

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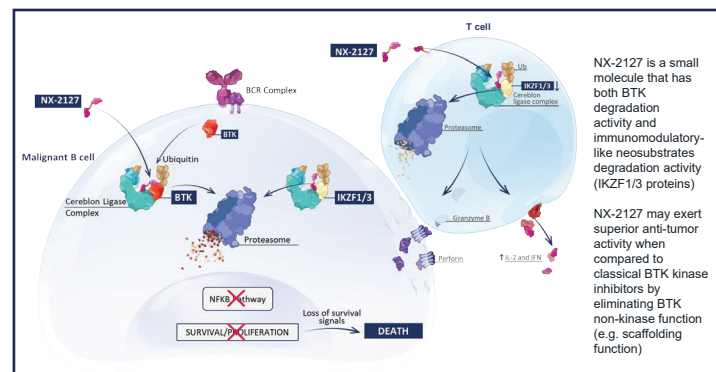
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## Relapsed diffuse large B cell lymphoma: A high unmet medical need

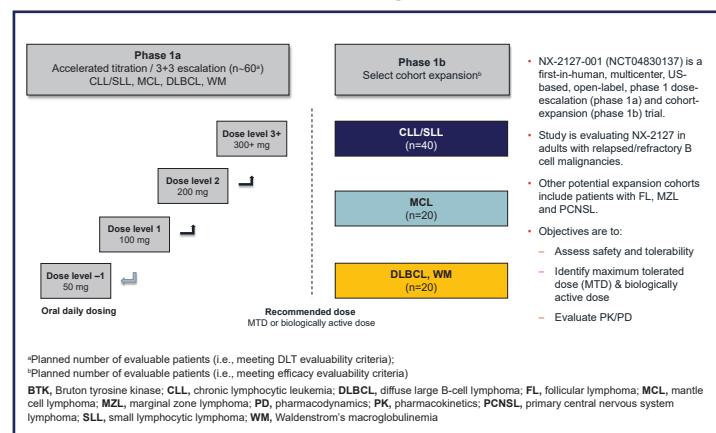
- Relapsed diffuse large B cell lymphoma (DLBCL) remains a high unmet medical need.
- Preclinical data suggest that drugs modulating E3 ligases may synergize with Bruton's tyrosine kinase (BTK) inhibition in certain subtypes of DLBCL.<sup>1</sup>
- Combination therapy with ibrutinib, lenalidomide and rituximab demonstrated clinical activity in recurrent DLBCL,<sup>2</sup> and ibrutinib + lenalidomide + R-CHOP was effective in *de novo* DLBCL.<sup>3</sup>
- 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.<sup>4</sup>
- 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-2127-001 phase 1a/b trial design



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

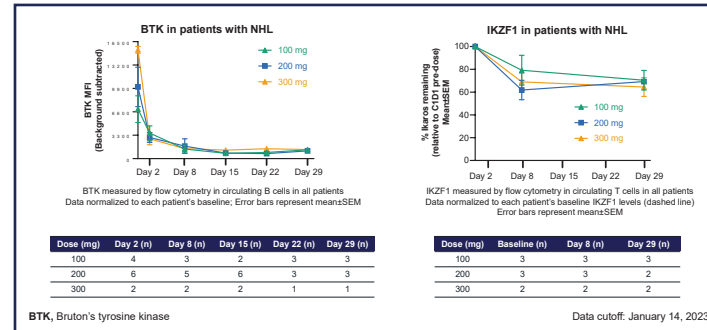
- As of January 14, 2023, 37 patients (14 with non-Hodgkin's lymphoma [NHL], 23 with CLL) are currently evaluable.
- Patients were predominantly male (64.9%) with a median age of 75 (range 50–92) years and a median of 4 (range 2–11) prior lines of therapy.

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. Data cutoff: January 14, 2023  
N/A = not applicable

## 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.<sup>5</sup>



## 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 <sup>a</sup>	17 (45.9)	16 (43.2)	–
Hypertension	12 (32.4)	3 (8.1)	–
Constipation	9 (24.3)	–	–
Contusion <sup>b</sup>	9 (24.3)	–	1 (2.7)
Dyspnea	9 (24.3)	1 (2.7)	–
Thrombocytopenia <sup>c</sup>	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 <sup>d</sup>	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)	–	–

<sup>a</sup>Aggregate of "neutropenia" and "neutrophil count decreased"; <sup>b</sup>Contusion includes episodes of bruising and other similar terms; <sup>c</sup>Aggregate of "thrombocytopenia" and "platelet count decreased"; <sup>d</sup>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.<sup>4</sup> 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 <sup>a</sup>	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 <sup>b</sup>	3 (21.4)	1 (25.0)	1 (16.7)	1 (25.0)
Contusion <sup>c</sup>	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, pruritis, pyrexia, rash, thrombocytopenia.  
<sup>a</sup>Aggregate of "neutropenia" and "neutrophil count decreased"; <sup>b</sup>Cases were confounded by risk factors such as: previous BTKI, previous atrial fibrillation, pulmonary infection, hypertension, and age; <sup>c</sup>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	
<b>Oncology history</b>	<ul style="list-style-type: none"> <li>Mar 2006: DLBCL</li> <li>Most recent progression/relapse date: Dec 2021</li> </ul>
<b>Prior anti-cancer therapy</b>	<ul style="list-style-type: none"> <li>Aug 2007: R-CHOP</li> <li>Apr 2009: cyclophosphamide + carbimustine + etoposide</li> <li>Aug 2012: rituximab</li> <li>Dec 2017: obinutuzumab</li> </ul>
<b>NX-2127 treatment</b>	<ul style="list-style-type: none"> <li>Jan 2022: NX-2127 (100 mg)</li> <li>Outcome: patient experienced stable disease followed by progressive disease, stopping treatment at cycle 4</li> </ul>

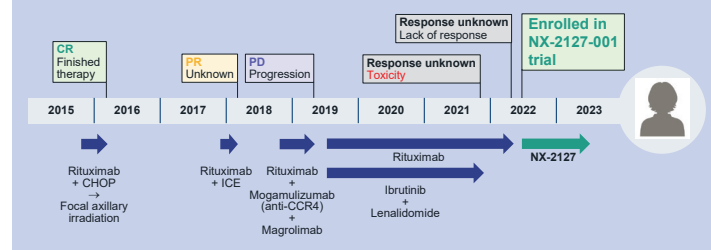
- This patient, who had received four prior lines of systemic therapy, experienced stable disease followed by progressive disease at the 100 mg dose of NX-2127.

### Patient case 2 (300 mg NX-2127)

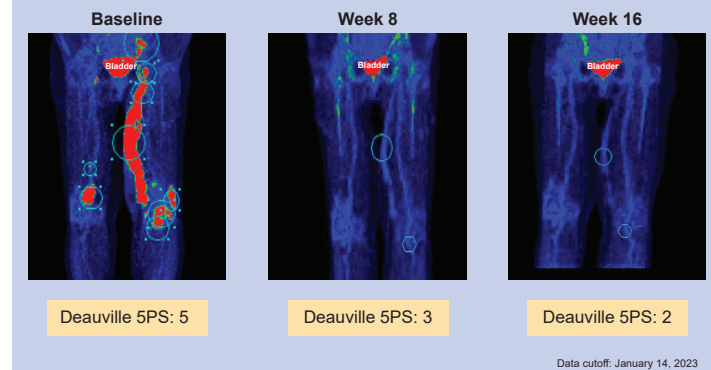
Patient demographics						
Age	Sex	Race	Tumor subtype	Stage	Time since diagnosis	Prior lines of anti-cancer therapy
84	Female	White	DLBCL (non-GCB)	IV	6.5 years	4

Oncology and medical history	
<b>Oncology history</b>	<ul style="list-style-type: none"> <li>2003: WM diagnosed on bone marrow biopsy</li> <li>Nov 2015: DLBCL</li> <li>MYD88 and CXCR4 mutated</li> <li>Most recent progression/relapse date: Oct 2021</li> </ul>
<b>Relevant past medical history</b>	<ul style="list-style-type: none"> <li>Hypogammaglobulinemia (Oct 2016)</li> <li>Pseudomonas infection (Dec 2017)</li> <li>Hepatitis B positive (Mar 2018)</li> <li>Diastolic dysfunction (Mar 2019); Aspergillus sinus infection (Jul 2019)</li> </ul>

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)



## 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 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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