Latest results from an ongoing first-in-human Phase 1a/b study of NX-5948, a selective Bruton's tyrosine kinase (BTK) degrader, in patients with relapsed/refractory CLL and other B-cell malignancies

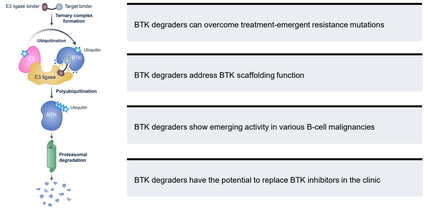
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Background

- 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 latest safety and efficacy findings from the Phase 1a portion of a trial of NX-5948 in relapsed/refractory B-cell malignancies, focusing on patients with CLL.

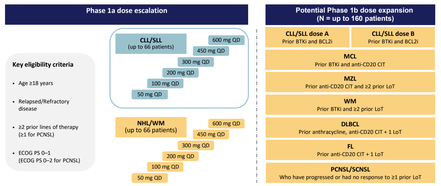
Figure 1. NX-5948 mechanism of action



- BTK degraders can overcome treatment-emergent resistance mutations
- BTK degraders address BTK scaffolding function
- BTK degraders show emerging activity in various B-cell malignancies
- BTK degraders have the potential to replace BTK inhibitors in the clinic

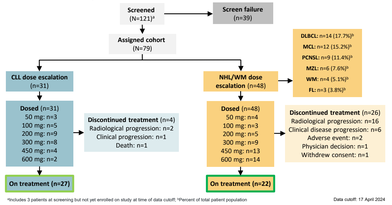
Methods

Figure 2. Trial design (ClinicalTrials.gov NCT05131022)



- 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 (Figure 2).
- Key eligibility criteria: ≥2 prior lines of therapy (≥1 for PCNSL); measurable or other evaluable disease per indication-specific response criteria; ECOG PS 0–1 (ECOG PS 0–2 for PCNSL).
- Phase 1a evaluates safety and tolerability of NX-5948 via a standard 3+3 dose escalation in two parallel patient cohorts - one with NHL/WM, and another with CLL.
- In Phase 1a up to 66 patients per cohort and in Phase 1b up to 160 patients total may be enrolled and treated until confirmed disease progression or unacceptable toxicity.
- Endpoints include DLTs; TEAEs; deaths; changes in safety parameters; and objective response rate per disease-specific response criteria. The planned dose-expansion portion of the trial (Phase 1b) will include up to 7 expansion arms. Eligibility criteria for this portion are still being refined.

Figure 3. Patient disposition



aIncludes 3 patients at screening but not yet enrolled on study at time of data cutoff; bPercent of total patient population

Data cutoff: 17 April 2024

Results

Table 1. Baseline characteristics

Characteristics	Patients with CLL (n=31)	Patients with NHL/WM (n=48)	Overall population (N=79)
Median age, years (range)	69.0 (35–88)	66.5 (42–87)	67.0 (35–88)
Male, n (%)	19 (61.3)	33 (68.8)	52 (65.8)
ECOG PS, n (%)			
0	13 (41.9)	13 (27.1)	26 (32.9)
1	18 (58.1)	33 (68.8)	51 (64.6)
CNS involvement, n (%)	2 (6.5)	10 (20.8)	12 (15.2)
Median prior lines of therapy (range)	4.0 (2–14)	4.0 (2–13)	4.0 (2–14)
Previous treatmentsa, n (%)			
BTKi	30 (96.8)	29 (60.4)	59 (74.7)
≥2 BTKi	11 (35.5)	NA	NA
Pirtobrutinib	7 (22.6)	7 (14.6)	14 (17.7)
BCL2i	28 (90.3)	7 (14.6)	35 (44.3)
BTKi and BCL2i	27 (87.1)	7 (14.6)	34 (43.0)
CAR-T therapy	2 (6.5)	11 (22.9)	13 (16.5)
Bispecific antibody	1 (3.2)	7 (14.6)	8 (10.1)
PI3Ki	9 (29.0)	4 (8.3)	13 (16.5)
Chemo/chemo-immunotherapies	24 (77.4)	48 (100.0)	72 (91.1)
Mutation status, n (%)			
TP53	14/30 (46.7)	4/42 (9.5)	18/72 (25.0)
BTK	13/30 (43.3)	0/42 (0.0)	13/72 (18.1)
PLCG2	6/30 (20.0)	2/42 (4.8)	8/72 (11.1)

aPatients could have received multiple prior treatments

Data cutoff: 17 April 2024

- Median number of prior therapies received in the overall population was 4.0 (range 2–14):
  - In patients with CLL, prior therapies included BTKi (96.8%) and BCL2i (90.3%).
  - For patients with NHL/WM, prior therapies included BTKi (60.4%), bispecific antibody (14.6%), and CAR-T therapy (22.9%).
- Median duration of treatment for the overall patient population was 2.2 (range 0.1–18.7) months, with 49 patients (27 CLL, 22 NHL/WM) remaining on treatment.
- Patient population included a large proportion of patients with mutations associated with poor prognosis and drug resistance.

Table 2. BTK mutations in CLL patient cohort

	Patients with CLL (n=30)
Mutation status, n (%)	
BTKa	**13 (43.3)**
C481S	7 (23.3)
L528b	2 (6.7)
T474I	3 (10.0)
V416I	1 (3.3)
G541V	1 (3.3)

aPatients could have multiple BTK mutations; BTK mutations were tested at baseline by NGS centrally. ≥5% allelic frequency is reported.
bL528W, L528S; T474F, T474I; V416L, V416M.

Table 3. Frequency of any grade TEAEs in ≥10% of overall population or grade ≥3 TEAEs or SAEs in >1 patient (N=79)

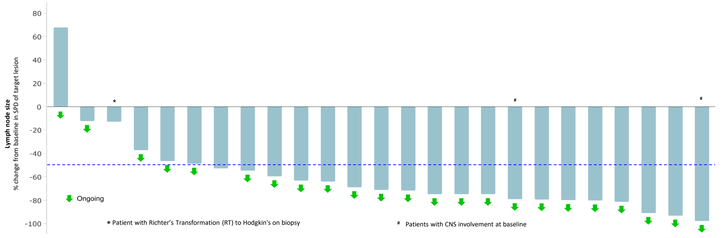
TEAEs, n (%)	Patients with CLL (n=31)			Overall population (N=79)		
	Any grade	Grade ≥3	SAEs	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	13 (41.9)	–	–	28 (35.4)	–	–
Thrombocytopenia[b]	7 (22.6)	1 (3.2)	–	21 (26.6)	7 (8.9)	–
Neutropenia[c]	7 (22.6)	6 (19.4)	–	16 (20.3)	12 (15.2)	–
Fatigue	7 (22.6)	–	–	14 (17.7)	2 (2.5)	–
Anemia	6 (19.4)	1 (3.2)	–	13 (16.5)	3 (3.8)	–
Petechiae	7 (22.6)	–	–	13 (16.5)	–	–
Rash[d]	8 (25.8)	–	1 (3.2)	13 (16.5)	1 (1.3)	1 (1.3)
Headache	6 (19.4)	–	–	12 (15.2)	–	–
Cough	4 (12.9)	–	–	11 (13.9)	1 (1.3)	–
Diarrhea	5 (16.1)	1 (3.2)	–	9 (11.4)	1 (1.3)	–
COVID-19[e]	2 (6.5)	–	–	8 (10.1)	2 (2.5)	2 (2.5)
Hypertension	1 (3.2)	1 (3.2)	–	6 (7.6)	4 (5.1)	–
Pneumonia[f]	2 (6.5)	1 (3.2)	1 (3.2)	5 (6.3)	4 (5.1)	4 (5.1)

[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'. [d]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'. [e]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'. [f]Aggregate of 'pneumonia' and 'pneumonia klebsiella'

Data cutoff: 17 April 2024

- The most common all-grade TEAEs in the overall population were purpura/contusion, thrombocytopenia, and neutropenia. This was similar in patients with CLL.
- The most frequent grade ≥3 TEAEs were neutropenia and thrombocytopenia, with neutropenia being the most frequent grade ≥3 TEAE in patients with CLL.
- There were no new cases of hypertension and cardiovascular AEs in patients with CLL – all were pre-existing.
- There were no additional safety signals with higher doses of NX-5948.
- There was 1 DLT (a non-protocol mandated drug hold in a patient with NHL) and 2 TEAEs resulting in drug discontinuation (both in patients with NHL).
- There was 1 related SAE tumor lysis syndrome based on laboratory parameters (with no clinical sequelae) and 1 grade 5 event (a patient with pulmonary embolism, which was not considered to be related to NX-5948 treatment).

Figure 4. NX-5948 efficacy: clinical response in patients with CLL

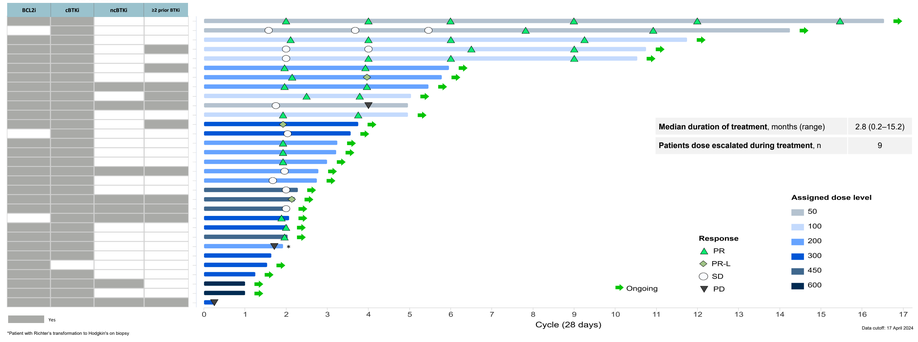


CLL disease-evaluable patients[a]	n=26
Objective response rate (ORR)[b], % (95% CI)	69.2 (48.2–85.7)
Best response, n (%)	
CR	0 (0.0)
PR / PR-L	18 (69.2)
SD	6 (23.1)
PD	2 (7.7)

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

- NX-5948 demonstrated lymph node reduction in almost all patients and an objective response rate of 69.2%.
- 18 of the 26 patients with CLL who are currently disease evaluable have either a partial response or a PR-L, 6 have stable disease, and only 2 have progressed.
- There are 2 patients with lymph node reductions who had CNS involvement at baseline.
- All but 2 patients shown in Figure 4 were still on treatment at the time of data cutoff.

Figure 5. NX-5948 efficacy: duration of treatment and best response to NX-5948 in patients with CLL

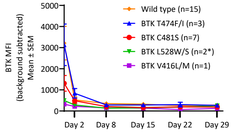


Median duration of treatment, months (range)	2.8 (0.2–15.2)
Patients dose escalated during treatment, n	9

[a]Patient with Richter's transformation to Hodgkin's on biopsy

- NX-5948 demonstrated robust and sustained activity:
  - Responses to NX-5948 were rapid – 15/18 were seen at first assessment at 8 weeks on treatment.
  - Responses were durable and sustained, even in patients who were heavily pretreated at baseline.
  - Responses were observed across dose levels as shown here by assigned dose and 9 patients were able to dose escalate during their treatment.
- 27/31 patients remain on treatment, and 5 of the patients with PRs have already received more than 10 treatment cycles.

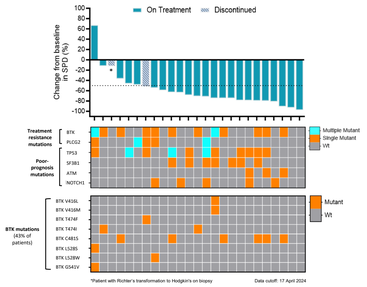
Figure 6. BTK degradation in CLL with BTK mutations



*1 patient has both BTK L528S and G541S

- NX-5948 rapidly and sustainably degraded wild type and mutant BTK in patients with CLL.
- Significant BTK degradation was achieved at Day 2 and was maintained during treatment.

Figure 7. Clinical activity in patients with baseline mutations



[a]Patient with Richter's transformation to Hodgkin's on biopsy

Data cutoff: 17 April 2024

- Lymph node reductions and clinical responses were achieved in patients with a variety of genetic profiles.
- No genetic profile was identified as linked to an intrinsic resistance pattern to NX-5948.

Conclusions

- Updated results from the ongoing Phase 1 study of a novel BTK degrader NX-5948 demonstrate deep and durable clinical responses in CLL in a patient population with high unmet clinical need:
  - Heavily pretreated population of patients with unfavorable genetic profiles:
    - Median of 4 (2–14) prior lines of therapy including prior BTKi /BCL2i (87.1%), pirtobrutinib (22.6%) and ≥2 BTKi (35.5%).
    - Patients with baseline genetic mutations associated with poor prognosis (e.g. TP53) and treatment resistance mutations (*BTK* and *PLCG2*).
  - Safety profile consistent with earlier disclosures – NX-5948 remains well tolerated in both CLL and NHL/WM; no new cardiac AEs.
  - Robust clinical activity in CLL:
    - 69.2% ORR with all responses ongoing as of April 17, 2024.
    - Majority of responses (15/18) seen at the first scan (8 weeks).
    - Durable and deepening responses with longer time on treatment (27/31 patients still on study).
    - No patient profile associated with intrinsic resistance to NX-5948.
- These data support the continued development of NX-5948 in the treatment of CLL where Phase 1b dose expansion is planned.
- Additional data in NHL/WM will be presented in the second half of 2024.

References

1. Wang E, et al. New Engl J Med 2022;386:735–43.
2. Noviski M, et al. Cancer Res 2023;83 (7_Suppl):2850.
3. Robbins DW, et al. Blood 2021;138 (Suppl 1):2251.

Abbreviations

AE, adverse event; **BCL2i**, B-cell lymphoma-2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, Bruton's tyrosine kinase inhibitor; **CAR-T**, chimeric antigen receptor T cells; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **CR**, complete response; **CRi,** complete response with incomplete marrow recovery; **DLBCL**, diffuse large B-cell lymphoma; **DLT**, dose-limiting toxicity; **ECOG**, Eastern Cooperative Oncology Group; **FL**, follicular lymphoma; **IwCLL,** international workshop on CLL; **LoT**, line of therapy; **MCL**, mantle cell lymphoma; **MFI**, mean fluorescence intensity; **MZL**, marginal zone lymphoma; **NHL**, non-Hodgkin's lymphoma; **nPR**, nodular partial response; **ORR,** overall response rate; **PCNSL**, primary central nervous system lymphoma; **PD**, progressive disease; **PI3Ki**, PI3 kinase inhibitor; **PR**, partial response; **PR-L**, partial response with rebound lymphocytosis; **QD**, once daily; **R/R**, relapsed and/or refractory; **RT,** Richter's Transformation; **SAE**, serious adverse event; **SCNSL**, secondary central nervous system lymphoma; **SD**, stable disease; **SEM**, standard error of the mean; **SLL**, small lymphocytic lymphoma; **SPD**, sum of perpendicular diameters; **TEAE**, treatment-emergent adverse event; **WM**, Waldenstrom's macroglobulinemia; **Wt**, wild-type

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For information about this clinical trial please scan the QR code

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