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# POSTER ABSTRACTS

## 626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

### Initial Findings from a First-in-Human Phase 1a/b Trial of NX-5948, a Selective Bruton's Tyrosine Kinase (BTK) Degrader, in Patients with Relapsed/Refractory B Cell Malignancies

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**Introduction:** Although BTK inhibitors (BTKi) are effective therapeutics in the treatment of B cell malignancies, emerging BTK resistance mutations in chronic lymphocytic leukemia (CLL), as well as potential growth-promoting kinase-independent scaffolding function of BTK, present a need for improved or new approaches. NX-5948 is a novel, orally administered small molecule that induces specific BTK protein degradation by the cereblon E3 ligase complex without degradation of other cereblon neo-substrates. Importantly, NX-5948 induces degradation of wild-type and mutant forms of *BTK* in B-cells [Noviski et al. 2023] at sub-nanomolar potencies and exhibits potent tumor growth inhibition in TMD8 xenograft models that contain either wild-type *BTK* or BTKi-resistant mutations [Robbins 2021]. Here we provide the first disclosure of preliminary safety and efficacy findings from a Phase 1a trial of NX-5948 in patients with relapsed/refractory B cell malignancies.
**Methods:** NX-5948-301 is a Phase 1, first-in-human, dose-escalation and cohort-expansion trial evaluating the safety, tolerability, and clinical activity of NX-5948 in relapsed/refractory CLL and various subtypes of non-Hodgkin's lymphoma (NHL). Key eligibility criteria: ≥2 prior lines of therapy; measurable or other evaluable disease per indication-specific response criteria; Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1. Phase 1a (dose escalation) evaluates safety and tolerability of NX-5948 via a standard 3+3 dose escalation in patients with relapsed/refractory B cell malignancies. Approximately 110 patients (30 in Phase 1a, 80 in Phase 1b) may be enrolled and treated until confirmed disease progression or unacceptable toxicity. Endpoints include dose-limiting toxicities (DLTs); treatment-emergent adverse events (TEAEs); deaths; changes in safety parameters; objective response rate per disease-specific response criteria. Phase 1b (dose expansion) will include up to four expansion cohorts.
**Results:** As of June 9, 2023, 14 patients were enrolled in Phase 1a and received NX-5948 at 50 mg (n=7), 100 mg (n=4), or 200 mg (n=3) orally once daily. Median age was 65 (range 46-79) years; female/male ratio 28.6%/71.4%; white 92.9%; ECOG PS 0/1 21.4%/78.6%; primary diagnoses were CLL (n=4), diffuse large B cell lymphoma (DLBCL, n=4), mantle cell lymphoma (MCL, n=3), marginal zone lymphoma (MZL, n=2), and follicular lymphoma (FL, n=1). Median number of prior therapies was 4.5 (range 2-10), which included: for CLL - BTKi (n=4/4) and BCL2 inhibitor (n=3/4); for NHL - BTKi (n=5/10), bispecific antibody (n=3/10), and CAR-T (n=2/10). NX-5948 was well tolerated with no DLTs and no TEAEs resulting in drug discontinuation or dose reduction. In addition, there were no NX-5948-related grade ≥3 TEAEs or related serious adverse events. The most common TEAEs were purpura/contusion (57.1%, all below grade 3), nausea (35.7%), and thrombocytopenia (35.7%). No atrial fibrillation/flutter or hypertension was reported. Median duration of treatment was 2.8 (range 0.5-9.6) months with 9/14 patients remaining on treatment. Current data indicate that NX-5948 exhibits dose-dependent pharmacokinetics (PK) and a half-life of ~24 hours, supporting once daily dosing (Figure a). Rapid, robust and sustained BTK degradation was

observed in all patients, regardless of absolute BTK starting level, tumor type, or NX-5948 dose (Figure b). Of three evaluable patients with CLL receiving the lowest dose of 50 mg, early signs of clinical activity were observed including one confirmed partial response (PR; at 8 and 16 weeks) and 2 patients with stable disease (SD; at 8 weeks). Further treatment responses will be reported at the time of presentation.

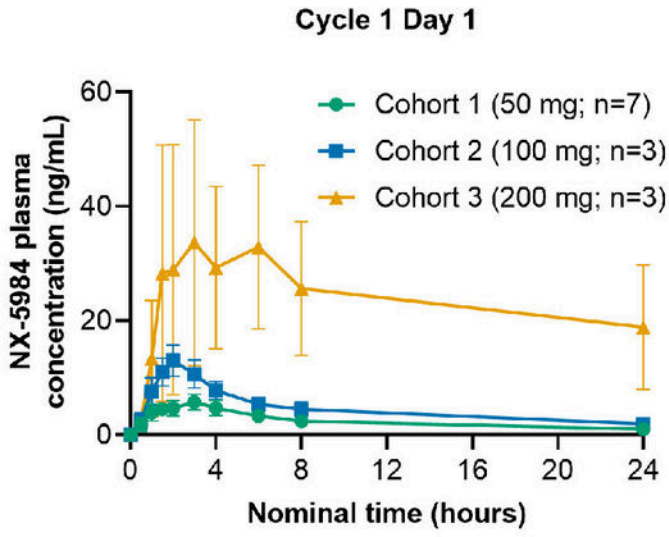
**Summary/conclusion:** Current findings in this heavily pre-treated population of patients with CLL and NHL are encouraging and indicate that NX-5948 is safe and well tolerated and has clinical activity, supporting continuation of its development in CLL and NHL. NX-5948 also exhibits dose-proportional PK, resulting in rapid, robust and sustained BTK degradation. Additional data with higher dose levels and longer treatment duration will be presented at the meeting.

**Disclosures Searle:** *Janssen:* Honoraria, Other: Conference travel; *Abbvie:* Honoraria, Other: Conference travel; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Shattuck Labs:* Membership on an entity's Board of Directors or advisory committees. **Forconi:** *Abbvie:* Honoraria, Other: Travel and accommodation, Speakers Bureau; *Janssen-cilag:* Honoraria, Other: Travel and accommodation, Speakers Bureau; *beigene:* Honoraria, Other: Travel and accommodation, Speakers Bureau; *Astra-Zeneca:* Honoraria, Speakers Bureau. **Linton:** *Genmab:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *AbbVie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Hoffman-La Roche:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Takeda:* Research Funding; *Roche:* Consultancy; *Gilead:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Danilov:** *Beigene:* Consultancy, Research Funding; *Abbvie:* Consultancy, Research Funding; *Bayer:* Research Funding; *Nurix:* Consultancy, Research Funding; *MEI:* Consultancy, Research Funding; *Lilly Oncology:* Consultancy, Research Funding; *Merck:* Consultancy; *Cyclacel:* Research Funding; *Janssen:* Consultancy; *Astra Zeneca:* Consultancy, Research Funding; *Bristol Meyers Squibb:* Consultancy, Research Funding; *Genentech:* Consultancy; *GenMab:* Consultancy, Research Funding. **McKay:** *Takeda:* Consultancy, Other: Travel to scientific conferences; *Roche:* Consultancy; *Janssen:* Consultancy, Honoraria, Other: Travel to scientific conferences; *Incyte:* Consultancy, Honoraria; *Gilead/Kite:* Consultancy, Honoraria, Other: Travel to scientific conferences; *Celgene/BMS:* Consultancy; *Beigene:* Consultancy; *AstraZeneca:* Consultancy; *Abbvie:* Consultancy. **Lewis:** *Janssen:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Lilly:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Roche:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Kite:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **El-Sharkawi:** *Abbvie, ASTEX, AstraZeneca, BeiGene, Janssen, Kyowa Kiirin:* Consultancy; *Abbvie, AstraZeneca, BeiGene; Gilead, Janssen, Lily, Novartis, F. Hoffman-La Roche, Takeda:* Honoraria; *Royal Marsden NHS Foundation trust:* Current Employment; *Abbvie:* Speakers Bureau. **Gleeson:** *Incyte:* Other: Speaker Fees. **Riches:** *Janssen:* Speakers Bureau. **Injac:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Shih:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Nandakumar:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Tan:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Cherala:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in publicly-traded company; *Gilead Sciences:* Current equity holder in private company, Ended employment in the past 24 months; *BioMarin:* Current equity holder in private company. **Meredith:** *Nurix Therapeutics, Inc.:* Current Employment, Current equity holder in publicly-traded company. **Collins:** *Daiichi Sankyo:* Consultancy, Honoraria; *BMS:* Research Funding; *Amgen:* Research Funding; *Pfizer:* Research Funding; *Astra Zeneca:* Consultancy, Honoraria, Research Funding; *Beigene:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Gilead:* Consultancy, Honoraria, Speakers Bureau; *Takeda:* Consultancy, Honoraria, Speakers Bureau; *Roche:* Consultancy, Honoraria, Speakers Bureau.

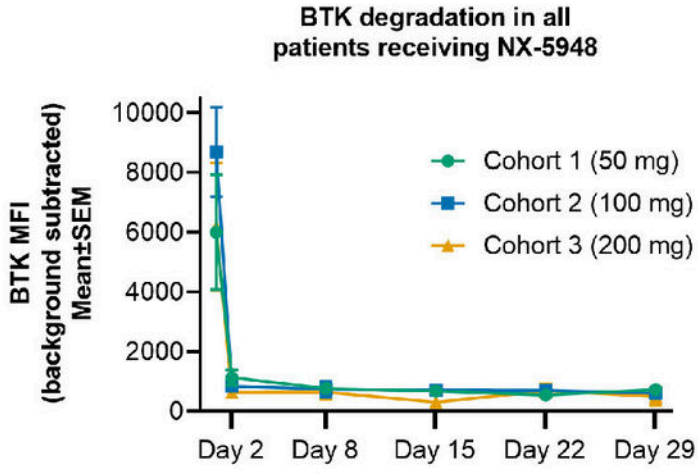
**OffLabel Disclosure:** NX-5948 is a novel, orally administered, small molecule that induces specific BTK protein degradation by the cereblon E3 ligase complex, but not of other cereblon neo-substrates.

Figure. PK (a) and BTK expression (b) in patients treated with NX-5948

(a)




(b)




| Dose (mg) | Number of patients per day | | | | |
|---|---|---|---|---|---|
| 50 | 7 | 7 | 6 | 5 | 6 |
| 100 | 3 | 2 | 3 | 3 | 3 |
| 200 | 3 | 3 | 2 | 2 | 2 |

**Figure 1**

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