A First-in-Human Phase 1 Trial of NX-5948, an Oral BTK Degrader, in Patients with Relapsed and Refractory B-cell Malignancies

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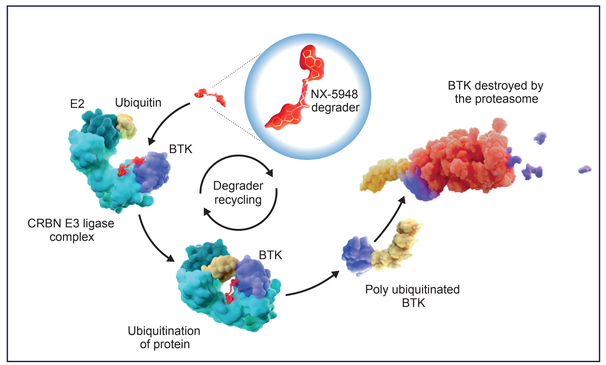
Background

- Bruton's tyrosine kinase (BTK) is a key component of the B-cell receptor signaling pathway; chronic activation of BTK-mediated B-cell receptor signaling is a hallmark of many B-cell malignancies:
  - BTK degraders have been shown to be safe and effective in a variety of B-cell lymphomas.[1]
  - Mutations in the BTK protein that prevent inhibitors from binding can cause resistance to approved BTK inhibitors.
  - BTK degradation may offer an alternative method of interrupting B-cell receptor signaling and overcoming such resistance.
- Chimeric targeting molecules catalyze ubiquitination and proteasomal degradation of target proteins and are comprised of a ubiquitin ligase-binding element ("harness"), a linker, and a target-binding element ("hook"):[2]
  - NX-5948 is a target protein degrader that contains a BTK hook linked to a cereblon (CRBN) harness.[2]
  - Some CRBN-binding drugs, such as lenalidomide and pomalidomide, possess immunomodulatory activity by promoting degradation of Ailolos and Ikaros. NX-5948, however, was engineered to not possess immunomodulatory activity.[2]
  - Additionally, NX-5948 penetrates the central nervous system (CNS) and has demonstrated activity in a model of brain malignancies, supporting research in B-cell malignancies, including CNS lymphoma.[2]

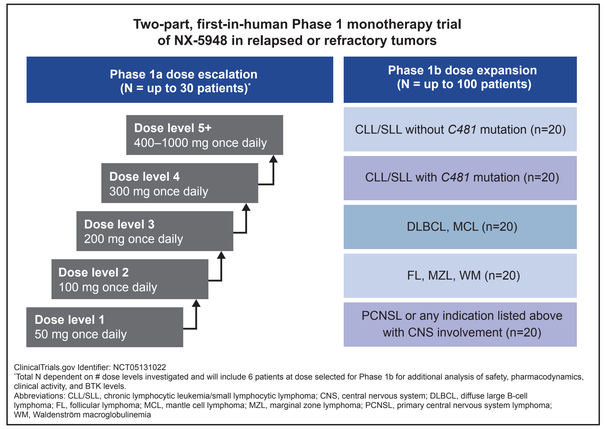
NX-5948: Mechanism of action



Methods

- NX-5948-301 is a first-in-human, two-part, multicenter, open-label, Phase 1 trial evaluating NX-5948, a BTK degrader, in adults with relapsed or refractory B-cell malignancies:
  - Phase 1a (dose escalation) will utilize a standard 3+3 dose-escalation design of 3 patients per dose level, in the absence of dose-limiting toxicities (DLTs).
  - Phase 1b (dose expansion) will include up to 5 expansion cohorts.
- NX-5948 will be given orally once daily at doses ranging from 50 to 1000 mg during Phase 1a, and at the recommended Phase 1b dose during Phase 1b.
- Eligible tumor types include chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström macroglobulinemia (WM), primary CNS lymphoma (PCNSL) or secondary CNS lymphoma.
- The main objectives are to establish the safety and tolerability of NX-5948, characterize pharmacokinetics/pharmacodynamics, and determine the recommended Phase 1b dose.

NX-2127-001: Study design



ClinicalTrials.gov Identifier: NCT05131022
*Total N dependent on # dose levels investigated and will include 6 patients at dose selected for Phase 1b for additional analysis of safety, pharmacodynamics, clinical activity, and BTK levels.
Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PCNSL, primary central nervous system lymphoma; WM, Waldenström macroglobulinemia

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. Evaluable disease is allowed
- ECOG performance status of 0 or 1
- Prior CAR-T therapy is allowed within 100 days (Phase 1a) or 30 days (Phase 1b) of study start
- Prior treatment within time to start of study drug:
  - chemotherapy within 4 weeks
  - monoclonal antibody within 4 weeks
  - small molecule therapy within 4 week or 5 half-lives, whichever is shorter
  - radiotherapy within 2 weeks, excluding limited palliative radiation
  - autologous or allogeneic stem cell transplant within 100 days
  - CAR-T therapy within 100 days (30 days for Phase 1b) and must have evidence of B-cell recovery
  - systemic steroids within 14 days (20 mg/day prednisone or equivalent is allowed; 40 mg/day is allowed for patients with CNSL)
- 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 14 days or 5 half-lives, whichever is longer
- Use of a proton pump inhibitor within 14 days or 5 half-lives, whichever is longer

Phase 1b only

- Must have failed 2 prior lines of therapy for CLL, SLL, DLBCL, FL, MZL or 1 prior line of therapy for WM, PCNSL, or secondary CNS involvement
- 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: BCPR, 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 macroglobulinemia

Study objectives and endpoints

Phase	Objectives	Endpoints
Primary (1a)	• **Evaluate safety and tolerability** • **Evaluate MTD and/or RP1bD**	• **Incidence of TEAEs** • **Incidence of all deaths** • **Changes from baseline in safety parameters** • **Incidence of DLTs**
Secondary (1a)	• Characterize PK profile • Characterize PD profile • Assess preliminary anti-tumor activity	• NX-5948 PK parameters in plasma • Changes from baseline in BTK levels in B-cells • ORR • CR • Time to first response, DOR, PFS, TTNT
Primary (1b)	• **Evaluate anti-tumor activity of NX-5948 at the RP1bD in expansion cohorts** • **Evaluate safety and tolerability**	• **ORR** – iwCLL criteria for CLL/SLL – WM response criteria for WM – Lugano Classification of Lymphoma response criteria for DLBCL, FL, MCL, and MZL – International PCNSL collaboration group criteria for PCNSL • **Incidence of TEAEs, deaths, and changes in safety parameters**
Secondary (1b)	• Further characterize PK profile • Further characterize PD profile	• NX-1607 PK parameters in plasma and CNS (patients with CNS disease only) • Changes from baseline of BTK levels in B-cells
Exploratory (1a, 1b)	• Assessment of OS • Evaluate NX-5948 metabolism • Explore mechanisms of response/resistance • Further characterize PK/PD relationship with anti-tumor activity, biomarkers, and/or safety	• OS • Identification of potential NX-5948 metabolites • BTK signaling pathway analysis which may include, but is not limited to, plasma cytokine levels, immunophenotyping, gene expression changes, and mutation analysis

Abbreviations: BTK, Bruton's tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DLTs, dose-limiting toxicities; DOR, duration of response; FL, follicular lymphoma; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PCNSL; primary central nervous system lymphoma; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; RP1bD, recommended phase 1b dose; TEAEs, treatment-emergent adverse events; TTNT, time to next treatment; WM, Waldenström macroglobulinemia

Target population

Phase 1a Dose escalation

- Adult patients with histologically confirmed relapsed/refractory B-cell malignancies
- Patients required to have any the following: CLL, SLL, DLBCL, FL, MCL, MZL, or WM
- Patients must have required and received at least 2 prior systemic therapies (or 1 prior therapy for patients with WM), and for whom no other therapies are known to provide clinical benefit

Phase 1b Cohort expansion

- Adult patients with histologically documented relapsed/refractory B-cell malignancies
- Must meet criteria for systemic treatment
- Patients must have required and received at least 2 prior systemic therapies or 1 prior therapy for patients with WM, PCNSL, or secondary CNS involvement, in addition to the criteria below for each indication

CLL/SLL without BTK *C481* mutation cohort
- BTK *C481* mutation-positive CLL/SLL with disease progression on a BTKi
- Patients who stopped BTKi due to side effects must have subsequent progression

CLL/SLL with a BTK *C481* mutation cohort
- CLL or SLL without BTK *C481* mutation with disease progression on a BTKi

DLBCL and MCL cohort
- DLBCL with disease progression on an anthracycline and an anti-CD20 mAb-based regimen, including Richter-transformed DLBCL, high-grade B-cell lymphoma, with *MYC* and *BCL2* and or *BCL6* rearrangements and high-grade B-cell lymphoma NOS
- MCL with disease progression on a BTKi and an anti-CD20 mAb-based regimen

FL, MZL, and WM cohort
- FL or MZL with disease progression on an anti-CD20 mAb-based regimen or WM with disease progression on a BTKi

PCNSL cohort
- PCNSL with disease progression on 1 prior therapy
- Any of the indications listed above with CNS involvement, with disease progression on 1 prior therapy

Abbreviations: BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; mAb, monoclonal antibody; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NOS, Not Otherwise Specified; PCNSL, primary central nervous system lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia

Current status

- Up to 130 patients (30 in Phase 1a; 100 in Phase 1b) will be enrolled at approximately 10 sites in the EU and the UK and treated until disease progression or unacceptable toxicity.
- Dose escalation is ongoing.
- Clinical trial information: NCT05131022
- Study contact: nx5948301@nurixtx.com

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