A Phase 1 Trial of Zelebrudomide (NX-2127), a First-in-Class BTK Dual-Targeted Protein Degrader, in Patients with Relapsed/Refractory B-cell Malignancies

[1]Alexey Danilov, [2]Michael Tees, [3]Harsh Shah, [4]Clare Sun, [5]Ian Flinn, [3]Daniel Ermann, [6]Jason Westin, [7]Michael Thirman, [8]Melannie Co, [8]Amanda Schwab, [8]Carolina Ryklansky, [8]May Tan, [8]Erin Meredith, [4]Adrian Wiestner

[1]City of Hope National Medical Center, Duarte, CA, USA; [2]Colorado Blood Cancer Institute/Sarah Cannon Research Institute, Denver, CO, USA; [3]Huntsman Cancer Institute, Salt Lake City, UT, USA; [4]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA; [5]Tennessee Oncology, Nashville, TN, USA; [6]MD Anderson Cancer Center, Houston, TX, USA; [7]University of Chicago, Chicago, IL, USA; [8]Nurix Therapeutics, Inc., San Francisco, CA, USA

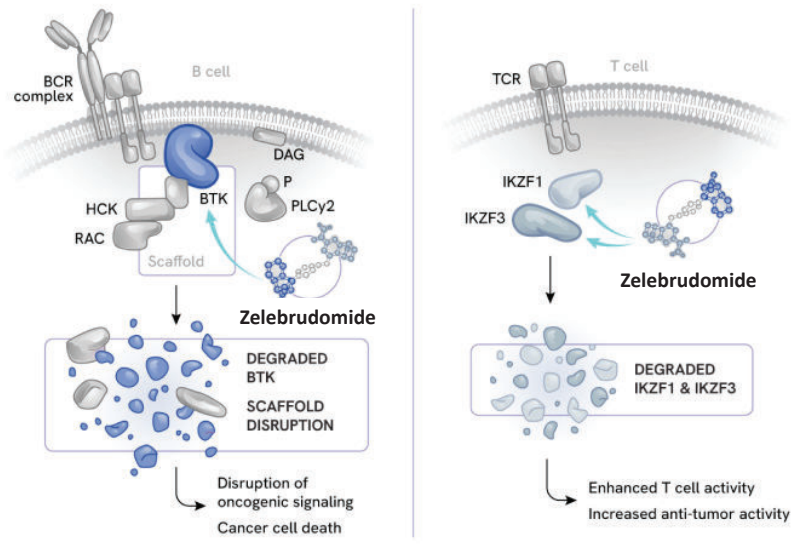
For information about this clinical trial please scan the QR code

Background

- BTKis have transformed the therapeutic landscape for patients with CLL and NHL because of the critical role of BTK in the proliferation and survival of B-cell malignancies.
- Although BTKis are effective for the treatment of B-cell malignancies, emerging BTK resistance mutations and the growth-promoting kinase-independent scaffolding function of BTK are unmet medical needs.[1]
- Therapeutic approaches that aim to harness innate protein degradation systems have the potential to address these critical needs. Degraders act by bringing together two key components, an E3 ligase and the disease-causing target protein, allowing the E3 ligase to tag the target protein with ubiquitin and marking it for disposal by proteasomes (**Figure 1**).

Figure 1. Zelebrudomide dual mechanism of action

Targeted degradation of BTK and IKZF1/3



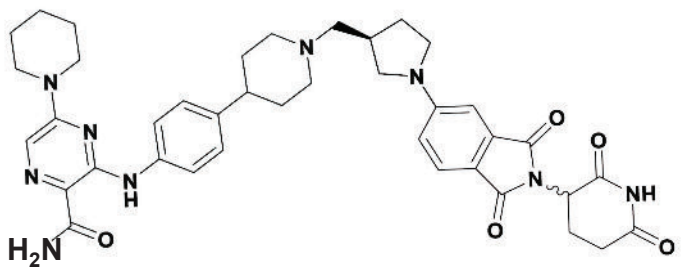
Zelebrudomide: an orally bioavailable, dual degrader of BTK and IKZF1/3

- Data from studies in patients with NHL and CLL suggest that dual degradation of BTK and IKZF1/3, transcription factors critical for B-cell development and immune homeostasis, offers a novel strategy to overcome BTKi resistance, reshape the tumor immune microenvironment, and enhance therapeutic efficacy.
- Zelebrudomide (NX-2127) is a first-in-class, oral, bi-functional small molecule degrader designed to degrade BTK and the immunomodulatory proteins Ikaros/Aiolos (**Figure 1**).[2] Zelebrudomide can efficiently engage the intracellular ubiquitin–proteasome system to simultaneously bind both BTK and the CRBN E3 ubiquitin ligase complex, inducing polyubiquitination and proteasome-dependent degradation of BTK, IKZF1, and IKZF3.[3]
- NX-2127-001 (NCT04830137) is an ongoing, multicenter, open-label, dose-escalation and cohort-expansion trial of zelebrudomide in patients with relapsed/refractory B-cell malignancies.
- Initial clinical data demonstrated preliminary antitumor activity across multiple B-cell malignancies in patients with prior BTKi exposure and BTK resistance mutations.[4–6]

Chirally controlled zelebrudomide

- Zelebrudomide has two chiral centers and is a mixture of two diastereomers (*R*,*R* and *S*,*R*). One of the chiral centers racemizes under physiological conditions. The other, at the pyrrolidine ring, is stable and is in the *R* configuration (**Figure 2**).
- Following a partial clinical hold to transition manufacturing away from the original drug product, enrollment has resumed with the new drug product, a chirally controlled *R*-diastereomer formulation.

Figure 2. Chirally controlled zelebrudomide[3]



BTK binder **Cereblon binder**

Methods

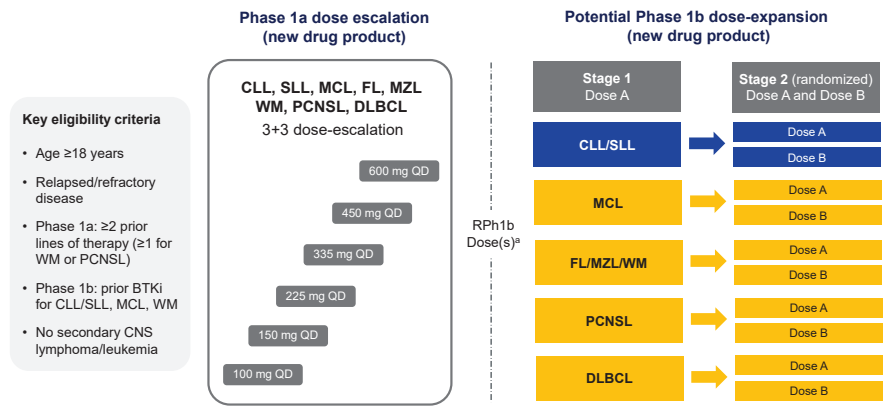
- The reinitiated NX-2127-001 trial includes a Phase 1a dose-escalation cohort (3+3 design) and a Phase 1b expansion cohort (**Figure 3**).
- Eligible patients have CLL, SLL, MCL, FL, MZL, WM, PCNSL, or DLBCL, ≥2 prior therapy lines (≥1 prior line for WM or PCNSL), and disease that failed to respond to prior BTKi. Patients with transformed lymphoma are eligible. Up to 48 patients will be enrolled in Phase 1a.
- In Phase 1b, up to 2 dose levels selected from Phase 1a will be evaluated in up to 5 dose-optimization cohorts of patients with relapsed/refractory B-cell malignancies who have received the specified prior therapies based on the indications.
- Patients in the original drug product cohorts may continue treatment until the recommended Phase 1b dose is identified and then switch to receiving the new drug product.
- Total study enrollment is up to 248 patients.

Study objectives

Objectives
Primary
Phase 1a • To evaluate the safety and tolerability of zelebrudomide • To establish the MTD and/or recommended Phase 1b dose(s)
Phase 1b • To evaluate clinical activity of zelebrudomide at the recommended Phase 1b dose(s)
Secondary
Phase 1a • To characterize the PK and PD profile of zelebrudomide • To assess preliminary anti-tumor activity of zelebrudomide
Phase 1b • To further evaluate the safety and tolerability of zelebrudomide • To further characterize the PK and PD profile of zelebrudomide

[a]Endpoints will be assessed in patients receiving new drug product zelebrudomide

Figure 3. NX-2127-001 study design



[a]*Recommended Phase 1b (RPh1b) doses may differ between indications; Dose A = RPh1b dose; Dose B = lower dose*

Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Age ≥18 years • Measurable disease • ECOG PS 0 or 1 (0–2 for PCNSL) • Adequate organ and bone marrow function	• Prolymphocytic leukemia, MCL with blastoid histology, MCL with pleomorphic morphology, or MCL with known *TP53* mutation • Active, uncontrolled autoimmune hemolytic anemia or autoimmune thrombocytopenia • History of known/suspected other autoimmune disease • Unable to swallow capsules or malabsorption syndrome • Bleeding diathesis, or other known risk for acute blood loss • Prior therapy – radiotherapy within 2 weeks (excluding limited palliative radiation) – nonsteroidal immunosuppressive drugs within 30 days – Strong CYP3A inducers or inhibitors within 14 days and moderate CYP3A inducers within 7 days • Major surgery in prior 4 weeks, planned during treatment period, or within 4 weeks after last dose of study drug
Phase 1a must have • Histologically confirmed R/R CLL, SLL, MCL, FL, MZL, WM, PCNSL, or DLBCL • Received ≥2 prior systemic therapies (or ≥1 prior therapy for patients with WM or PCNSL) and have no other therapies known to provide clinical benefit • ≥2 weeks between last therapy and first dose of study drug or ≥4 weeks for antibody-containing therapies (small molecule therapy requires longer of ≥5 half-lives or 2 days) • Requirement for systemic therapy	
Phase 1b must have 1 of the following and have failed ≥2 prior treatments (or ≥1 for WM or PCNSL) • CLL, SLL, or WM that failed prior BTKi • MCL that failed prior BTKi and anti-CD20 mAb-based regimen • FL or MZL that failed prior anti-CD20 mAb-based regimen • PCNSL that failed ≥1 prior line of therapy • DLBCL that failed prior anti-CD20 mAb-based regimen, and one other therapy either: anthracycline-based regimen; or an anti-CD19-based regimen, or another/palliative regimen (either progressed post stem cell transplant or transplant-ineligible)	

NX-2127-001 current status and next steps

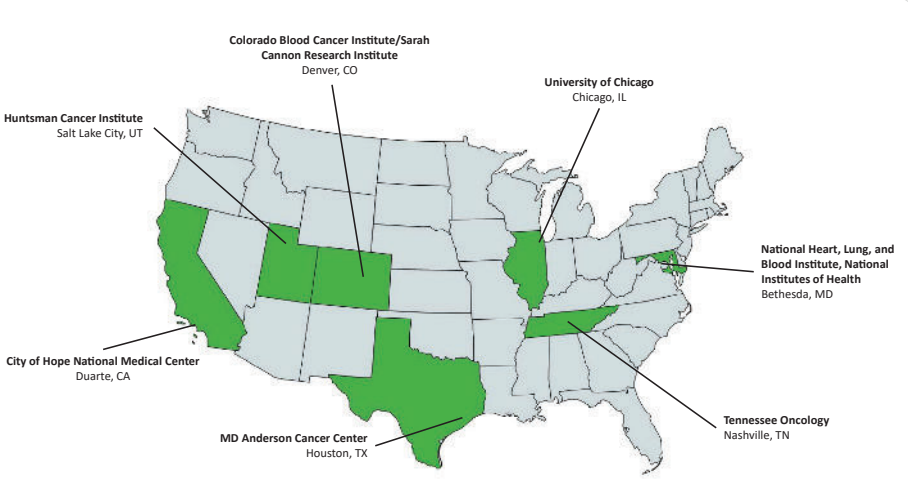
Status

- Enrollment with the new, chirally controlled drug product has been re-initiated.
- Enrollment of patients with aggressive lymphomas is prioritized, where the combination of BTK degradation and IKZF1/3 degradation has the potential for synergy and significant therapeutic benefit.

Next steps

- To complete dose escalation with the new drug product and select the recommended phase 1b dose for selected indications.
- Additional clinical data will be shared after selection of phase 1b expansion dose(s) and indication(s).

NX-2127-001: 7 Participating U.S. Sites



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Abbreviations

BCR, B-cell receptor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitors; **CLL**, chronic lymphocytic leukemia; **CRBN**, cereblon; **DLBCL**, diffuse large B-cell lymphoma; **ECOG**, Eastern Cooperative Oncology Group; **FL**, follicular lymphoma; **mAb**, monoclonal antibody; **MCL**, mantle cell lymphoma; **MTD**, maximum tolerated dose; **MZL**, marginal zone lymphoma; **NHL**, non-Hodgkin's lymphoma; **PCNSL**, primary central nervous system lymphoma; **PD**, pharmacodynamic; **PK**, pharmacokinetic; **PS**, performance status; **QD**, once daily; **R/R**, relapsed/refractory; **SLL**, small lymphocytic lymphoma; **WM**, Waldenstrom's macroglobulinemia.