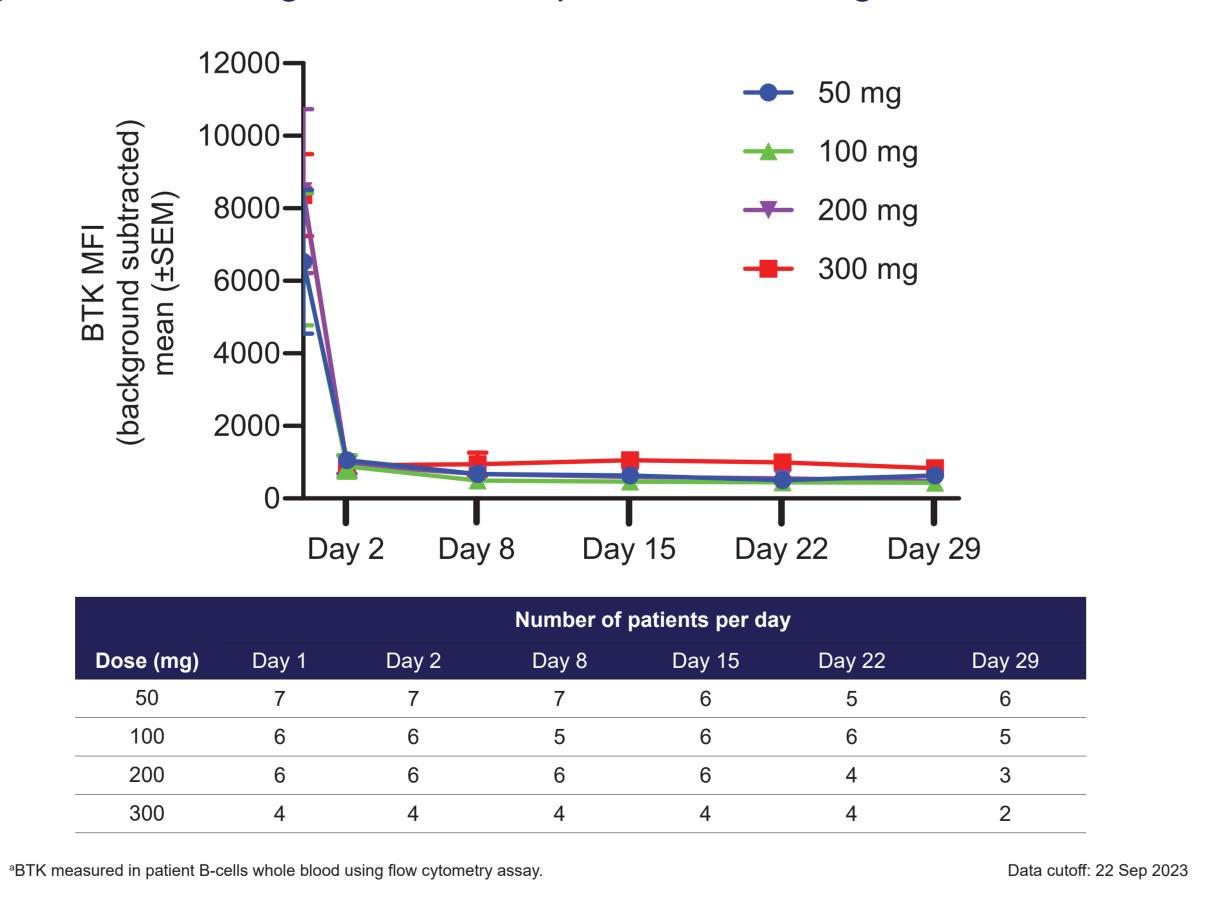


Figure 5. BTK<sup>a</sup> degradation in all patients receiving NX-5948



- 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).

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

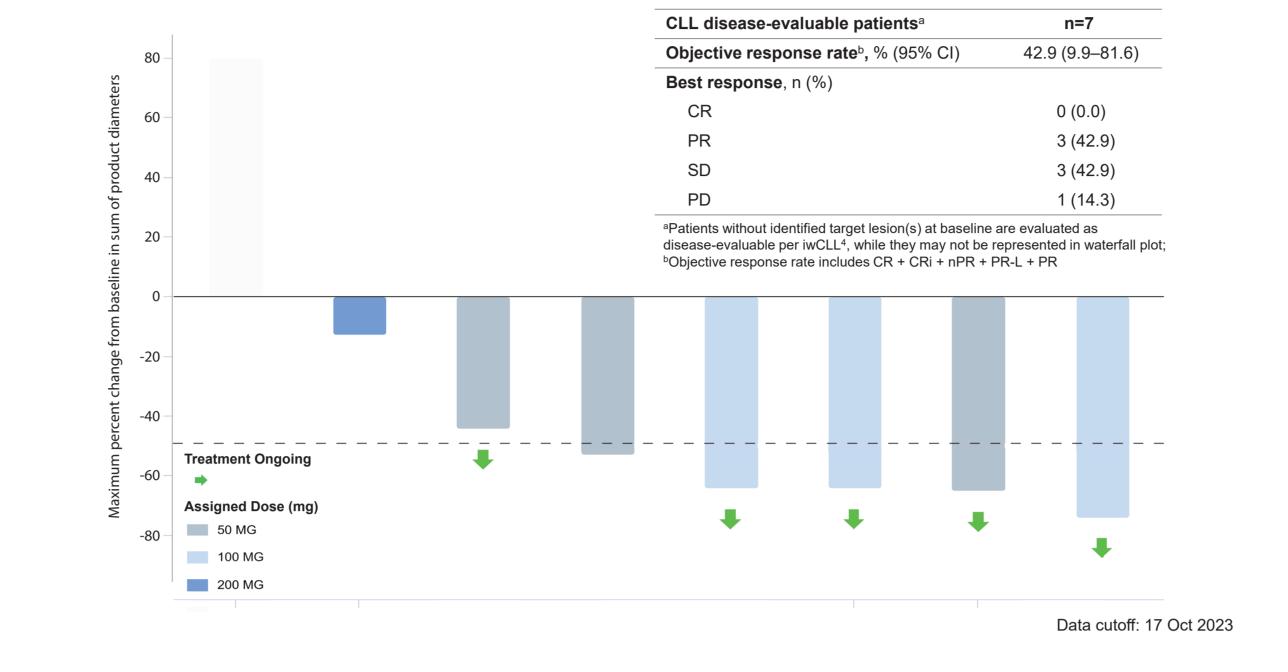
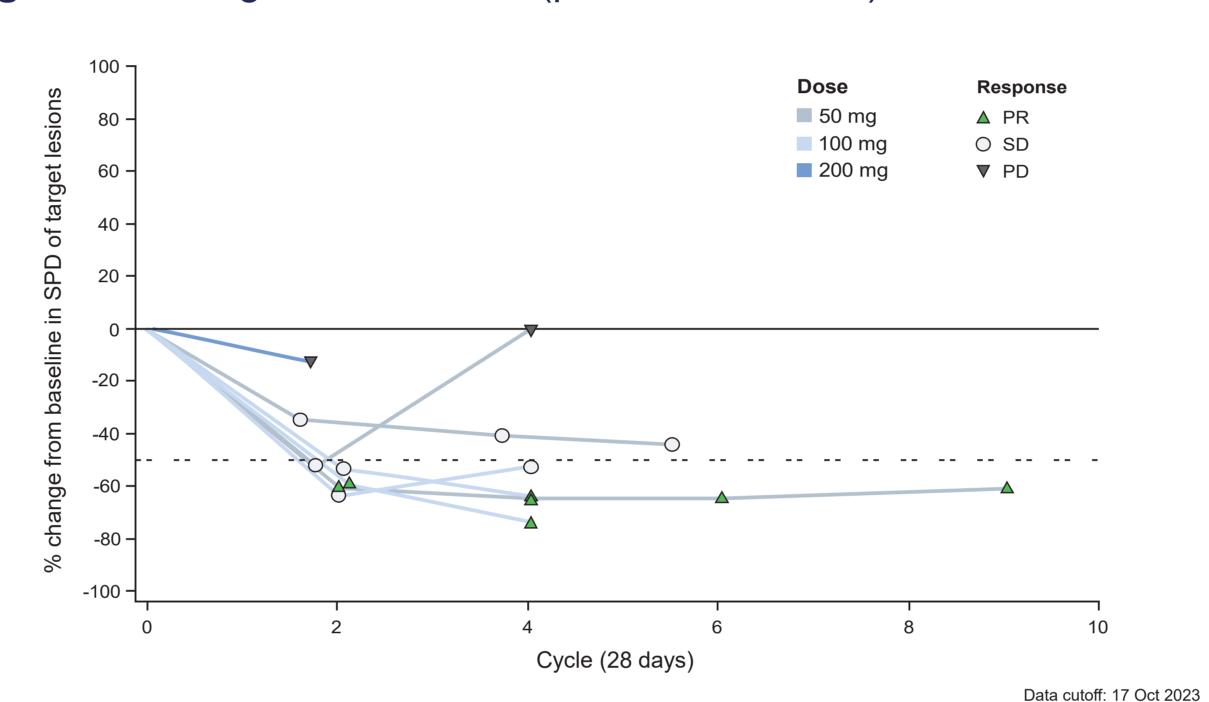
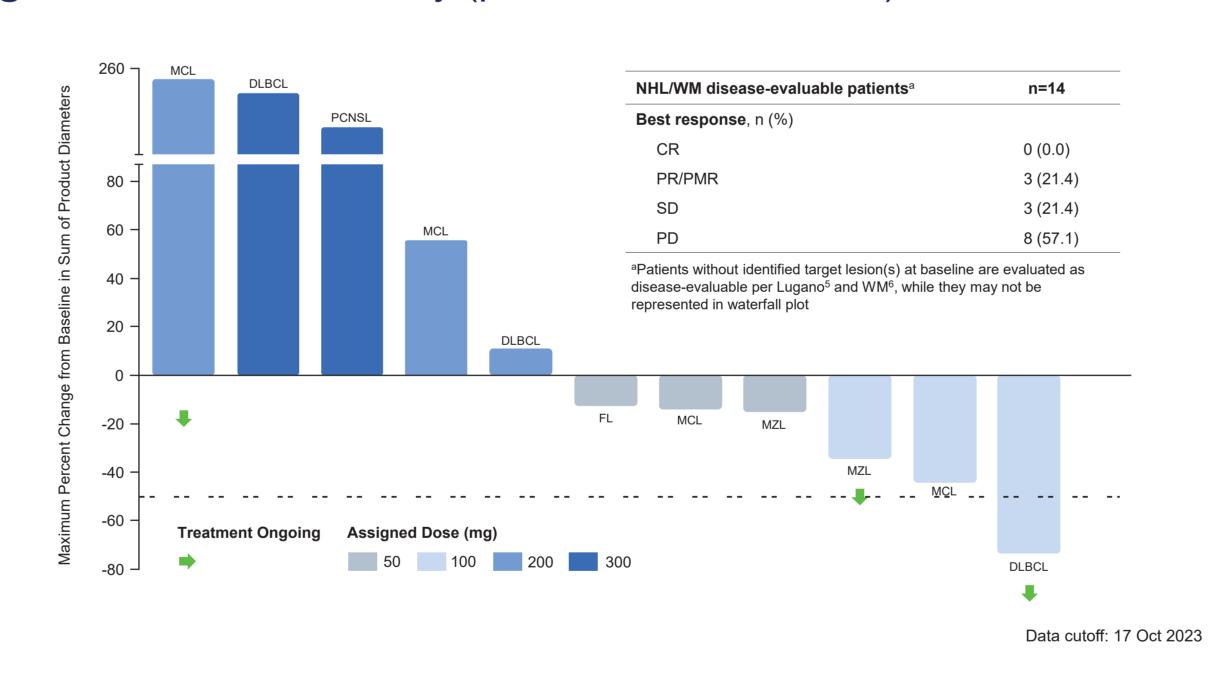


Figure 7. Change in tumor size (patients with CLL)



 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.

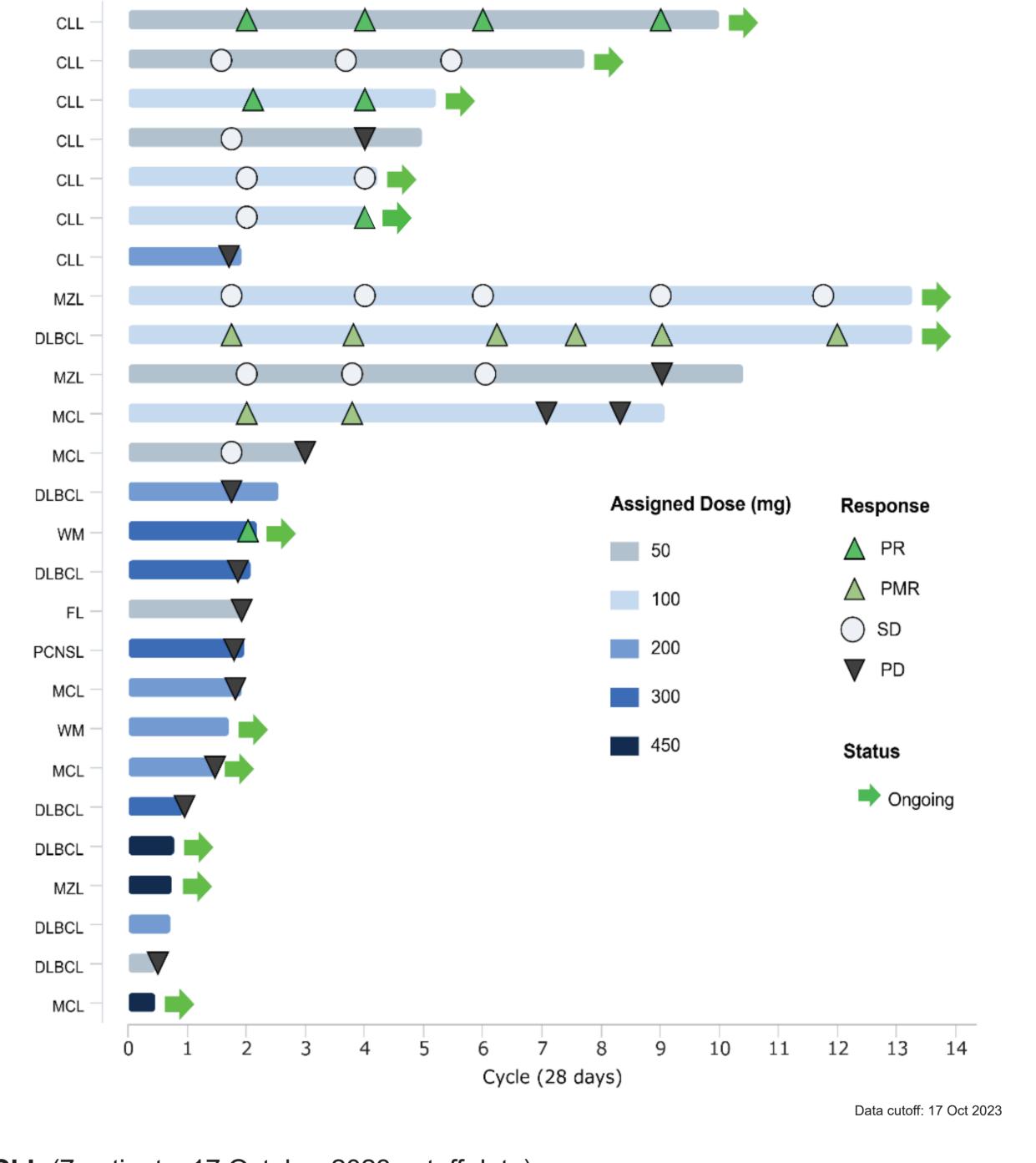
Figure 8. NX-5948 efficacy (patients with NHL/WM)



**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 <sup>a</sup>	12 (46.2)	_	_
Thrombocytopenia <sup>b</sup>	10 (38.5)	2 (7.7)	_
Neutropenia <sup>c</sup>	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)
Purpura/contusion includes episodes of contusion or po Aggregate of neutrophil count decreased or neutropeni	Data cutoff: 17 Oct 2023		

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



- 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.

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

TEAEs, n (%)	<b>50 mg</b> (n=7)	100 mg (n=6)	200 <b>mg</b> (n=6)	300 mg (n=4)	<b>450 mg</b> (n=3)	(n=26)
Purpura/contusion <sup>a</sup>	5 (71.4)	2 (33.3)	1 (16.7)	2 (50.0)	2 (66.7)	12 (46.2)
Thrombocytopeniab	2 (28.6)	2 (33.3)	2 (33.3)	3 (75.0)	1 (33.3)	10 (38.5)
Neutropenia <sup>c</sup>	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)
Purpura/contusion includes episodes o Aggregate of neutrophil count decrease  The most commo	ed or neutropenia					Data cutoff: 17 Oct 202

- 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.

## 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:

- √ 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; Pl3Ki, Pl3 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

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