A First-in-Human Phase 1 Trial of NX-2127, a First-in-Class Bruton's Tyrosine Kinase Dual-Targeted Protein Degrader with Immunomodulatory Activity, in Patients with Relapsed/Refractory B-Cell Malignancies

Poster #4463

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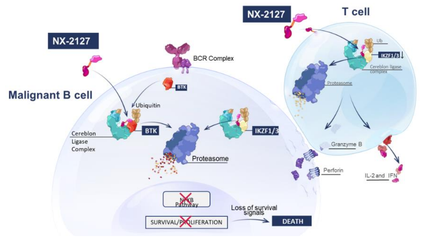
Background

- Emerging resistance mutations to BTK inhibitors (BTKi) in CLL and NHL, and the related growth-promoting kinase-independent scaffolding function of BTK, present a need for improved or new approaches that address the shortcomings of existing BTKi.[1]
- Additionally, preclinical and clinical data in NHL suggest that modulation of cereblon to degrade Ikaros family proteins may demonstrate synergy with BTK inhibition in providing a therapeutic effect.[1]
- NX-2127 is an oral, first-in-class, dual-function, small-molecule degrader that combines BTK degradation with the immunomodulatory activity of a degrader for the transcription factor Ikaros (IKZF1/3, Figure 1).[2]

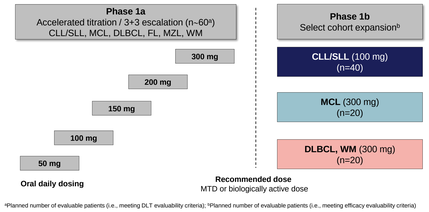
Figure 1. NX-2127 mechanism of action



- NX-2127 may exert superior anti-tumor activity compared with classical BTKi by overcoming *BTK* mutation-driven resistance to BTKi, eliminating BTK non-kinase function (e.g. scaffolding) and modulating immune response by regulating activity of Ikaros family transcription factors.
- NX-2127 is currently being evaluated in a Phase 1a/1b study in patients with advanced B-cell malignancies (NX-2127-001). Preliminary safety data across B-cell malignancies and efficacy in patients with CLL have been presented previously.[3,4]
- Here we report updated safety and efficacy data from patients with NHL and CLL.

Methods

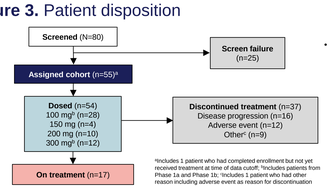
Figure 2. Trial design (ClinicalTrials.gov NCT04830137)



[a]Planned number of evaluable patients (i.e., meeting DLT evaluability criteria); [b]Planned number of evaluable patients (i.e., meeting efficacy evaluability criteria)

- 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 NHL and CLL:
  - Phase 1a (dose escalation) will use 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 evaluate efficacy in indication-specific cohorts.
- Key eligibility criteria: ≥2 prior lines of therapy; measurable or other evaluable disease per indication-specific response criteria; ECOG performance status 0 or 1.
- Primary objectives:
  - Phase 1a: evaluate safety and tolerability and determine the MTD of NX-2127.
  - Phase 1b: evaluate early clinical activity of NX-2127 in expansion cohorts.
- NX-2127 is administered orally once daily in 28-day cycles.

Figure 3. Patient disposition



[a]Includes 1 patient who had completed enrollment but not yet received treatment at time of data cutoff; [b]Includes patients from Phase 1a and Phase 1b; [c]Includes 1 patient who had other reason including adverse event as reason for discontinuation

Data cutoff: 15 Sep 2023

- Patients dosed include:
  - **CLL/SLL:** n=33 (61.1%)
  - **DLBCL:** n=6 (11.1%)
  - **MCL:** n=7 (13.0%)
  - **MZL:** n=3 (5.6%)
  - **WM:** n=3 (5.6%)
  - **FL:** n=2 (3.7%)

Results

Table 1. Baseline characteristics

Characteristic	NHL/WM (n=21)	CLL/SLL (n=33)	Overall population (N=54)
Median age, years (range)	70.0 (50.0–92.0)	74.0 (58.0–90.0)	72.5 (50.0–92.0)
Female, n (%)	6 (28.6)	11 (33.3)	17 (31.5)
Male, n (%)	15 (71.4)	22 (66.7)	37 (68.5)
ECOG PS, n (%)			
0	10 (47.6)	18 (54.5)	28 (51.9)
1	11 (52.4)	15 (45.5)	26 (48.1)
Previous targeted treatments[a], n (%)			
BTKi	15 (71.4)	33 (100.0)	48 (88.9)
Pirtobrutinib	5 (23.8)	9 (27.3)	14 (25.9)
BTKi and BCL2i	1 (4.8)	26 (78.8)	27 (50.0)
cBTKi, ncBTKi, and BCL2i	0 (0.0)	8 (24.2)	8 (14.8)
CAR-T/-NK therapy	3 (14.3)	1 (3.0)	4 (7.4)
Bispecific antibody	2 (9.5)	0 (0.0)	2 (3.7)
Immunomodulatory therapy (lenalidomide)	4 (19.0)	4 (12.1)	8 (14.8)
Median number of lines of prior therapy (median, range)	4 (2–10)	5 (2–11)	4 (2–11)
Mutations[a], n (%)			
BTK	3 (14.3)	12 (36.4)	15 (27.8)
C481S or C481R	1 (4.8)	7 (21.2)	8 (14.8)
L528W	1 (4.8)	4 (12.1)	5 (9.3)
T474F or T474I	1 (4.8)	4 (12.1)	5 (9.3)
V416L	0 (0.0)	1 (3.0)	1 (1.9)
L512V	1 (4.8)	0 (0.0)	1 (1.9)
PLCG2[b]	2 (9.5)	1 (3.0)	3 (5.6)
BCL2 *(G101V)*	0 (0.0)	4 (12.1)	4 (7.4)

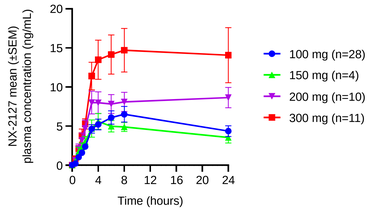
[a]Patients could have multiple prior treatments and BTK mutations; mutations were tested centrally at baseline by next-generation sequencing (allelic frequency ≥5% is reported); [b]*L845F, D334H, D1140N, T961M, S707F*

Data cutoff: 15 Sep 2023

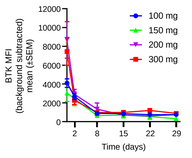
- Patient population was predominantly elderly with multiple prior lines of targeted therapies and acquired mutations associated with drug resistance (see Table 1).
- Median follow-up for the study was 9.7 (range 0.6–27.5) months.
- The most common reasons for treatment discontinuation were disease progression (n=16) and adverse events (n=12).

Figure 4. NX-2127 pharmacokinetics and proximal biomarker changes

A) NX-2127 C1D1 pharmacokinetics

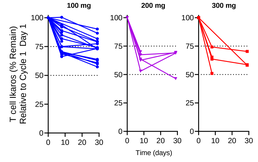


B) BTK[a] degradation in patients receiving NX-2127



Dose (mg)	Number of patients per day						
	Day 0	Day 2	Day 8	Day 15	Day 22	Day 29
100	28	27	24	23	22	20
150	4	4	4	3	2	2
200	9	9	8	9	7	6
300	10	10	8	9	6[a]	4

C) Ikaros[b] degradation in patients receiving NX-2127



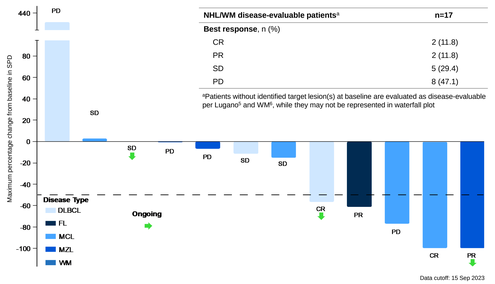
Dose (mg)	Number of patients per day		
	Day 1	Day 8	Day 29
100	23	19	16
200	5	5	4
300	5	4	3[c]

Data cutoff: 15 Sep 2023

[a]BTK measured in patient B-cells whole blood using flow cytometry assay; [b]Ikaros measured in patient T-cells in PBMC using flow cytometry assay; [c]1 patient had dose modification from Day 19 onwards

- NX-2127 exhibited dose-dependent pharmacokinetics with a mean half-life of 2–4 days across cohorts (Figure 4A).
- Rapid, robust, and sustained BTK degradation was observed in all patients, regardless of their absolute BTK starting level, tumor type, or dose level of NX-2127 (Figure 4B).
- Consistent with the immunomodulatory activity of NX-2127, degradation of the cereblon neo-substrate Ikaros was observed (Figure 4C).

Figure 5. NX-2127 efficacy (patients with NHL/WM)

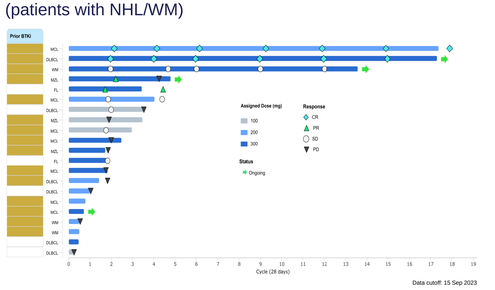


NHL/WM disease-evaluable patients[a]	n=17
Best response, n (%)	
CR	2 (11.8)
PR	2 (11.8)
SD	5 (29.4)
PD	8 (47.1)

[a]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per Lugano[5] and WM[6], while they may not be represented in waterfall plot

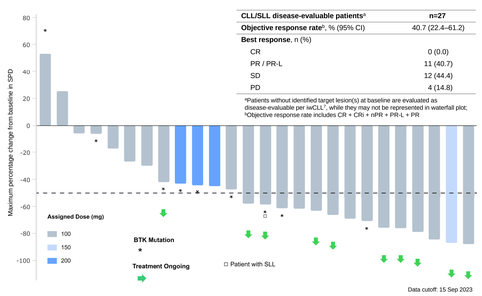
- As of the 15 Sep 2023 cutoff date, 17 patients with NHL were disease-evaluable.
- Two patients (one MCL and one DLBCL), had a CR (Figure 5):
  - Treatment was ongoing in the patient with DLBCL (17 months' duration; Figure 6).
  - The patient with MCL discontinued treatment in the setting of a CR

Figure 6. Duration of treatment and best response to NX-2127 (patients with NHL/WM)



- Two further patients (one FL and one MZL) had a PR (Figure 6):
  - FL patient had prior CAR-T/bispecific therapy.
- Treatment was ongoing in the patient with MZL (4+ months' duration) and in one other patient with WM who had SD (see Figure 6).

Figure 7. NX-2127 efficacy (patients with CLL/SLL)



CLL/SLL disease-evaluable patients[a]	n=27
Objective response rate[b], % (95% CI)	40.7 (22.4–61.2)
Best response, n (%)	
CR	0 (0.0)
PR / PR-L	11 (40.7)
SD	12 (44.4)
PD	4 (14.8)

[a]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL[7], while they may not be represented in waterfall plot; [b]Objective response rate includes CR + CRi + nPR + PR-L + PR

- As of the 15 Sep 2023 cut-off date, 27 patients with CLL/SLL were disease-evaluable:
  - 11 patients had a PR or PR-L (Figure 7).
  - 12 patients had SD at the time of data cutoff (Figure 7).
  - Responses were seen in double- and triple-exposed (including pirtobrutinib) patients.
  - Treatment is ongoing in 13 patients (see Figure 8).
  - Eight patients have been on treatment for longer than 12 months.

Table 2. Frequency of any grade TEAEs in ≥20% of patients, or grade ≥3 TEAEs or SAEs in >1 patient (N=54)

TEAEs, (%)	Any grade	Grade ≥3	SAEs
Fatigue	25 (46.3)	–	–
Neutropenia[a]	25 (46.3)	23 (42.6)	–
Hypertension	18 (33.3)	8 (14.8)	–
Bruising/contusion[b]	16 (29.6)	–	1 (1.9)
Diarrhea	16 (29.6)	–	–
Anemia	13 (24.1)	8 (14.8)	1 (1.9)
Dizziness	13 (24.1)	–	–
Dyspnea	13 (24.1)	1 (1.9)	–
Thrombocytopenia[c]	13 (24.1)	4 (7.4)	–
Constipation	12 (22.2)	–	–
Headache	11 (20.4)	–	–
Upper GI hemorrhage[d]	2 (3.7)	2 (3.7)	2 (3.7)
Pruritus	11 (20.4)	1 (1.9)	–
COVID-19	7 (13.0)	4 (7.4)	3 (5.6)
Atrial fibrillation[e]	6 (11.1)	3 (5.6)	3 (5.6)
Pneumonia	6 (11.1)	3 (5.6)	3 (5.6)
Pain in extremity	5 (9.3)	2 (3.7)	1 (1.9)
Leukocytosis	3 (5.6)	3 (5.6)	–
Lymphocyte count increased	2 (3.7)	2 (3.7)	–
Sepsis[f]	2 (3.7)	2 (3.7)	2 (3.7)

[a]Aggregate of 'neutropenia' and 'neutrophil count decreased'; [b]Bruising/contusion includes episodes coded as contusion; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [d]Includes one grade 5 event; [e]Aggregate of 'atrial fibrillation' and 'atrial flutter'; [f]Includes two grade 5 events

Data cutoff: 15 Sep 2023

Figure 8. Duration of treatment and best response to NX-2127 (patients with CLL/SLL)

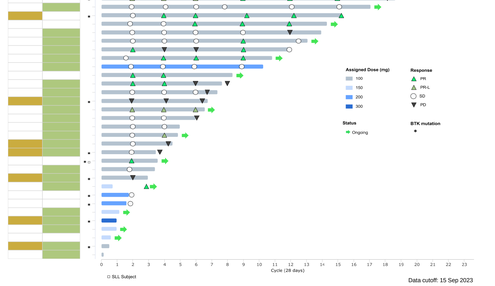


Table 3. Frequency of any grade TEAEs by dose in ≥20% of patients (N=54)

TEAEs, n (%)	All doses (N=54)	100 mg (n=28)	150 mg (n=4)	200 mg (n=10)	300 mg (n=12)
Fatigue	25 (46.3)	16 (57.1)	1 (25.0)	5 (50.0)	3 (25.0)
Neutropenia[a]	25 (46.3)	9 (32.1)	1 (25.0)	6 (60.0)	9 (75.0)
Hypertension	18 (33.3)	12 (42.9)	0 (0.0)	2 (20.0)	4 (33.3)
Bruising/contusion[b]	16 (29.6)	7 (25.0)	1 (25.0)	4 (40.0)	4 (33.3)
Diarrhea	16 (29.6)	9 (32.1)	1 (25.0)	2 (20.0)	4 (33.3)
Anemia	13 (24.1)	6 (21.4)	0 (0.0)	4 (40.0)	3 (25.0)
Dizziness	13 (24.1)	4 (14.3)	3 (75.0)	2 (20.0)	4 (33.3)
Dyspnea	13 (24.1)	6 (21.4)	0 (0.0)	4 (40.0)	3 (25.0)
Thrombocytopenia[c]	13 (24.1)	6 (21.4)	0 (0.0)	3 (30.0)	4 (33.3)
Constipation	12 (22.2)	9 (32.1)	1 (25.0)	1 (10.0)	1 (8.3)
Headache	11 (20.4)	4 (14.3)	2 (50.0)	3 (30.0)	2 (16.7)
Pruritus	11 (20.4)	7 (25.0)	0 (0.0)	1 (10.0)	3 (25.0)

[a]Aggregate of 'neutropenia' and 'neutrophil count decreased'; [b]Bruising/contusion includes episodes of bruising and contusion; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'

Data cutoff: 15 Sep 2023

- The most common TEAEs (any grade) were fatigue, neutropenia, hypertension, bruising/contusion, and diarrhea (see Tables 2 and 3). The most common grade ≥3 TEAEs were neutropenia, hypertension, and anemia.
- Neutropenia showed evidence of dose response.
- Atrial fibrillation was observed in 6 patients (11.1%; down from 17% reported previously), with 3 patients (5.6%) having grade ≥3 events.
- Twenty-one patients (38.9%) had serious TEAEs, of whom 8 (14.8%) had SAEs considered related to NX-2127 treatment.
- Two patients experienced DLTs (cognitive disturbance, neutropenia; both at 300 mg dose level), and 13 patients developed TEAEs that resulted in discontinuation of NX-2127.

Conclusions

- NX-2127 exposure in patients with **NHL** and **CLL** results in robust and sustained degradation of BTK and biologically-relevant degradation of Ikaros.
- NX-2127 had a manageable safety profile that was consistent with previous reports for BTK-targeted and immunomodulatory therapies.
- Treatment with NX-2127 resulted in encouraging and durable responses in a heavily pre-treated patient population:

NHL

✓ Rapid (8-week) and durable CRs were observed in 2 patients (DLBCL, MCL).

✓ Rapid (8-week) PRs were observed in 2 patients (FL, MZL).

CLL

✓ PRs were observed in 11 patients (9 PRs, 2 PR-Ls).

✓ Objective response rate was 40.7% as of the cutoff date, and treatment was ongoing in 13 patients.

- Dose-expansion cohorts of patients with **NHL** have been initiated at the 300 mg daily dose.

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Abbreviations

BCR, B-cell receptor; **BCL2i**, B-cell lymphoma-2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **ncBTKi**, non-covalent BTKi; **CAR-T**, chimeric antigen receptor T cell; **CAR-NK**, chimeric antigen receptor natural killer cell; **CI**, confidence interval; **CLL**, chronic lymphocytic leukemia; **CR**, complete response; **CRBN**, cereblon; **DLBCL**, diffuse large B-cell lymphoma; **DLT**, dose-limiting toxicity; **ECOG**, Eastern Cooperative Oncology Group; **FL**, follicular lymphoma; **GI,** gastrointestinal; **IFN**, interferon; **IL**, interleukin; **MCL**, mantle cell lymphoma; **MFI**, mean fluorescence intensity; **MTD**, maximum tolerated dose; **MZL**, marginal zone lymphoma; **NHL**, non-Hodgkin's lymphoma; **PD**, progressive disease; **PLCG**, phospholipase C gamma 2 gene; **PR**, partial response; **PR-L**, partial response with rebound lymphocytosis; **SAE,** serious adverse event; **SD**, stable disease; **SEM**, standard error of the mean; **SLL**, small lymphocytic lymphoma; **SPD**, sum of product diameters; **TEAE,** treatment-emergent adverse event; **VAF**, variant allele frequency; **WM**, Waldenstrom's macroglobulinemia.

Acknowledgments

The authors would like to thank all patients, their caregivers, and their treating physicians for participating in the NX-2127-001 study, which was sponsored by Nurix Therapeutics, Inc.

Nurix Therapeutics, Inc. also funded the editorial/layout support for this poster, which was provided by Miller Medical Communications.

For information about this clinical trial please follow the QR code

Presented at the 65th ASH Meeting, December 9–12, 2023, San Diego, CA, USA