A First-in-Human Phase 1 Trial of NX-2127, a First-in-Class Oral BTK Degrader With Immunomodulatory Activity, in Patients With Relapsed and Refractory B-Cell Malignancies

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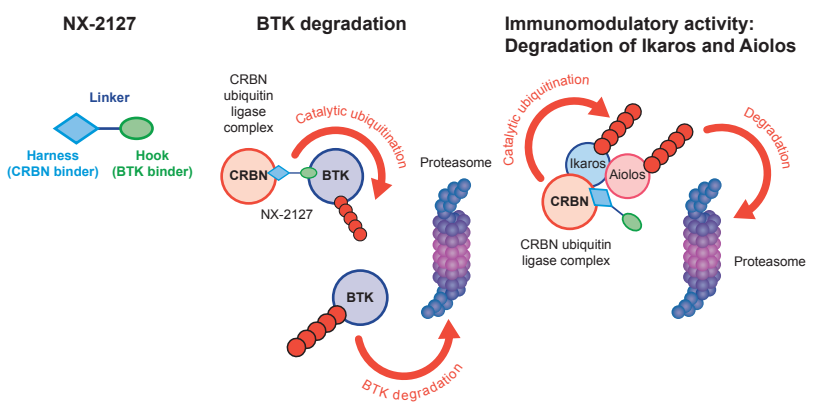
Background

- Inhibiting Bruton's tyrosine kinase (BTK) has been shown to be effective in treating B-cell malignancies:
  - Mutations in the BTK protein that prevent inhibitors from binding can cause resistance to approved BTK inhibitors.[1]
  - BTK degradation may offer an alternative method of interrupting B-cell receptor signaling and overcoming such resistance.
  - Immunomodulatory drugs utilizing cereblon activity, such as lenalidomide and pomalidomide, can increase T-cell release of interferon gamma and interleukin-2 leading to anti-tumor activity in some B-cell malignancies.
- 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-2127 is a chimeric targeting molecule that contains a BTK hook linked to a cereblon harness.[2]
  - In addition to inducing BTK degradation, NX-2127 possesses activity similar to immunomodulatory drugs utilizing cereblon activity.[2]
  - The combination of BTK degradation and immunomodulatory activity may be an effective strategy for treating relapsed/refractory B-cell malignancies.

NX-2127: Structure and mechanism of action

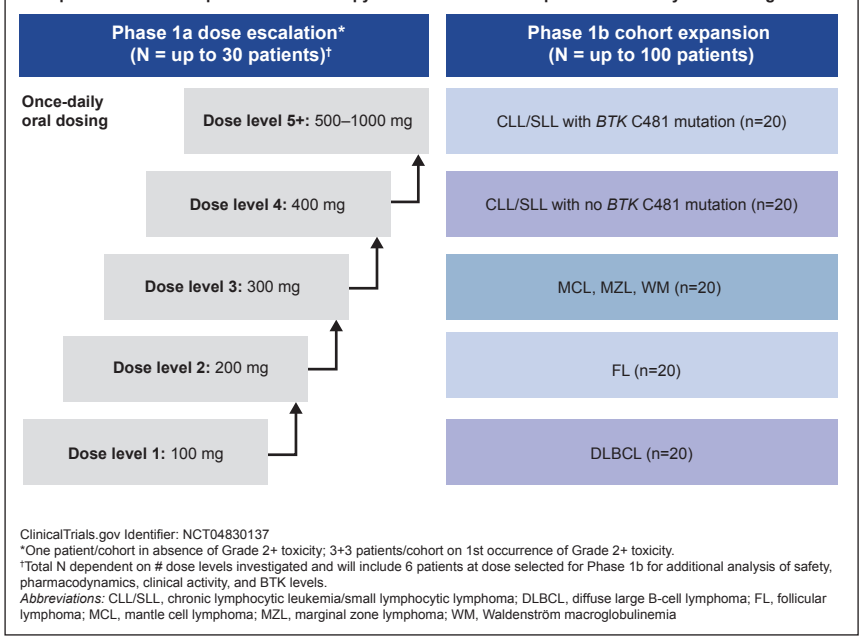


Abbreviations: BTK, Bruton's tyrosine kinase; CRBN, cereblon

Methods

- NX-2127-001 is a first-in-human, Phase 1a (dose escalation) and Phase 1b (cohort expansion) study designed to evaluate the safety, tolerability, and preliminary efficacy of NX-2127 in adult patients with relapsed/refractory chronic lymphocytic leukemia (CLL) and B-cell malignancies with once daily oral dosing:
  - Phase 1a (dose escalation) will proceed using an accelerated modified Fibonacci dose escalation design that transitions to a standard 3 + 3 design based on protocol-specific criteria.
  - Phase 1b (cohort expansion) will include up to 5 expansion cohorts in the indications listed.
- The primary objectives are:
  - To evaluate safety and tolerability and to determine the maximum tolerated dose (Phase 1a).
  - To evaluate the early clinical activity of NX-2127 in expansion cohorts (Phase 1b).

NX-2127-001: Study design



ClinicalTrials.gov Identifier: NCT04830137
*One patient/cohort in absence of Grade 2+ toxicity; 3+3 patients/cohort on 1st occurrence of Grade 2+ toxicity.
†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; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinemia

Study objectives and endpoints

Phase	Objectives	Endpoints
Primary (1a)	• **Evaluate the safety and tolerability of BTK degrader NX-2127, when taken orally, in adult patients with relapsed/refractory B-cell malignancies** • **Establish the MTD and/or recommended Phase 1b dose of NX-2127**	• **Incidence of DLTs, TEAEs, Grade ≥3 TEAEs, SAEs, TEAEs leading to study drug discontinuation, and deaths due to TEAEs** • **Incidence of all deaths** • **Changes from baseline in safety parameters**
Secondary (1a)	• Characterize the PK and PD profiles • Characterize any relationship between PK/PD • Assess preliminary anti-tumor activity	• NX-2127 PK parameters in plasma (C_{max}, T_{max}, half-life, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-tau}}$, C_{min}, accumulation ratio) • Changes from baseline of BTK levels in B cells • ORR, CR rate / CRi rate, DOR, PFS
Primary (1b)	• **Evaluate the clinical activity at the recommended dose selected in Phase 1a in up to 5 relapsed/refractory B-cell malignancy indication populations**	• **ORR based on B-cell malignancy indication-specific criteria, i.e.:** – iwCLL criteria[3] for CLL/SLL – WM response criteria[4] for WM – Lugano Classification of Lymphoma response criteria[5] for DLBCL, FL, MCL, and MZL
Secondary (1b)	• Evaluate safety and tolerability • Further characterize anti-tumor activity • Further characterize PK and PD profiles • Further characterize any relationship between PK/PD and anti-tumor activity	• Incidence of TEAEs, Grade ≥3 TEAEs, deaths due to TEAEs, SAEs, TEAEs leading to discontinuation, and changes in safety parameters • Incidence of all deaths • NX-2127 PK parameters in plasma • Changes from baseline of BTK levels in B cells • CR rate / CRi rate, DOR, PFS, OS

Abbreviations: AUC, area under the time-concentration curve; BTK, Bruton's tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; C_{max}, peak plasma concentration; C_{min}, minimum plasma concentration; CR, complete response; CRi, complete response with incomplete marrow recovery; 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; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; T_{max}, time to C_{max}; WM, Waldenström macroglobulinemia

Target population

Phase 1a Dose escalation	Phase 1b Cohort expansion
• Adult patients with histologically confirmed relapsed/refractory B-cell malignancies	**CLL/SLL with *BTK* C481 mutation cohort** • *BTK* C481 mutation-positive CLL/SLL whose disease has failed treatment with a BTKi
• Patients required to have any the following: – CLL, SLL, MCL, MZL, WM, FL (grade 1–3b), or DLBCL (high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements and high-grade B-cell lymphoma NOS)	**CLL/SLL with no *BTK* C481 mutation cohort** • CLL or SLL with no *BTK* C481 mutation whose disease has failed treatment with a BTKi
• 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	**MCL, MZL, WM cohort** • MCL or MZL whose disease has failed treatment with BTKi and an anti-CD20 mAb-based regimen or WM whose disease has failed treatment with BTKi
	Relapsed/refractory FL cohort • FL (grade 1–3b) whose disease has failed treatment with an anti-CD20 mAb-based regimen
	Relapsed/refractory DLBCL cohort • DLBCL (including transformed FL and transformed MZL; not Richter's) whose disease has failed treatment with an anti-CD20 mAb-based regimen and an anthracycline. DLBCL histologies include high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements and high-grade B-cell lymphoma NOS

Note: Failed treatment in Phase 1b is defined as: i) Best response of stable disease during treatment and then subsequently had progressive disease; ii) Any response with secondary progression; or iii) Best response of progressive disease at any time while on 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; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia

Key eligibility criteria

Abbreviated inclusion criteria
• ≥18 years of age
• At least 2 weeks must have elapsed between the last therapy and the first dose of study drug or at least 4 weeks for antibody-containing therapies, except for patients with CLL on a small molecule therapy who require at least 5 half-lives or 2 days (whichever is longer) • Must require systemic therapy
• Patients must have radiographically measurable disease per response criteria specific to the malignancy
• ECOG performance status of 0 or 1
• Adequate organ and bone marrow function, in the absence of growth factors, as defined per protocol laboratory parameters
Abbreviated exclusion criteria
• Richter's transformation, prolymphocytic leukemia, or blastoid transformation of FL into DLBCL prior to planned start of study drug
• Patients who have undergone autologous or allogeneic stem cell transplant within 100 days prior to planned start of study drug
• History of CAR-T therapy within 100 days prior to start of study drug. Must have evidence of B-cell recovery if patient received prior CAR-T therapy
• Prior radiotherapy within 2 weeks of planned start of study drug (excluding limited palliative radiation)
• Prior chemotherapy within 2 weeks of planned start of study drug
• Prior monoclonal antibody therapy within 4 weeks of planned start of study drug
• Toxicities from previous anticancer therapies must have resolved to baseline levels or to Grade 1 (except for alopecia, hypothyroidism with adequate replacement therapy, hypopituitarism with adequate replacement therapy, peripheral neuropathy, or hematologic parameters meeting inclusion criteria)
• History of Grade ≥2 hemorrhage within 28 days
• Patients requiring ongoing treatment with warfarin or patients treated with dual anti-platelet therapy and vitamin K antagonists

Abbreviations: CAR-T, Chimeric Antigen Receptor T-cell; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; WM, Waldenström macroglobulinemia

Current status

- Phase 1a dose escalation is ongoing in non-CLL indications.
- Phase 1b dose expansion is currently enrolling for patients with CLL.
- Clinical trial information: NCT04830137.
- Study contact: nx2127001@nurixtx.com

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