

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

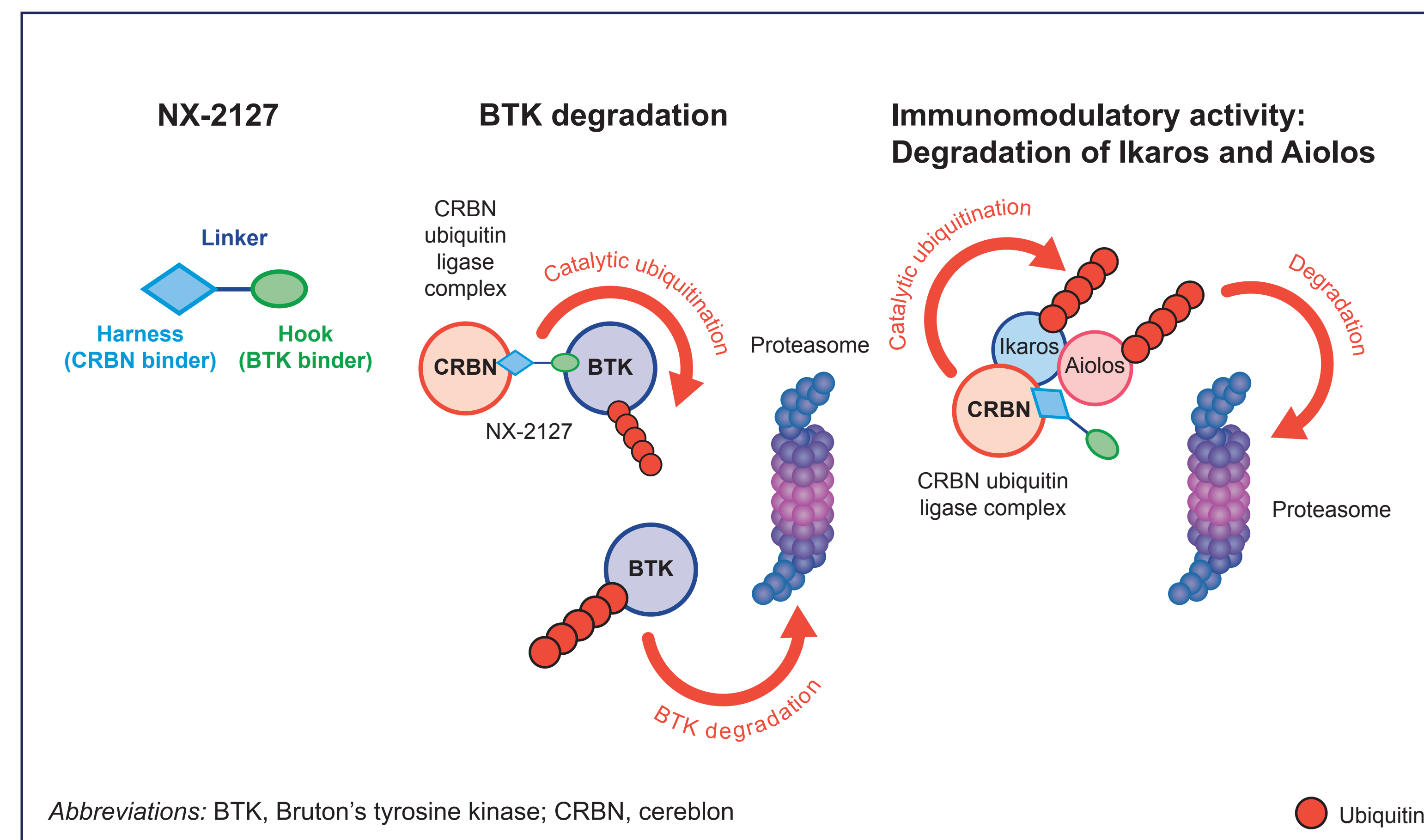
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## Background

- 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.<sup>1</sup>
  - 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"):<sup>2</sup>
  - NX-2127 is a chimeric targeting molecule that contains a BTK hook linked to a cereblon harness.<sup>2</sup>
  - In addition to inducing BTK degradation, NX-2127 possesses activity similar to immunomodulatory drugs utilizing cereblon activity.<sup>2</sup>
  - The combination of BTK degradation and immunomodulatory activity may be an effective strategy for treating relapsed/refractory B-cell malignancies.

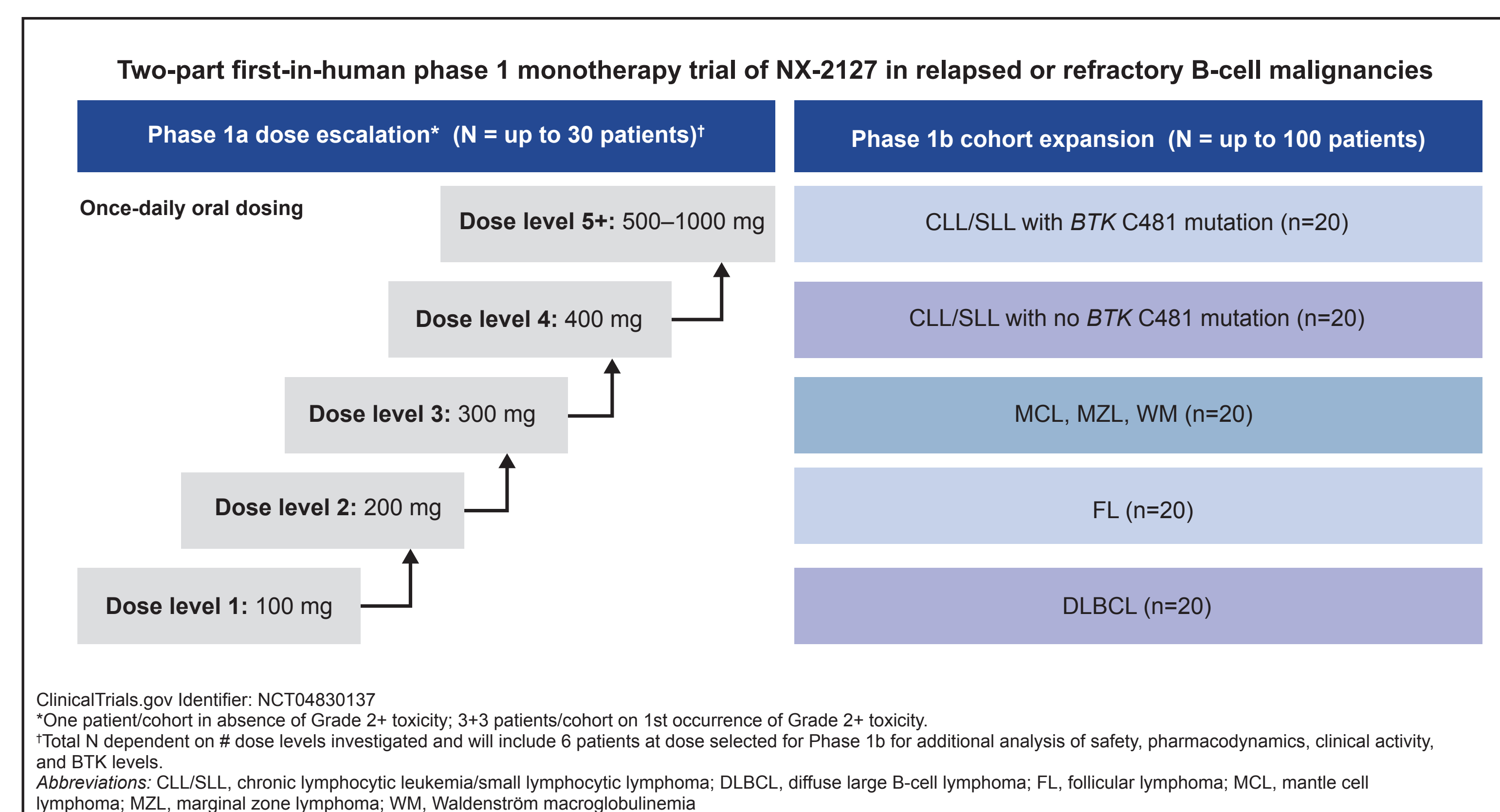
## NX-2127: Structure and mechanism of action



## 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



## References

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## Acknowledgements

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## Study objectives and endpoints

Phase	Objectives	Endpoints
Primary (1a)	<ul style="list-style-type: none"> <li>Evaluate the safety and tolerability of BTK degrader NX-2127, when taken orally, in adult patients with relapsed/refractory B-cell malignancies</li> <li>Establish the MTD and/or recommended Phase 1b dose of NX-2127</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of DLTs, TEAEs, Grade ≥3 TEAEs, SAEs, TEAEs leading to study drug discontinuation, and deaths due to TEAEs</li> <li>Incidence of all deaths</li> <li>Changes from baseline in safety parameters</li> </ul>
Secondary (1a)	<ul style="list-style-type: none"> <li>Characterize the PK and PD profiles</li> <li>Characterize any relationship between PK/PD</li> <li>Assess preliminary anti-tumor activity</li> </ul>	<ul style="list-style-type: none"> <li>NX-2127 PK parameters in plasma (<math>C_{max}</math>, <math>T_{max}</math>, half-life, <math>AUC_{0-12h}</math>, <math>AUC_{0-24h}</math>, <math>AUC_{0-48h}</math>, <math>C_{min}</math>, accumulation ratio)</li> <li>Changes from baseline of BTK levels in B cells</li> <li>ORR, CR rate / CRi rate, DOR, PFS</li> </ul>
Primary (1b)	<ul style="list-style-type: none"> <li>Evaluate the clinical activity at the recommended dose selected in Phase 1a in up to 5 relapsed/refractory B-cell malignancy indication populations</li> </ul>	<ul style="list-style-type: none"> <li>ORR based on B-cell malignancy indication-specific criteria, i.e.:                             <ul style="list-style-type: none"> <li>iwCLL criteria<sup>3</sup> for CLL/SLL</li> <li>WM response criteria<sup>4</sup> for WM</li> <li>Lugano Classification of Lymphoma response criteria<sup>5</sup> for DLBCL, FL, MCL, and MZL</li> </ul> </li> </ul>
Secondary (1b)	<ul style="list-style-type: none"> <li>Evaluate safety and tolerability</li> <li>Further characterize anti-tumor activity</li> <li>Further characterize PK and PD profiles</li> <li>Further characterize any relationship between PK/PD and anti-tumor activity</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of TEAEs, Grade ≥3 TEAEs, deaths due to TEAEs, SAEs, TEAEs leading to discontinuation, and changes in safety parameters</li> <li>Incidence of all deaths</li> <li>NX-2127 PK parameters in plasma</li> <li>Changes from baseline of BTK levels in B cells</li> <li>CR rate / CRi rate, DOR, PFS, OS</li> </ul>

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
<ul style="list-style-type: none"> <li>Adult patients with histologically confirmed relapsed/refractory B-cell malignancies</li> </ul>	<ul style="list-style-type: none"> <li><b>CLL/SLL with BTK C481 mutation cohort</b> <ul style="list-style-type: none"> <li>BTK C481 mutation-positive CLL/SLL whose disease has failed treatment with a BTKi</li> </ul> </li> <li><b>CLL/SLL with no BTK C481 mutation cohort</b> <ul style="list-style-type: none"> <li>CLL or SLL with no BTK C481 mutation whose disease has failed treatment with a BTKi</li> </ul> </li> <li><b>MCL, MZL, WM cohort</b> <ul style="list-style-type: none"> <li>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</li> </ul> </li> <li><b>Relapsed/refractory FL cohort</b> <ul style="list-style-type: none"> <li>FL (grade 1–3b) whose disease has failed treatment with an anti-CD20 mAb-based regimen</li> </ul> </li> <li><b>Relapsed/refractory DLBCL cohort</b> <ul style="list-style-type: none"> <li>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</li> </ul> </li> </ul>

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	Abbreviated exclusion criteria
<ul style="list-style-type: none"> <li>≥18 years of age</li> <li>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)</li> <li>Must require systemic therapy</li> <li>Patients must have radiographically measurable disease per response criteria specific to the malignancy</li> <li>ECOG performance status of 0 or 1</li> <li>Adequate organ and bone marrow function, in the absence of growth factors, as defined per protocol laboratory parameters</li> </ul>	<ul style="list-style-type: none"> <li>Richter's transformation, polycythemic leukemia, or blastoid transformation of FL into DLBCL prior to planned start of study drug</li> <li>Patients who have undergone autologous or allogeneic stem cell transplant within 100 days prior to planned start of study drug</li> <li>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</li> <li>Prior radiotherapy within 2 weeks of planned start of study drug (excluding limited palliative radiation)</li> <li>Prior chemotherapy within 2 weeks of planned start of study drug</li> <li>Prior monoclonal antibody therapy within 4 weeks of planned start of study drug</li> <li>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)</li> <li>History of Grade ≥2 hemorrhage within 28 days</li> <li>Patients requiring ongoing treatment with warfarin or patients treated with dual anti-platelet therapy and vitamin K antagonists</li> </ul>

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

