An ongoing first-in-human phase 1 trial of NX-5948, an oral Bruton's tyrosine kinase (BTK) degrader, in patients with relapsed/refractory B cell malignancies, including chronic lymphocytic leukemia (CLL)

[1]Francesco Forconi, [2]Graham P. Collins, [3]Emma Searle, [4]Dima El-Sharkawi, [5]David Lewis, [6]Mary Gleeson, [7]John Riches, [8]Pam McKay, [9]Jeanette Doorduijn, [10]Rogier Mous, [11]Wendy B.C. Stevens, [12]Sarah G. Injac, [3]Kim Linton

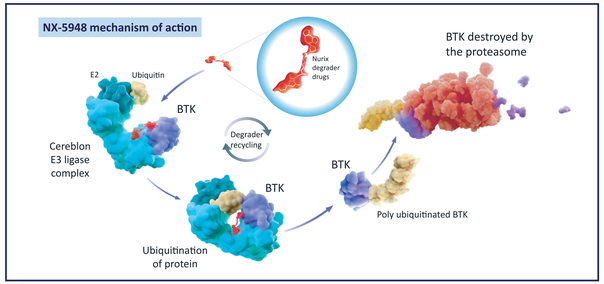
[1]University Hospital Southampton NHS Trust, Southampton, UK; [2]Oxford University Hospitals Foundation NHS Trust, Oxford, UK; [3]Manchester Cancer Research Centre, Division of Cancer Sciences, Manchester, UK; [4]Royal Marsden NHS Foundation Trust, Sutton, UK; [5]Derriford Hospital, Plymouth, UK; [6]Sarah Cannon Research Institute, Guy's and St Thomas' NHS Foundation Trust, London, UK; [7]Barts Cancer Institute, Queen Mary University of London, UK; [8]Beatson West of Scotland Cancer Centre, Glasgow, Scotland; [9]Erasmus MC Cancer Institute, Rotterdam, The Netherlands, on behalf of the Lunenburg Lymphoma Phase I/II Consortium – HOVON /LLPC; [10]UMC Utrecht Cancer Center, University Medical Center Utrecht, The Netherlands, on behalf of the Lunenburg Lymphoma Phase I/II Consortium – HOVON/LLPC; [11]Radboud UMC, Nijmegen, The Netherlands, on behalf of the Lunenburg Lymphoma Phase I/II Consortium – HOVON /LLPC; [12]Nurix Therapeutics, Inc., San Francisco, CA, USA

Background

- BTK is a key component of the B cell receptor (BCR) signaling pathway; chronic activation of BTK-mediated BCR signaling is a hallmark of many B cell malignancies.
- In various B cell malignancies, including CLL, *BTK* mutations confer broad resistance to both covalent and non-covalent BTK inhibitors, limiting their utility in later lines of therapy. Surprisingly, some of these mutations render BTK 'kinase dead' while preserving enhanced oncogenic BCR signaling, pointing to a scaffolding function of BTK.[1]
- Novel therapeutics that can overcome emerging resistance mutations may represent an alternative treatment option for patients with CLL who have developed resistance to BTK inhibitors or in B cell indications where treatment with BTK inhibitors has been less effective.[2]
- NX-5948 is a novel, orally administered, small molecule that induces BTK degradation via recruitment of the cereblon E3 ubiquitin ligase complex, without inducing degradation of other cereblon neo-substrates (Figure 1):
  - NX-5948 induces sub-nanomolar potency degradation of both wild-type and known mutant forms of *BTK in vitro*,[3] demonstrating rapid *in vivo* degradation in mouse and non-human primate B cells within two hours of oral administration.[4]
  - NX-5948 can cross the blood-brain barrier and degrade BTK intracranially, translating to preclinical efficacy in mouse brain lymphoma disease models.[4]

Figure 1. Targeted protein degradation with NX-5948

Harnessing the ubiquitin proteosome system to eliminate disease proteins



Methods

Design and patient population

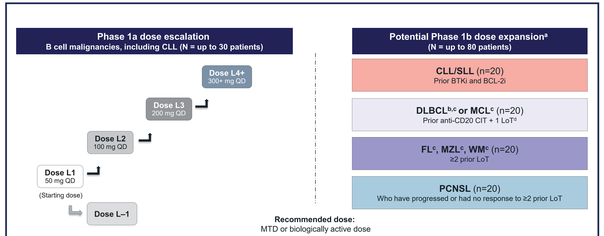
- NX-5948-301 is a first-in-human, dose-escalation (Phase 1a) and cohort-expansion (Phase 1b) study designed to evaluate the safety, tolerability, and preliminary efficacy of NX-5948 in adult patients with relapsed and refractory B cell malignancies, including CLL (Figure 2):
  - Phase 1a is evaluating the safety and tolerability of NX-5948 in patients with relapsed/refractory CLL, small lymphocytic lymphoma (SLL), non-germinal center B cell (non-GCB) diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Waldenström's macroglobulinemia (WM), including those with secondary central nervous system (CNS) involvement in any disease indication listed or primary CNS lymphoma (PCNSL).
  - Phase 1b will investigate longer-term safety and anti-tumor activity of NX-5948 at the recommended dose(s) selected in Phase 1a in patients with relapsed/refractory B cell malignancies across four cohorts.

Primary objectives and endpoints – Phase 1a

- Safety and tolerability (incidence and characterization of treatment-emergent adverse events (AEs), serious AEs and deaths).
- Maximum tolerated dose (MTD) and/or recommended Phase 1b dose (changes from baseline in safety parameters and dose-limiting toxicities).

Figure 2. NX-5948-301 trial design

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



[a]Potential dose-expansion cohorts are expected to open in the second half of 2023; [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]Includes patients with secondary CNS involvement; [d]Additional lines of therapy include anthracycline for non-GCB DLBCL and BTKi for MCL.

Abbreviations: BCL-2i, B cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CIT, chemo-immunotherapy; CLL, chronic lymphocytic leukemia; CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; GCB, germinal center B cell; L, level; MCL, mantle cell lymphoma; LoT, line of therapy; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NOS, not otherwise specified; PCNSL, primary central nervous system lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

Secondary objectives – Phase 1a

- Pharmacokinetics (NX-5948 pharmacokinetic parameters in plasma).
- Pharmacodynamics (changes from baseline of BTK levels in B cells).
- Assess preliminary anti-tumor activity of NX-5948 (objective response rate [ORR], complete response [CR] rate for patients with CLL, CR with incomplete recovery, time to first response, duration of response, progression-free survival [PFS], time to next therapy).

Primary objectives and endpoints – Phase 1b

- Evaluate the anti-tumor activity (ORR) of NX-5948 at the recommended dose(s) selected in Phase 1a in expansion cohorts.
- Further evaluate the safety and tolerability of NX-5948.

Secondary objectives and endpoints – Phase 1b

- Further characterize the PK profile of NX-5948 (PK parameters in plasma and CNS).
- Further characterize the PD profile of NX-5948 (changes from baseline of BTK levels in B cells).
- Further assess anti-tumor activity of NX-5948 (CR rate, time to first response, DOR, PFS, time to next therapy).

Exploratory objectives and endpoints – Phase 1a/1b

- Overall survival.
- NX-5948 metabolism (identification of potential NX-5948 metabolites).
- Explore mechanisms of response/resistance (biomarkers of BTK signaling and resistance pathways).
- Characterize any PK/PD relationships with anti-tumor activity, biomarkers, and/or safety.
- Assess impact of NX-5948 on cognitive function (Mini Mental State Exam, 2nd edition: Brief Version).

Target population

- Full details on the target population in the dose-escalation (Phase 1a) and cohort expansion (Phase 1b) portions of the trial are shown in Table 1.

Key eligibility criteria

- Key eligibility criteria include: ≥two prior lines of therapy; measurable disease per indication-specific response criteria; and an Eastern Cooperative Oncology Group (ECOG) score of 0–2.
- Further details on key inclusion criteria are shown in Table 2.

Table 1. Target population

Phase 1a Dose escalation	Phase 1b Cohort expansion
• Patients with histologically confirmed relapsed/refractory B cell malignancies.	• Patients with histologically confirmed relapsed/refractory B cell malignancies.
• Patients must have required and received at least two prior systemic therapies, and for whom no other therapies are known to provide clinical benefit.	• Patients must have received at least two prior lines of therapy in up to the following four cohorts:
• Patients with CLL, SLL, non-GCB DLBCL as determined by Hans algorithm (including transformed indolent lymphoma, Richter-transformed DLBCL, high-grade B cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangements, high-grade B cell lymphomas not otherwise specified), FL (grade 1–3a; eligibility for systemic treatment as determined by GELF criteria), MCL, MZL (including EMZL, MALT, NMZL, SMZL) or WM, including any of the diagnoses with CNS involvement of their disease, as well as patients with PCNSL.	**CLL/SLL (Cohort A)** • Patients with CLL or SLL with prior exposure to both a BTKi and BCL-2 inhibitor, unless previously deemed ineligible for those therapies, including those with secondary CNS involvement of their disease.
	DLBCL or MCL (Cohort B) • Patients with non-GCB DLBCL (as determined by the Hans algorithm) with prior exposure to an anthracycline and an anti-CD20 mAb-based chemo-immunotherapy regimen, including 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, and patients with secondary CNS involvement of their disease. • Patients with MCL with prior exposure to a BTKi and an anti-CD20 mAb-based chemo-immunotherapy regimen including those with secondary CNS involvement of their disease.
	FL, MZL, WM (Cohort C) • Patients with FL (grade 1–3a; eligibility for systemic treatment as determined by GELF criteria) with prior exposure to an anti-CD20 mAb-based chemo-immunotherapy regimen and one additional line of therapy. • Patients with MZL with prior exposure to an anti-CD20 mAb-based chemo-immunotherapy regimen and one additional line of therapy. • Patients with WM with prior exposure to a BTKi and one additional line of therapy. • Patients with FL (grade 1–3a; eligibility for systemic treatment as determined by GELF criteria), MZL (EMZL, MALT, NMZL, SMZL), and WM meeting above criteria with secondary CNS involvement.
	PCNSL (Cohort D) • Patients with PCNSL who have progressed or had no response to at least two prior lines of therapy.

Abbreviations: BCL-2, B cell lymphoma-2; BCL-6, B cell lymphoma-6; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; CLL, chronic lymphocytic leukemia; CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomas Folliculaires; mAb, monoclonal antibody; MALT, mucus-associated-lymphoid tissue; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NMZL, nodal MZL; NOS, Not Otherwise Specified; PCNSL, primary central nervous system lymphoma; SLL, small lymphocytic lymphoma; SMZL, splenic MZL; WM, Waldenström's macroglobulinemia.

Treatment

- NX-5948 is given orally, once daily, with dose escalation according to a standard 3+3 design.
- Dose-limiting toxicities (DLTs) will be assessed following the first cycle (28 days) of therapy.
- The recommended Phase 1b dose(s) will be determined following assessment of pharmacokinetics/ pharmacodynamics, safety, and anti-tumor activity.

Evaluations

Safety

- Safety will be determined from evaluation of DLTs, AEs, clinical laboratory assessments, vital signs assessments, physical examinations, and electrocardiograms.
- All patients will be evaluable for safety.

Efficacy

- Tumor response will be assessed based on iwCLL criteria for CLL/SLL[5], response criteria for WM[6], Lugano Classification of Lymphoma response criteria for DLBCL, FL, MCL, and MZL[7], and International PCNSL Collaboration Group criteria for PCNSL.[8]

Table 2. Key eligibility criteria

Abbreviated inclusion criteria
Phase 1a and Phase 1b
• Age ≥18 years.
• Histologic diagnosis confirmed.
• Radiographically measurable disease per response criteria specific to the malignancy.
• ECOG performance status of 0 or 1 (0–2 for patients with PCNSL and secondary CNS involvement).
• Prior CAR-T therapy is allowed within 100 days (Phase 1a) or 30 days (Phase 1b) of study start.
• Minimum of 4 weeks or five half-lives since last dose of systemic cancer therapy (unless otherwise specified) or minimum of 2 weeks since last radiotherapy, or minimum of 100 days autologous or allogeneic stem cell transplant.
• Adequate organ/bone marrow function, as defined per protocol laboratory parameters.
• Immunosuppressive drug, other than systemic corticosteroids, are not allowed within 30 days of first dose of study drug.
• Use of any strong or moderate CYP3A inhibitors or inducers or substrates or inhibitors of P-glycoprotein, BCRP, or OATP1B1/1B3 transporters, proton pump inhibitors within 7 days or five half-lives, whichever is longer.
Phase 1a only
• Patients must have histologically confirmed relapsed or refractory CLL, SLL, non-GCB DLBCL, FL, MCL, MZL, WM, including those with secondary CNS involvement in any disease indication listed or PCNSL.
• Received at least two prior lines of therapy and have no other therapies known to provide clinical benefit.
Phase 1b only
• Relapsed or refractory malignancy, per the intended expansion cohort (i.e., Phase 1b target indications [see study design]).
• Must have failed two prior lines of therapy.
• Lymph node biopsy will be mandatory, if feasible, for up to 10 patients per indication expansion cohort.
• Patients with PCNSL or secondary CNS involvement must consent to on-study CSF collection.

Abbreviations: BCRP, breast cancer resistance protein; CAR-T, Chimeric Antigen Receptor T-cell; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CSF, cerebrospinal fluid; DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; OATP1B1/1B3, organic anion transporter polypeptide 1B1/1B3; PCNSL, primary central nervous system lymphoma; SLL, small lymphocytic lymphoma WM, Waldenström's macroglobulinemia.

Sample size, statistics and current status

Phase 1a dose escalation

- Up to 30 evaluable patients, dependent on the number of dose levels investigated.

Phase 1b dose expansion

- Up to approximately 80 evaluable patients, in up to four expansion cohorts.

Current status

- The Phase 1a portion of the study is enrolling at 12 sites in the UK and the US. Enrollment in the Netherlands is anticipated to begin in Fall 2023.
- The Phase 1b portion of the study is expected to begin enrolling in the first half of 2024.

References

1. Montoya S, et al. ASH 2022 (abstract #750).
2. Wang E. et al. N Engl J Med 2022;386;735–43.
3. Noviski M. et al. AACR 2023 (abstract #2850).
4. Robbins DW. et al. ASH 2021 (abstract #2251).
5. Hallek M, et al. Blood 2018;131:2745–60.
6. Owen RG, et al. Br J Haematol 2013;160:171–6.
7. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.
8. Abrey LE, et al. J Clin Oncol 2005;23:5034–43.

Acknowledgements

- NX-5948-301 is sponsored by Nurix Therapeutics, Inc.
- Nurix Therapeutics, Inc. funded the medical writing/layout support provided for this poster by Miller Medical Communications.

Presented at the biennial iwCLL main meeting, Boston, Massachusetts, October 7–9, 2023

Study contact: nx5948301@nurixtx.com