Proof of concept of NX-2127, a first-in-class Bruton's Tyrosine Kinase (BTK) dual-targeted protein degrader with immunomodulatory activity, in patients with DLBCL

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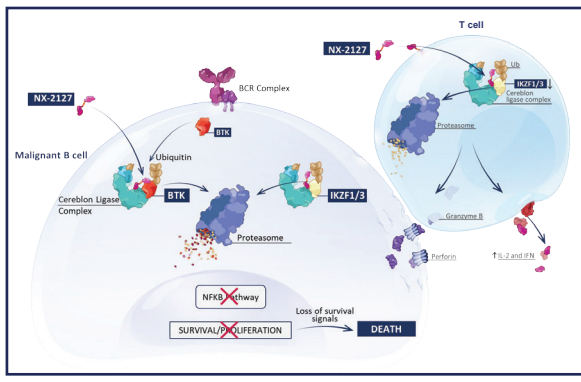
Relapsed diffuse large B cell lymphoma: A high unmet medical need

- Relapsed diffuse large B cell lymphoma (DLBCL) remains a high unmet medical need.
- Preclinical data suggest that drugs modulating E3 ligases may synergize with Bruton's tyrosine kinase (BTK) inhibition in certain subtypes of DLBCL.[1]
- Combination therapy with ibrutinib, lenalidomide and rituximab demonstrated clinical activity in recurrent DLBCL,[2] and ibrutinib + lenalidomide + R-CHOP was effective in *de novo* DLBCL.[3]
- NX-2127 is an oral, first-in-class, dual-function small molecule degrader that combines the activity of a targeted BTK degrader with the immunomodulatory activity of an Ikaros and Aiolos degrader (Figure 1).
- Preliminary safety of NX-2127 in all patients and efficacy in patients with chronic lymphocytic leukemia (CLL) have been presented.[4]
- In this poster, we report safety for all patients and preliminary efficacy in two patients with DLBCL from a phase 1 dose-escalation and cohort-expansion trial evaluating NX-2127 in adults with relapsed/refractory B cell malignancies.

NX-2127 dual mechanism of action:

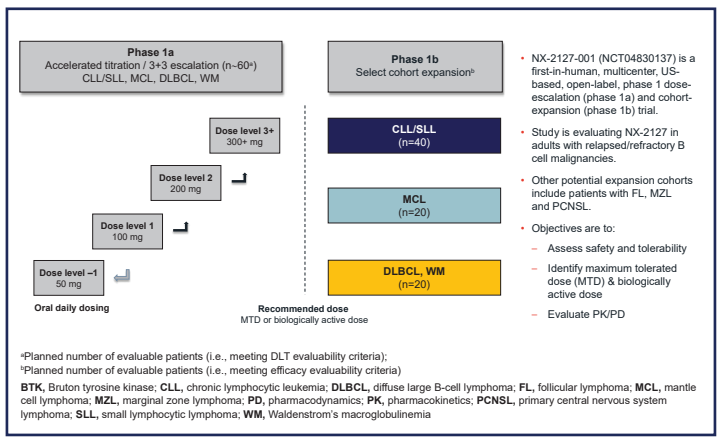
Targeted degradation of BTK and CRBN immunomodulatory substrates IKZF1/3



NX-2127 is a small molecule that has both BTK degradation activity and immunomodulatory-like neosubstrates degradation activity (IKZF1/3 proteins)

NX-2127 may exert superior anti-tumor activity when compared to classical BTK kinase inhibitors by eliminating BTK non-kinase function (e.g. scaffolding function)

NX-2127-001 phase 1a/b trial design



- NX-2127-001 (NCT04830137) is a first-in-human, multicenter, US-based, open-label, phase 1 dose-escalation (phase 1a) and cohort-expansion (phase 1b) trial.
- Study is evaluating NX-2127 in adults with relapsed/refractory B cell malignancies.
- Other potential expansion cohorts include patients with FL, MZL and PCNSL.
- Objectives are to:
  - Assess safety and tolerability
  - Identify maximum tolerated dose (MTD) & biologically active dose
  - Evaluate PK/PD

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

BTK, Bruton tyrosine kinase; **CLL,** chronic lymphocytic leukemia; **DLBCL,** diffuse large B-cell lymphoma; **FL,** follicular lymphoma; **MCL,** mantle cell lymphoma; **MZL,** marginal zone lymphoma; **PD,** pharmacodynamics; **PK,** pharmacokinetics; **PCNSL,** primary central nervous system lymphoma; **SLL,** small lymphocytic lymphoma; **WM,** Waldenstrom's macroglobulinemia

Baseline characteristics of all patients currently evaluable in the NX-2127-001 trial

- As of January 14, 2023, 37 patients (14 with non-Hodgkin's lymphoma [NHL], 23 with CLL) are currently evaluable.
- Patients were predominantly male (64.9%) with a median age of 75 (range 50–92) years and a median of 4 (range 2–11) prior lines of therapy.

Characteristics	Patients with NHL (n=14)	All patients (N=37)
Median age, years (range)	73 (50–92)	75 (50–92)
Female, n (%)	4 (28.6)	13 (35.1)
Male, n (%)	10 (71.4)	24 (64.9)
Median time since initial diagnosis, years (range)	4.7 (0.3–15.9)	9.4 (0.3–21.7)
Lines of prior therapy, median (range)	4 (2–11)	4 (2–11)
CAR-T, n (%)	2 (14.3)	3 (8.1)
Bispecific antibody, n (%)	2 (14.3)	2 (5.4)
Type of disease at study entry, n (%)		
CLL	N/A	23 (62.2)
DLBCL	5 (35.7)	5 (13.5)
MCL	4 (28.6)	4 (10.8)
WM	3 (21.4)	3 (8.1)
MZL	1 (7.1)	1 (2.7)
FL	1 (7.1)	1 (2.7)

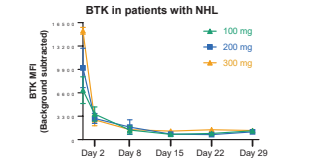
Two additional patients were dosed, but are not included in the total count of N=37 since their dosing information was not available at data cutoff.

N/A = not applicable

Data cutoff: January 14, 2023

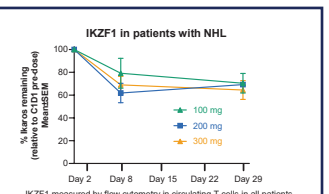
NX-2127 leads to BTK and IKZF1 degradation across dose levels in patients with NHL

- NX-2127 led to robust BTK degradation of >85% (89±2%) at Cycle 2 Day 1 across dose levels in patients with NHL.
- NX-2127 promoted IKZF1 degradation in all patients at all dose levels:
  - In humans, lenalidomide treatment was shown to achieve transient 46-63% Ikaros degradation in immune cells.[5]



BTK measured by flow cytometry in circulating B cells in all patients
Data normalized to each patient's baseline; Error bars represent mean±SEM

Dose (mg)	Day 2 (n)	Day 8 (n)	Day 15 (n)	Day 22 (n)	Day 29 (n)
100	4	3	2	3	3
200	6	5	6	3	3
300	2	2	2	1	1



IKZF1 measured by flow cytometry in circulating T cells in all patients
Data normalized to each patient's baseline IKZF1 levels (dashed line)
Error bars represent mean±SEM

Dose (mg)	Baseline (n)	Day 8 (n)	Day 29 (n)
100	3	3	3
200	3	3	2
300	2	2	2

BTK, Bruton's tyrosine kinase

Data cutoff: January 14, 2023

Most common all-grade treatment-emergent adverse events (TEAEs) in patients (N=37) evaluable in the NX-2127-001 trial

- The most common TEAEs were fatigue (51.4%), neutropenia (45.9%), and hypertension (32.4%).

Treatment-emergent AEs occurring in >15% of total population, n (%)	Any grade (N=37)	Grade 3+ (N=37)	SAE (N=37)
Fatigue	19 (51.4)	–	–
Neutropenia[a]	17 (45.9)	16 (43.2)	–
Hypertension	12 (32.4)	3 (8.1)	–
Constipation	9 (24.3)	–	–
Contusion[b]	9 (24.3)	–	1 (2.7)
Dyspnea	9 (24.3)	1 (2.7)	–
Thrombocytopenia[c]	9 (24.3)	3 (8.1)	–
Anemia	7 (18.9)	5 (13.5)	1 (2.7)
Diarrhea	7 (18.9)	–	–
Headache	7 (18.9)	–	–
Pruritis	7 (18.9)	–	–
Atrial fibrillation/Atrial flutter[d]	6 (16.2)	3 (8.1)	2 (5.4)
Confusional state	6 (16.2)	–	1 (2.7)
Nausea	6 (16.2)	–	–
Petechiae	6 (16.2)	–	–
Rash maculo-papular	6 (16.2)	–	–

[a]Aggregate of "neutropenia" and "neutrophil count decreased"; [b]Contusion includes episodes of bruising and other similar terms; [c]Aggregate of "thrombocytopenia" and "platelet count decreased"; [d]Cases were confounded by risk factors such as: previous BTKi, previous atrial fibrillation, pulmonary infection, hypertension, and age. Two additional patients were dosed, but are not included in the total count of N=37 since their dosing information was not available at data cutoff.

Data cutoff: January 14, 2023

NX-2127 safety summary in patients (n=14) with NHL (by dose)

- TEAEs were similar in patients with NHL to that previously reported in those with CLL.[4] The single dose-limiting toxicity of cognitive disturbance observed in a patient with CLL at the 300 mg dose was not observed in any patients with NHL.
- 10/14 (71.4%) patients have discontinued NX-2127 due to: progressive disease (n=5); adverse events (n=4); other (n=1).

Treatment-emergent AEs occurring in >15% of patients with NHL, n (%)	Total (N=14)	100 mg (n=4)	200 mg (n=6)	300 mg (n=4)
Fatigue	8 (57.1)	4 (100)	3 (50.0)	1 (25.0)
Neutropenia[a]	5 (35.7)	0	3 (50.0)	2 (50.0)
Hypertension	4 (28.6)	2 (50.0)	0	2 (50.0)
Atrial fibrillation/Atrial flutter[b]	3 (21.4)	1 (25.0)	1 (16.7)	1 (25.0)
Contusion[c]	3 (21.4)	0	1 (16.7)	2 (50.0)
Dyspnea	3 (21.4)	0	3 (33.3)	1 (25.0)
Headache	3 (21.4)	0	3 (33.3)	1 (25.0)
Rash maculo-papular	3 (21.4)	2 (50.0)	1 (16.7)	0

Other TEAEs occurring in 2 patients were: anemia, arthropod bite, blood creatinine increased, diarrhea, electrocardiogram QT prolonged, myalgia, oropharyngeal pain, palpitations, petechiae, pruritus, pyrexia, rash, thrombocytopenia.

[a]Aggregate of "neutropenia" and "neutrophil count decreased"; [b]Cases were confounded by risk factors such as: previous BTKi, previous atrial fibrillation, pulmonary infection, hypertension, and age; [c]Contusion includes episodes of bruising and other similar terms.

Data cutoff: January 14, 2023

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Patient cases

Patient case 1 (100 mg NX-2127)

Patient demographics

Age	Sex	Race	Tumor subtype	Stage	Time since diagnosis	Prior lines of anti-cancer therapy
77	Male	Asian	DLBCL (non-GCB)	IV	15.8 years	4

GCB: Germinal center B cell-like

Oncology history and prior anti-cancer therapies

Oncology history	• Mar 2006: DLBCL • Most recent progression/relapse date: Dec 2021
Prior anti-cancer therapy	• Aug 2007: R-CHOP • Apr 2009: cyclophosphamide + carmustine + etoposide • Aug 2012: rituximab • Dec 2017: obinutuzumab
NX-2127 treatment	• Jan 2022: NX-2127 (100 mg) • Outcome: patient experienced stable disease followed by progressive disease, stopping treatment at cycle 4

- This patient, who had received four prior lines of systemic therapy, experienced stable disease followed by progressive disease at the 100 mg dose of NX-2127.

Patient case 2 (300 mg NX-2127)

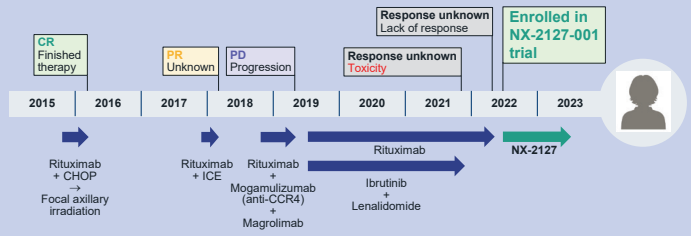
Patient demographics

Age	Sex	Race	Tumor subtype	Stage	Time since diagnosis	Prior lines of anti-cancer therapy
84	Female	White	DLBCL (non-GCB)	IV	6.5 years	4

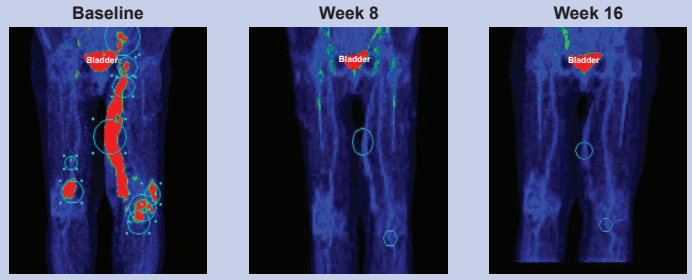
Oncology and medical history

Oncology history	• 2003: WM diagnosed on bone marrow biopsy • Nov 2015: DLBCL • MYD88 and CXCR4 mutated • Most recent progression/relapse date: Oct 2021
Relevant past medical history	• Hypogammaglobulinemia (Oct 2016) • Pseudomonas infection (Dec 2017) • Hepatitis B positive (Mar 2018) • Diastolic dysfunction (Mar 2019); Aspergillus sinus infection (Jul 2019)

Patient received 4 systemic lines of therapy for DLBCL prior to receiving NX-2127



FDG-PET CT scan disease assessment:
complete response at week 8/maintained at week 16 and at week 24 (not shown)



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Data cutoff: January 14, 2023

Summary/conclusion

- Early phase 1 data from this study of NX-2127, a first-in-class BTK degrader with immunomodulatory activity, demonstrates BTK degradation and clinically meaningful responses:
  - A safety profile that is consistent with previous reports for BTK-targeted therapies in heavily pretreated patients with B cell malignancies.
  - Sustained BTK degradation.
  - One patient with stage IV DLBCL and four prior lines of systemic therapy experienced stable disease followed by progressive disease at the 100 mg dose of NX-2127.
  - A second patient, also with four prior lines of systemic therapy for DLBCL, experienced a complete response response following 300 mg NX-2127 at the time of first response assessment (week 8); this response was maintained at week 16 and week 24.
- Overall, the findings from this first-in-human, first-in-class study of a BTK degrader, indicate that NX-2127 was well tolerated and showed promising activity in a patient with DLBCL.
- Current phase 1b cohorts include patients with CLL/SLL, MCL, and DLBCL/WM. Other potential expansion cohorts include patients with FL, MZL and PCNSL.

References

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