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

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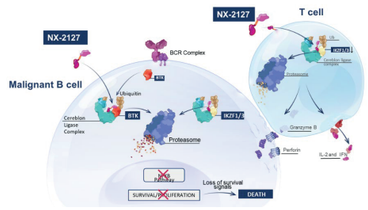
Background

- 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]

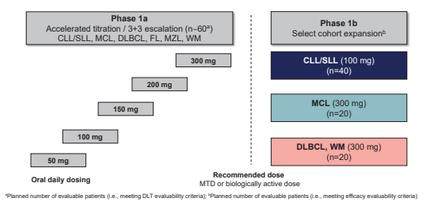
Figure 1. NX-2127 mechanism of action



- 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

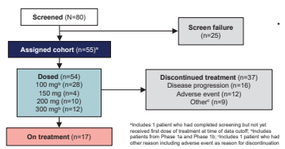
Figure 2. Trial design (ClinicalTrials.gov NCT04830137)



[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 screening but not yet received first dose of 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

- 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%)

Data cutoff: 15 Sep 2023

Results

Table 1. Baseline characteristics

Characteristics	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)

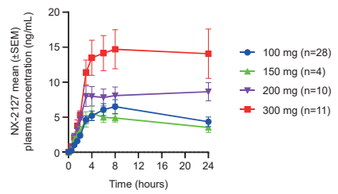
[a]Patients could have multiple prior treatments and BTK mutations; mutations were tested centrally at baseline by next-generation sequencing (allelic frequency ≥5% is reported); [b]*L845F, D334H, D1140N, T961M, S707F*

Data cutoff: 15 Sep 2023

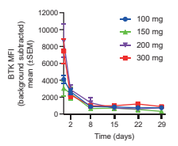
- Patient population was predominantly elderly with multiple prior lines of targeted therapies and acquired mutations associated with drug resistance (see Table 1).
- Median follow-up for the study was 9.7 (range 0.6–27.5) months.
- The most common reasons for treatment discontinuation were disease progression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

Figure 4. NX-2127 pharmacokinetics and proximal biomarker changes

A) NX-2127 Cycle 1 Day 1 plasma pharmacokinetics

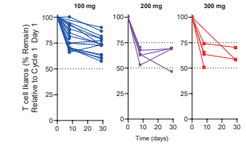


B) BTK[a] degradation in patients receiving NX-2127



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[c]	4

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



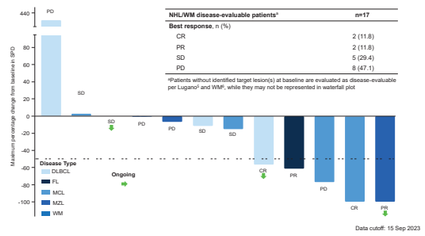
Dose (mg)	Number of patients per day		
	Day 1	Day 8	Day 29
100	23	19	16
200	5	5	4
300	5	4	3[c]

[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

Data cutoff: 15 Sep 2023

- 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)



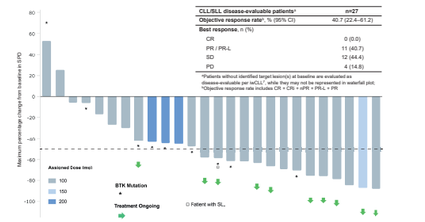
NHL/WM disease-evaluable patients[a]	n=17
Best response, n (%)	
CR	2 (11.8)
PR	2 (11.8)
SD	5 (29.4)
PD	8 (47.1)

[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

Data cutoff: 15 Sep 2023

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



CLL/SLL disease-evaluable patients[a]	n=27
Objective response rate[a], % (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 + CR-i + nPR + PR-L + PR

Data cutoff: 15 Sep 2023

- 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.

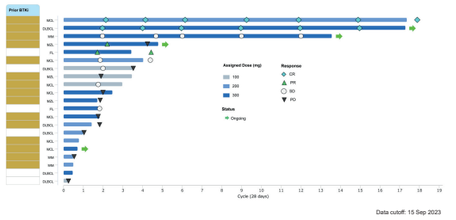
Table 2. Frequency of any grade TEAEs in ≥20% of patients, or grade ≥3 TEAEs or SAEs in >1 patient (N=54)

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 ascontusion; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [d]includes one grade 5 event; e[e]Aggregate of 'atrial fibrillation' and 'atrial flutter'; f[f]ncludes two grade 5 events

Data cutoff: 15 Sep 2023

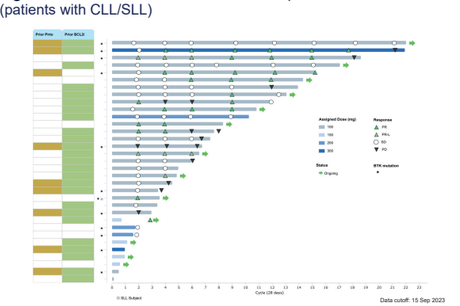
Figure 6. Duration of treatment and best response to NX-2127 (patients with NHL/WM)



Data cutoff: 15 Sep 2023

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



Data cutoff: 15 Sep 2023

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.

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