Leader in Targeted Protein Modulation

Findings From the First-in-Human Phase 1 Trials of NX-2127 and NX-5948, Bruton's Tyrosine Kinase (BTK) Degraders, in Patients with Relapsed/Refractory B-Cell Malignancies

Paula O'Connor, MD
EVP, Head of Clinical Development

4th Targeted Protein Degradation Summit Europe
London, UK
March 21, 2024

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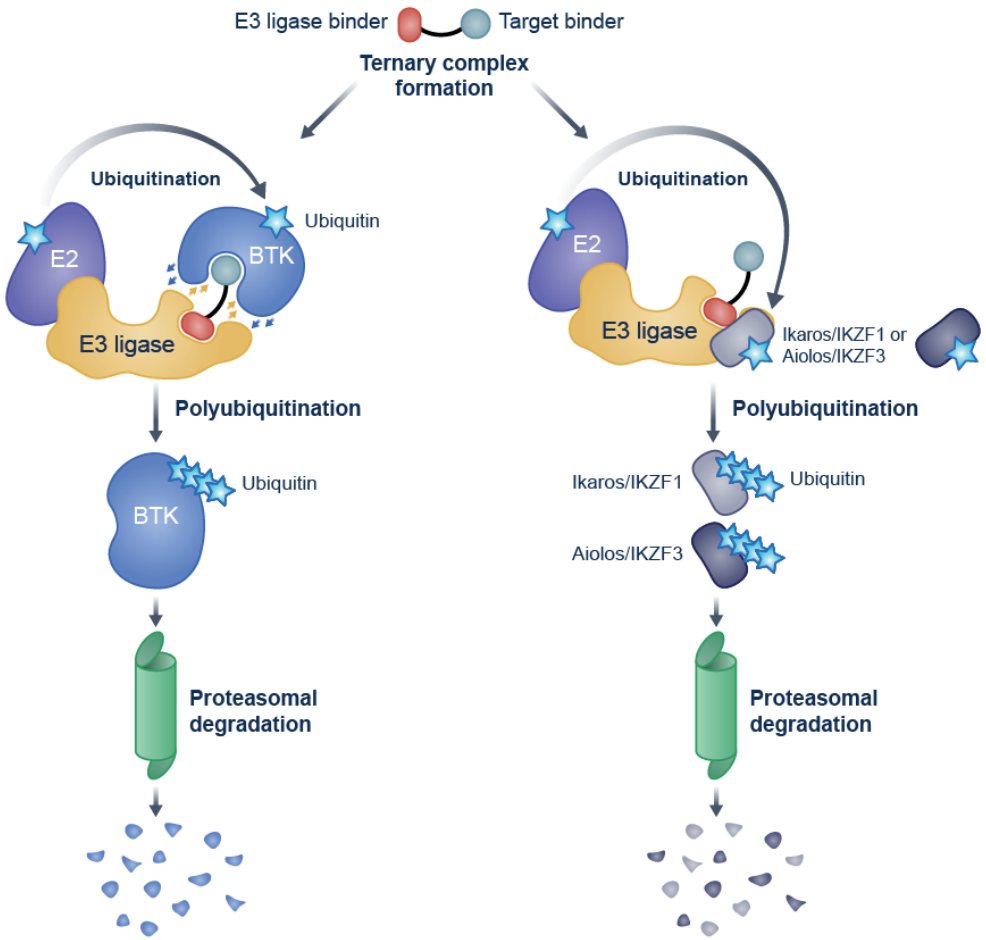
Nurix Degraders NX-2127 and NX-5948

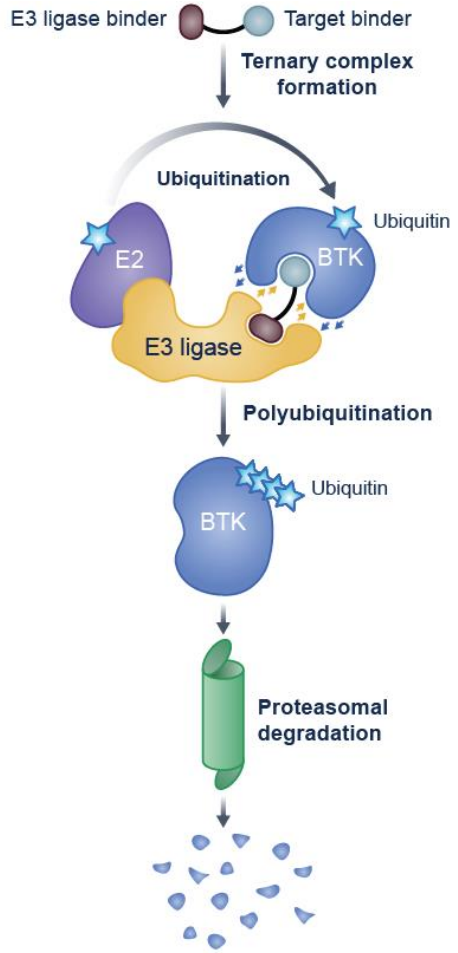
Utilize the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in B-cell malignancies

NX-2127 MOA



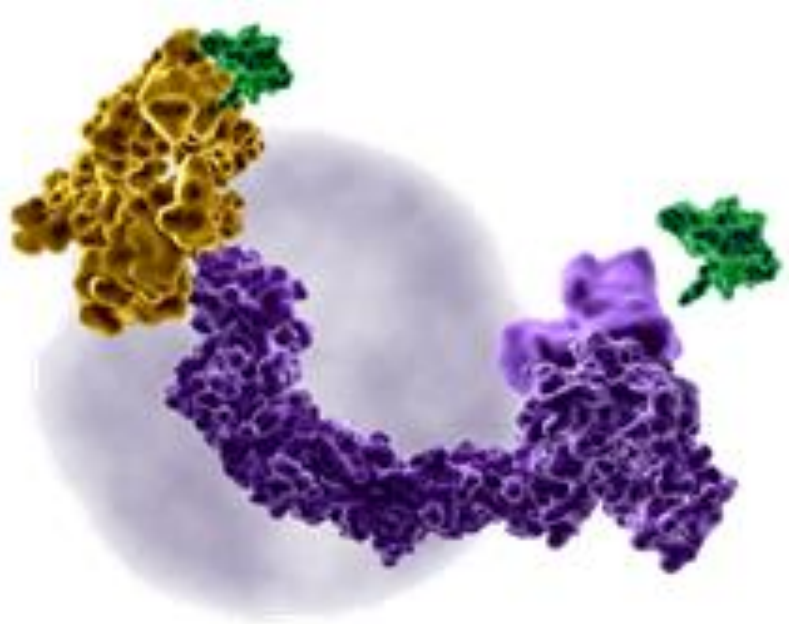
Results in tumor inhibition

NX-5948 MOA



Results in tumor inhibition

Why Do We Need BTK Degraders?



BTK degraders can overcome treatment emergent resistance mutations

BTK degraders eliminate BTK scaffolding function

BTK degraders may be useful in other B-cell malignancies and autoimmune diseases

BTK degraders have the potential to displace inhibitors

Proof of Concept for BTK Degradation with NX-2127 in CLL Patients with Wild Type (WT) and Mutated *BTK*

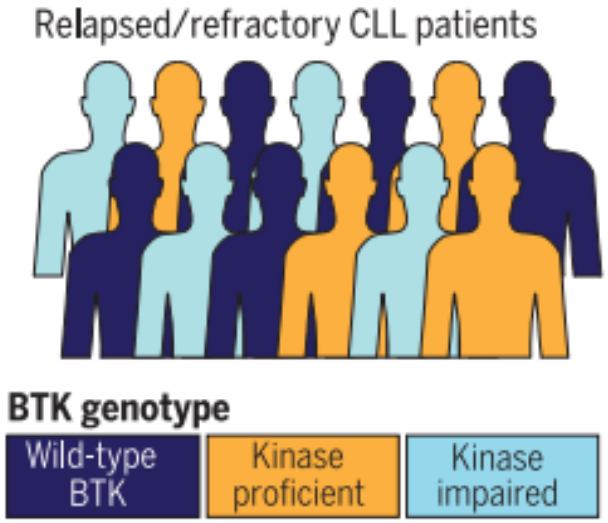
Science
AAAS

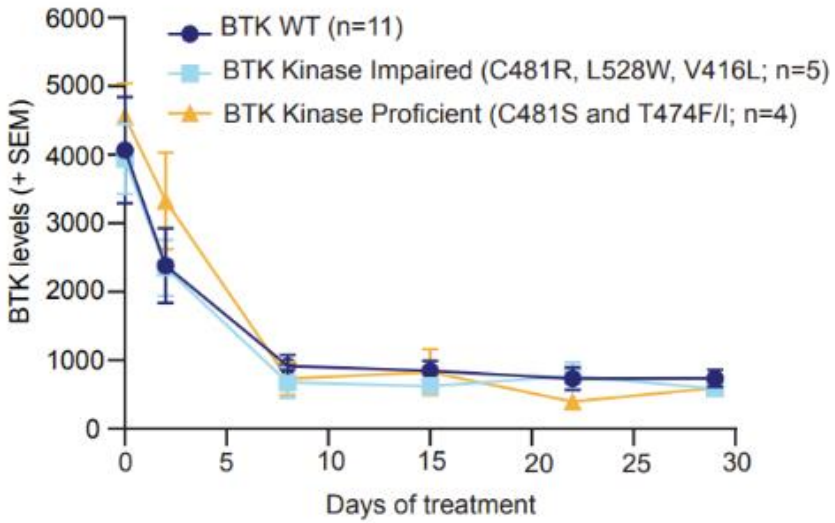
RESEARCH ARTICLE

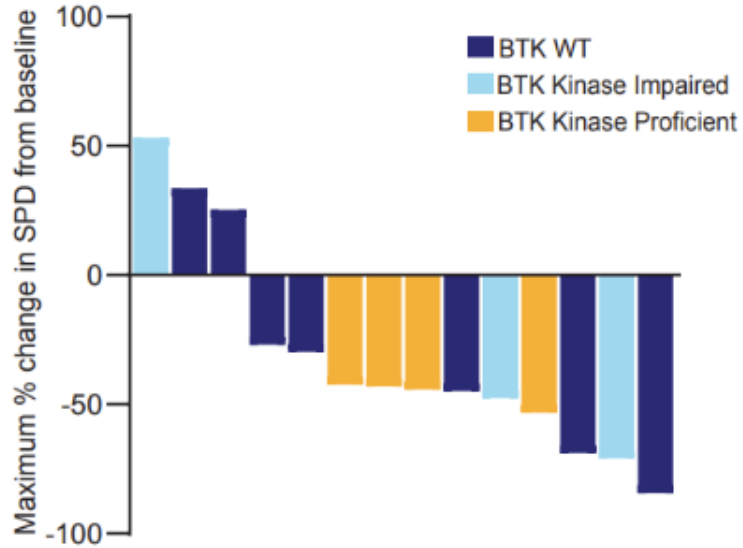
DRUG DEVELOPMENT

Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127

Montoya *et al.*, Science 383, 496 (2024)



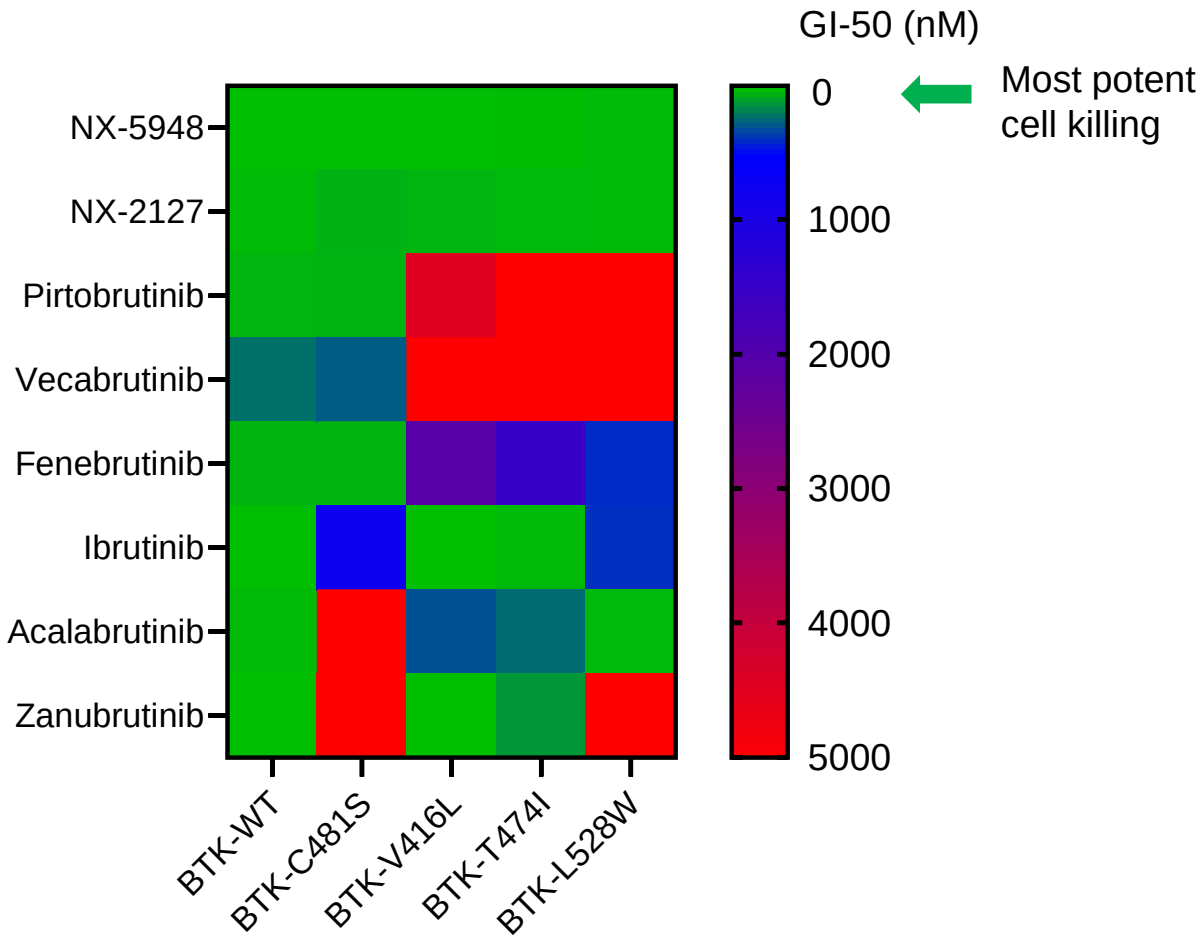




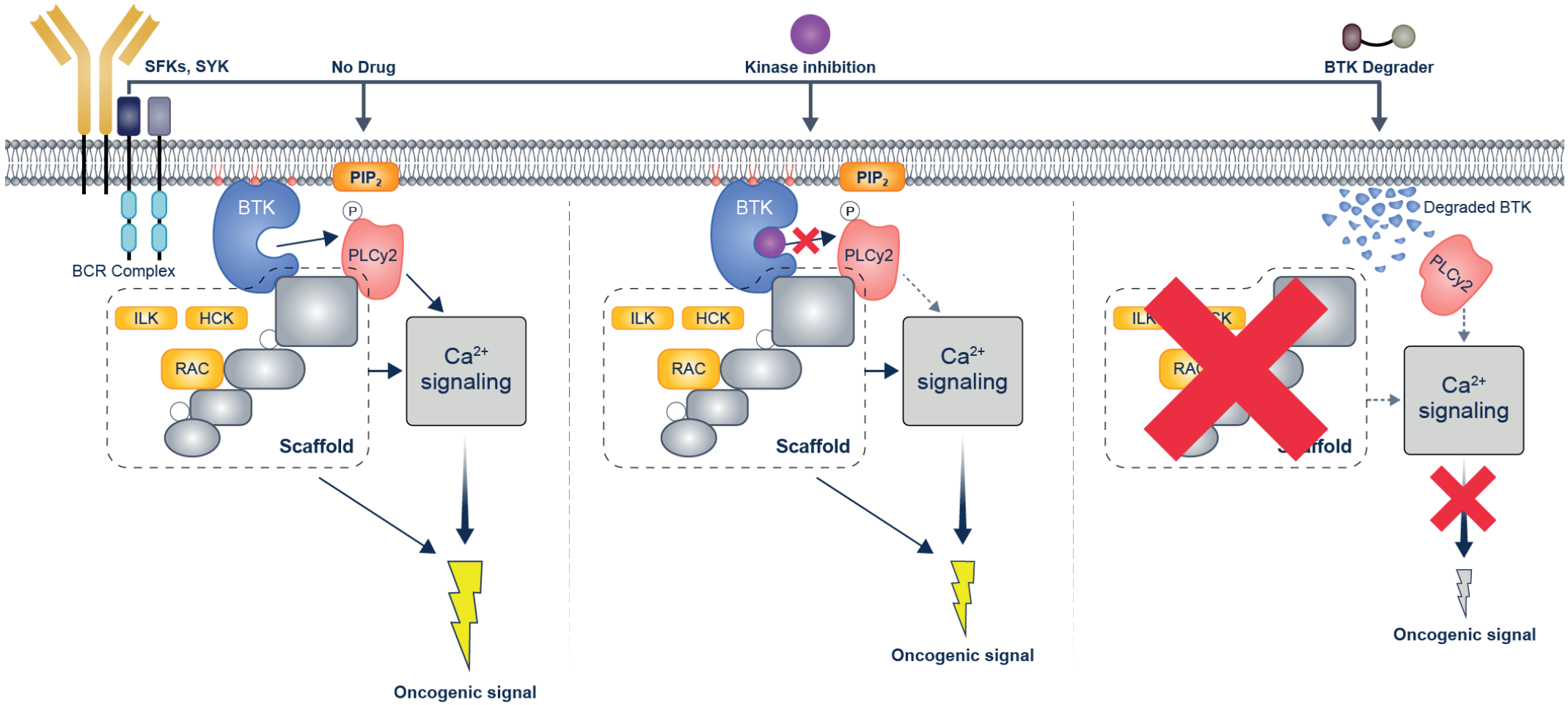
NX-5948 Is More Potent and Broadly Active Than All BTK Inhibitors Tested

- All inhibitors have resistance mutation liabilities
- NX-5948 displays potent cell killing in the context of key resistance mutations
- We have shown that BTK degradation translates into clinical responses across mutation classes

NX-5948 demonstrates broad preclinical activity



BTK Degraders Disrupt BCR Signaling by Removing the Protein and All of Its Functions

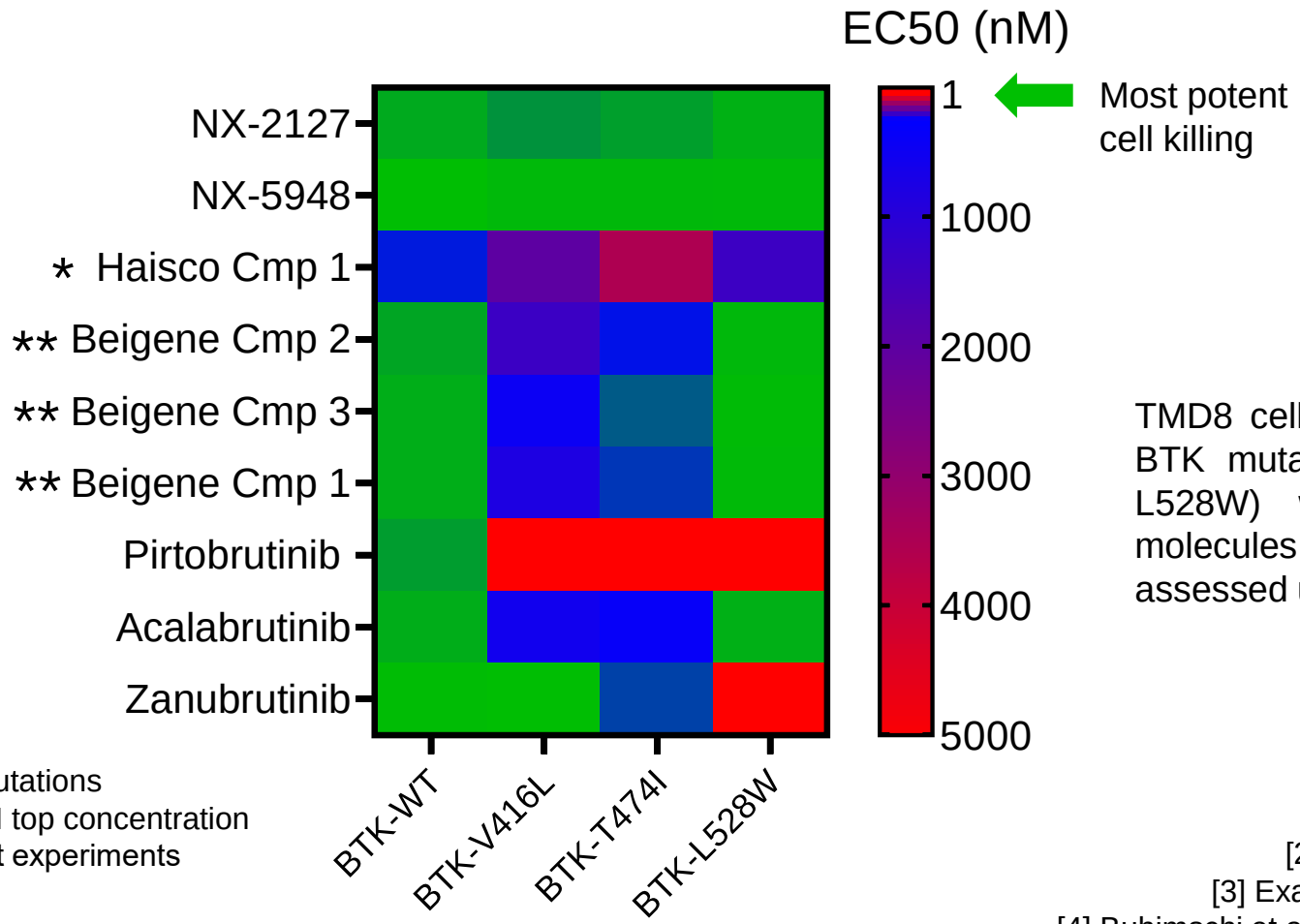


References

1. Montoya et al. Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127. Science. 2024; 383
2. Eisen et al. Conditional Requirement for Dimerization of the Membrane-Binding Module of BTK. BioRxiv. January 17, 2024
3. Yuan et al. BTK kinase activity is dispensable for the survival of diffuse large B-cell lymphoma. J Biol Chem. 2022; 298 (11):102555

Not All BTK Degraders Are Created Equal

NX-5948 and NX-2127 Comparative Efficacy (TMD8 DLBCL Line)



TMD8 cells harboring WT BTK or knock-in BTK mutations (C481S, V416L, T474I, or L528W) were incubated with degrader molecules for 72 hours, and viability was assessed using CellTiter-Glo 2.0 (Promega)

TMD8 cells with knock-in mutations
72-hour time point, 5000 nM top concentration
Average of n≥4 independent experiments

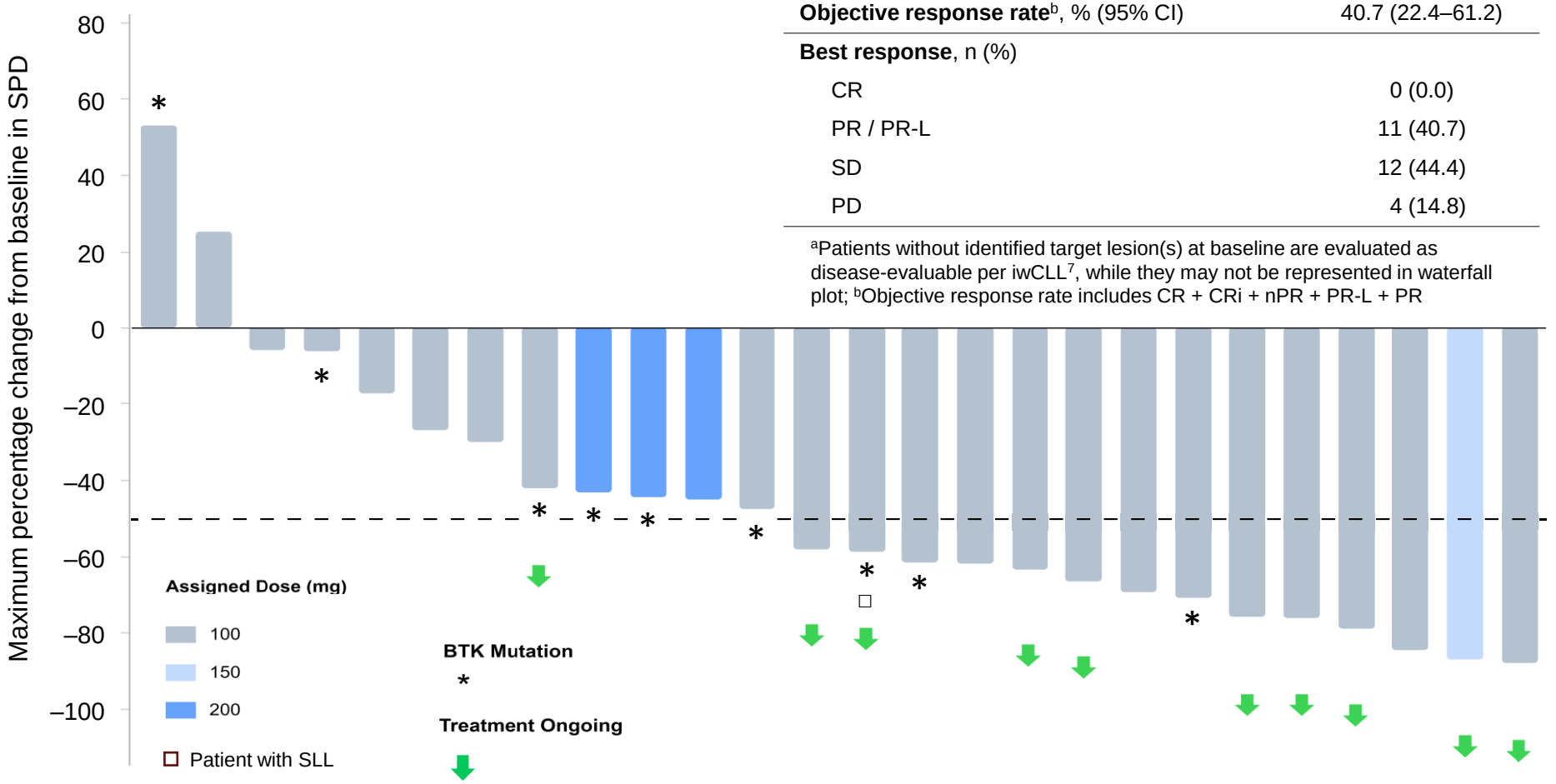
[2] Example 1. WO 2022/111449 (Haisco)
[3] Examples 1-3. WO 2021/219071 (BeiGene)
[4] Buhimschi et al. 2018. Biochemistry 57(26): 3564-3575
[5] Dobrovolsky et al. 2019. Blood 133(9): 952-961

Proof of Concept for BTK Degradation with NX-2127: Update ASH 2023

Significant lymph node reduction and objective response rate

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



CI, confidence interval; **CLL**, chronic lymphocytic leukemia; **CR**, complete response; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **SLL**, small lymphocytic leukemia; **SPD**, sum of product diameters

NX-2127 Safety Summary: Frequency of Any Grade TEAEs in ≥20% of Patients, or Grade ≥3 TEAEs or SAEs in >1 Patient (n=54)

TEAEs, n (%)	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

nurix

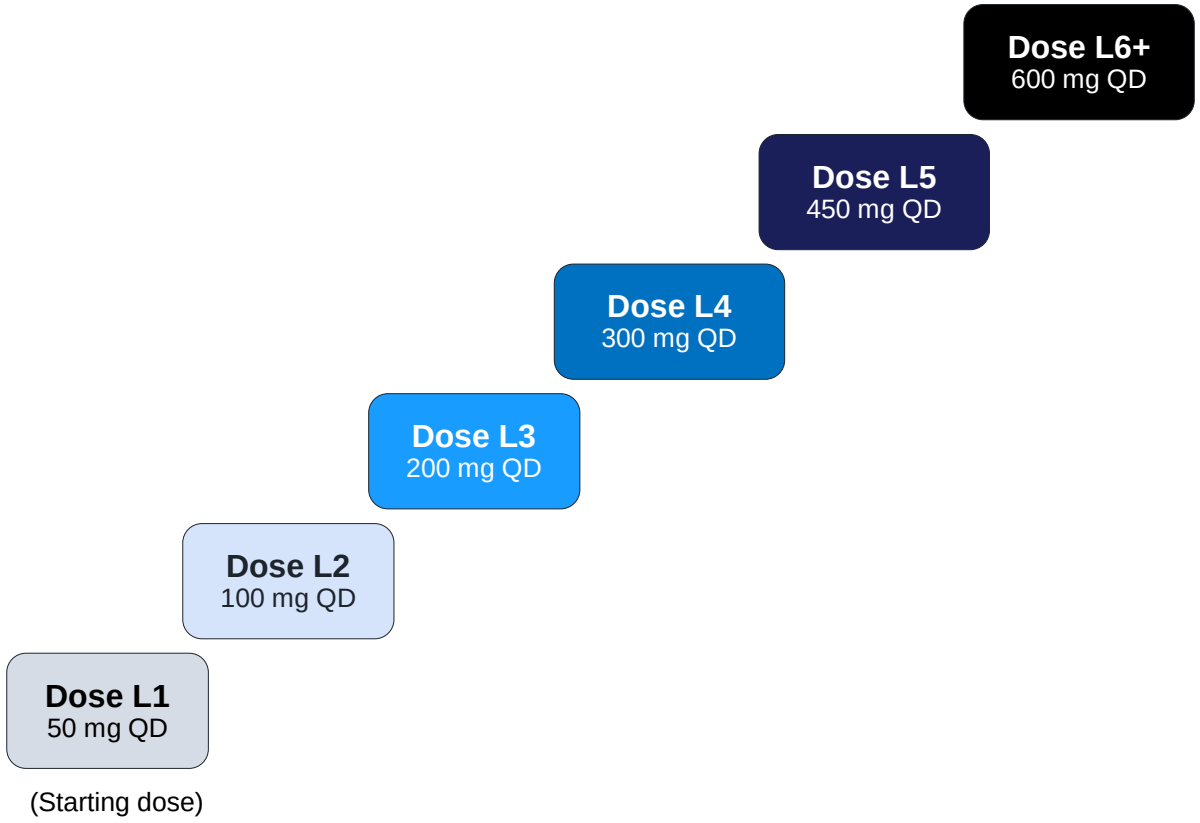
2 DLTs have been reported: cognitive disturbance (300 mg DL) and neutropenia (300 mg DL)

Data cutoff: 15 Sep 2023

NX-5948-301: Trial Design

Phase 1a/b trial in adults with relapsed/refractory B-cell malignancies

Phase 1a dose escalation
B-cell malignancies, including CLL (N = up to 66 patients)



Potential Phase 1b dose expansion
(N = up to 160 patients)

CLL/SLL dose level A Prior BTKi and BCL-2i	**CLL/SLL dose level B** Prior BTKi and BCL-2i

MCL[a]
Prior BTKi and anti-CD20 CIT

MZL[a]
Prior anti-CD20 CIT and ≥2 prior LoT

WM[a]
Prior BTKi and ≥2 prior LoT

DLBCL[a,b]
Prior anthracycline, anti-CD20 CIT + 1 LoT[c]

FL
Prior anti-CD20 CIT + 1 LoT[c]

PCNSL/SCNSL
Who have progressed or had no response to ≥2 prior LoT

[a]Includes patients with secondary CNS involvement; [b]Subtypes include: transformed indolent lymphoma (e.g., grade 3b/transformed FL), Richter-transformed DLBCL, high-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangements, high-grade B-cell lymphomas NOS; [c]Additional lines of therapy include anthracycline for non-GCB DLBCL and BTKi for MCL

NX-5948-301 Baseline Demographics/Disease Characteristics

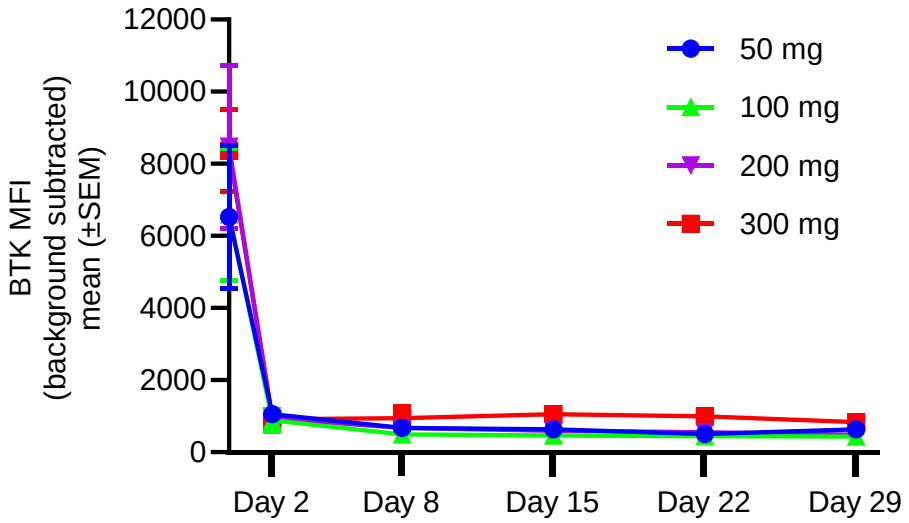
Characteristics	Patients with CLL (n=7)	Patients with NHL/WM (n=19)	Overall population (N=26)
Median age, years (range)	64.0 (53–75)	63.0 (42–79)	63.5 (42–79)
Male, n (%)	5 (71.4)	13 (68.4)	18 (69.2)
Female, n (%)	2 (28.6)	6 (31.6)	8 (30.8)
ECOG PS, n (%)			
0	1 (14.3)	5 (26.3)	6 (23.1)
1	6 (85.7)	14 (73.7)	20 (76.9)
Previous targeted treatments[a], n (%)			
BTKi	7 (100.0)	10 (52.6)	17 (65.4)
Pirtobrutinib	1 (14.3)	2 (10.5)	3 (11.5)
BCL2i	6 (85.7)	3 (15.8)	9 (34.6)
BTKi and BCL2i	6 (85.7)	3 (15.8)	9 (34.6)
CAR-T therapy	0 (0.0)	7 (36.8)	7 (26.9)
Bispecific antibody	0 (0.0)	5 (26.3)	5 (19.2)
PI3Ki	2 (28.6)	2 (10.5)	4 (15.4)
Median prior lines of therapy (range)	3.0 (2–5)	5.0 (2–10)	4.0 (2–10)
Mutation status[b], n (%)	n=6	n=15	n=21
BTK (T474)	1 (16.7)	0 (0.0)	1 (4.8)
PLCG1/2[c]	2 (33.3)	2 (13.3)	4 (19.0)
TP53	2 (33.3)	3 (20.0)	5 (23.8)
BCL2 (G101V and R107-R110dup)	2 (33.3)	0 (0.0)	2 (9.5)

[a]Patients could have received multiple prior treatments; [b]Patients could have multiple mutations, which were tested at baseline by central NGS (≥5% allelic frequency is reported); [c]*PLCG1 (A902V); PLCG2 (K35R, V886A, V105I)*

Data cutoff: 17 Oct 2023

NX-5948 Treatment Produces Rapid, Robust and Sustained BTK Degradation in Patients with B-cell Malignancies

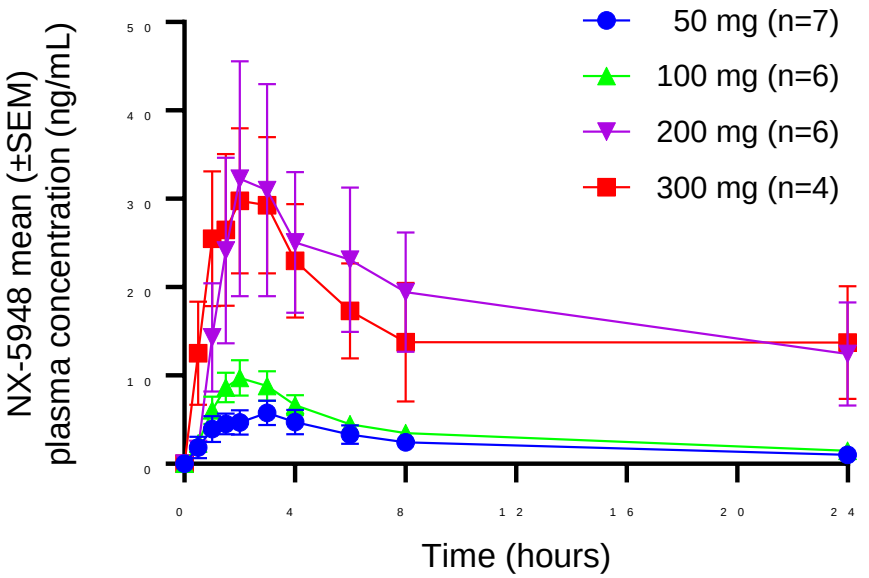
BTK[a] degradation in patients receiving NX-5948



Dose (mg)	Number of patients per day					
	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29
50	7	7	7	6	5	6
100	6	6	5	6	6	5
200	6	6	6	6	4	3
300	4	4	4	4	4	2

[a]BTK measured in patient B-cells whole blood using flow cytometry assay

NX-5948 C1D1 pharmacokinetics



Robust BTK degradation seen across all exposure levels

BTK, Bruton's tyrosine kinase; **MFI,** mean fluorescence intensity; **SEM**, standard error of the mean

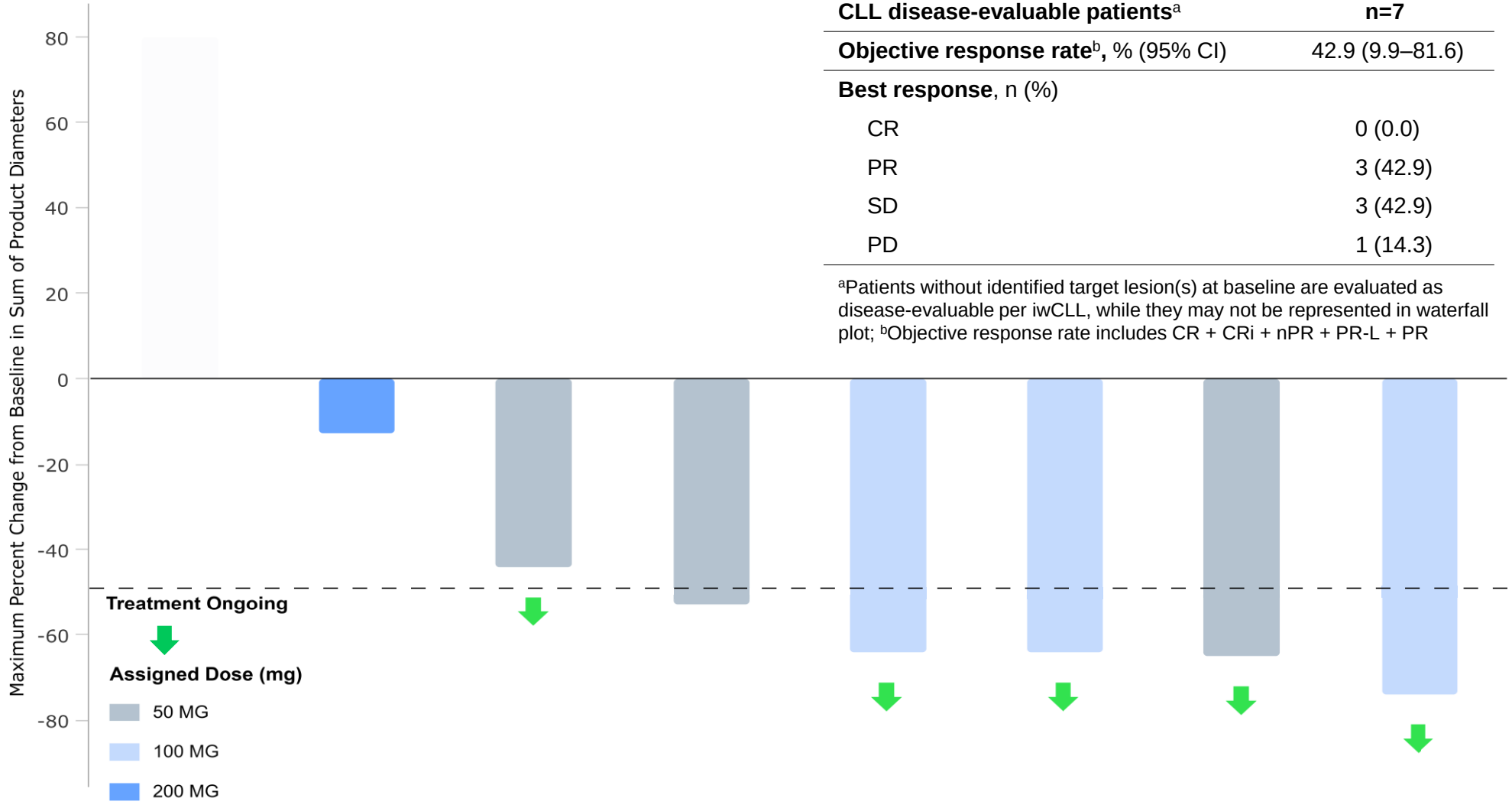
NX-5948 Safety Summary: Frequency of Any Grade TEAEs in ≥15% of Patients or Grade ≥3 TEAEs in >1 Patient or SAEs in >1 Patient (N=26)

TEAEs, n (%)	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	12 (46.2)	–	–
Thrombocytopenia[b]	10 (38.5)	2 (7.7)	–
Neutropenia[c]	8 (30.8)	5 (19.2)	–
Anemia	6 (23.1)	1 (3.8)	–
Cough	5 (19.2)	–	–
Headache	5 (19.2)	–	–
Nausea	5 (19.2)	–	–
Rash	4 (15.4)	–	–
COVID-19	3 (11.5)	2 (7.7)	2 (7.7)
Pneumonia	2 (7.7)	2 (7.7)	2 (7.7)

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

No DLTs and no TEAEs resulting in drug discontinuation
Four NX-5948-related grade ≥3 TEAEs (3 neutropenia, 1 thrombocytopenia); no related serious adverse events;
No atrial fibrillation/flutter or hypertension

Lymph Node Reduction and Overall Response Rate in Patients With CLL Enrolled in the NX-5948-301 Clinical Trial

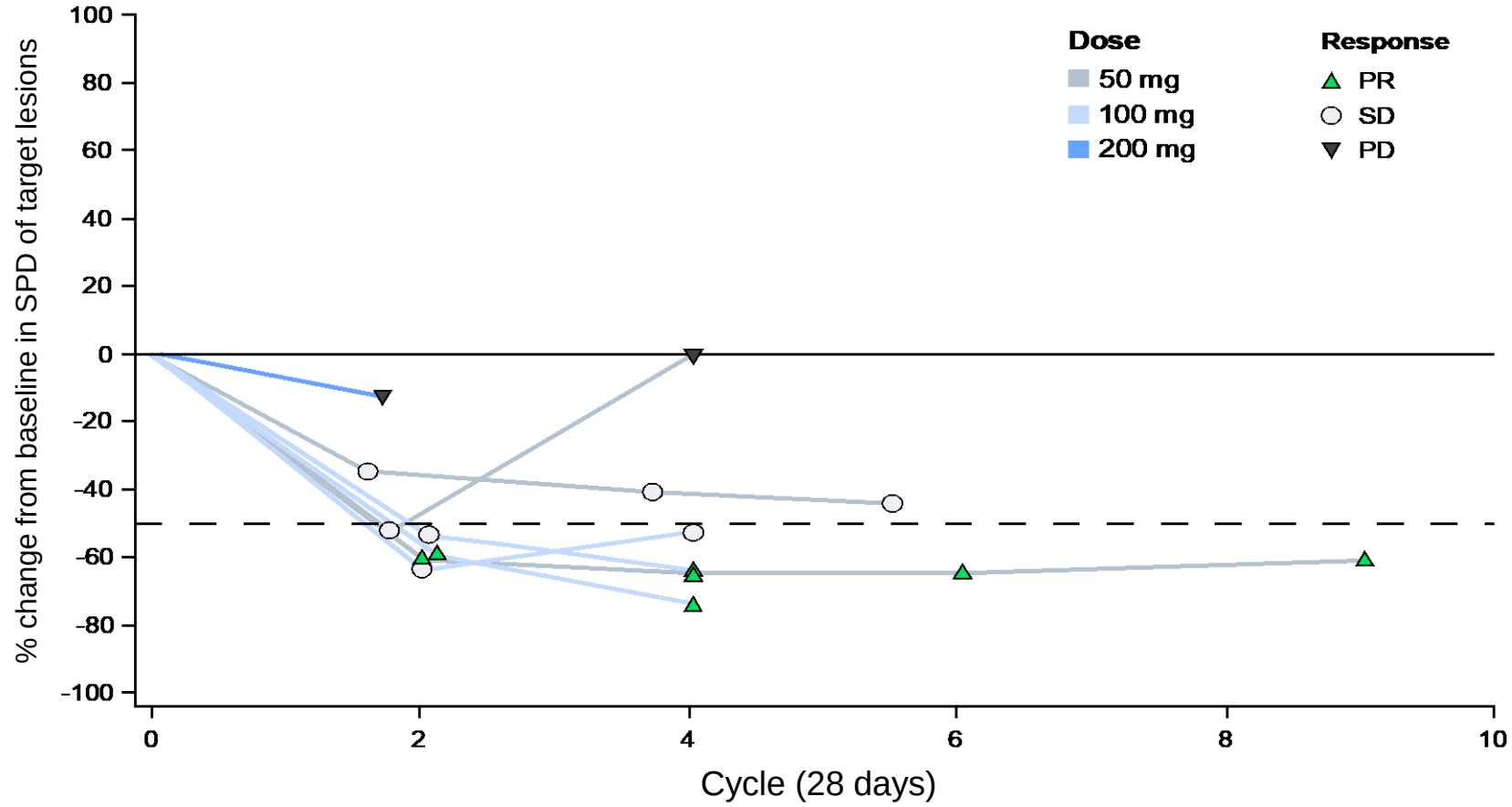


CLL disease-evaluable patients[a]	**n=7**
Objective response rate[b]**,** % (95% CI)	42.9 (9.9–81.6)
Best response, n (%)	
CR	0 (0.0)
PR	3 (42.9)
SD	3 (42.9)
PD	1 (14.3)

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

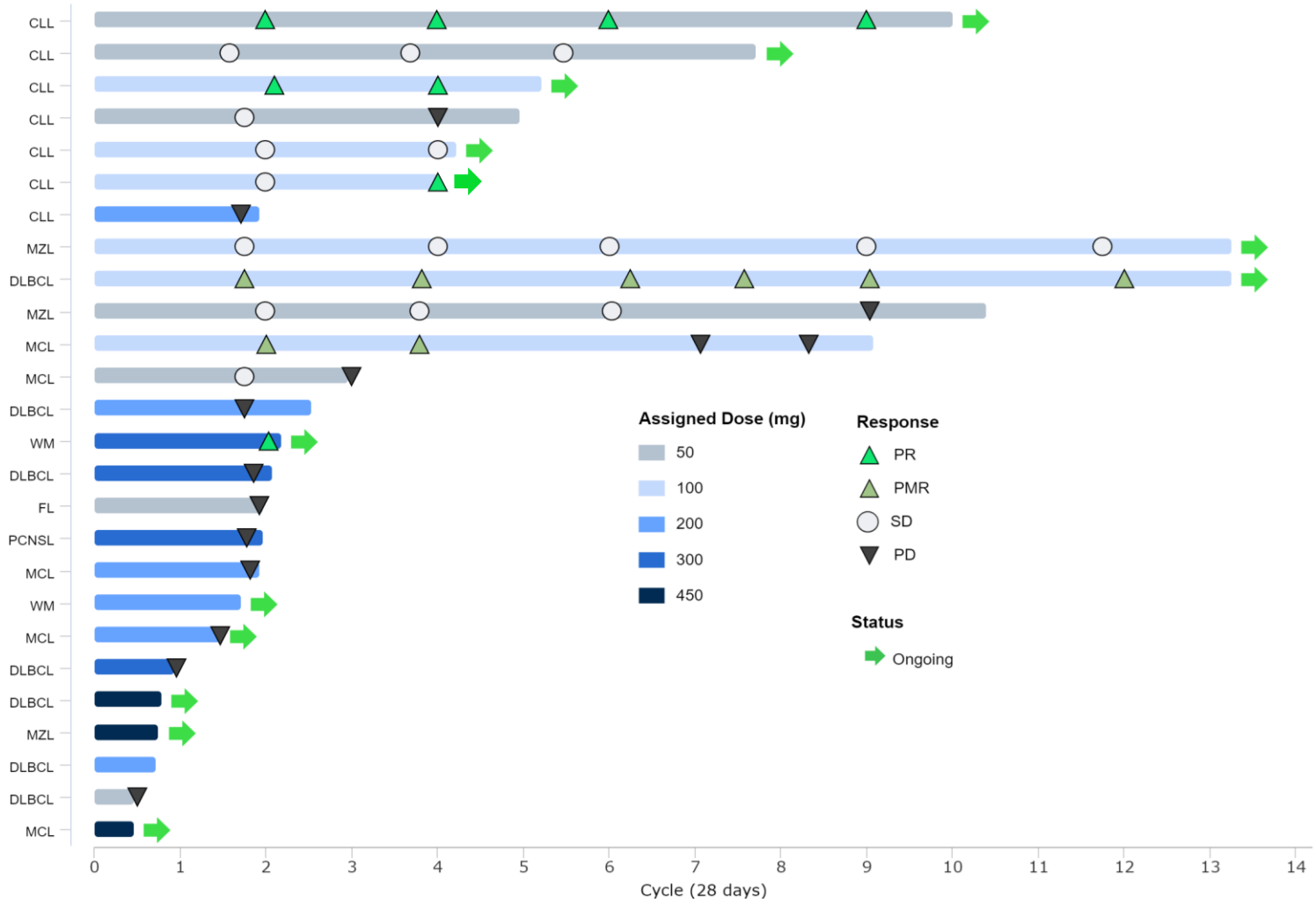
Change in Tumor Size (Patients with CLL) Enrolled in NX-5948-301

Lymph node reduction and responses seen as early as 8 weeks on therapy



An initial decrease in lymph node size (sum of the perpendicular diameters) was observed in all patients regardless of best clinical response, with the majority demonstrating a continued decrease over time

Duration of Treatment and Best Response to NX-5948 (all patients)



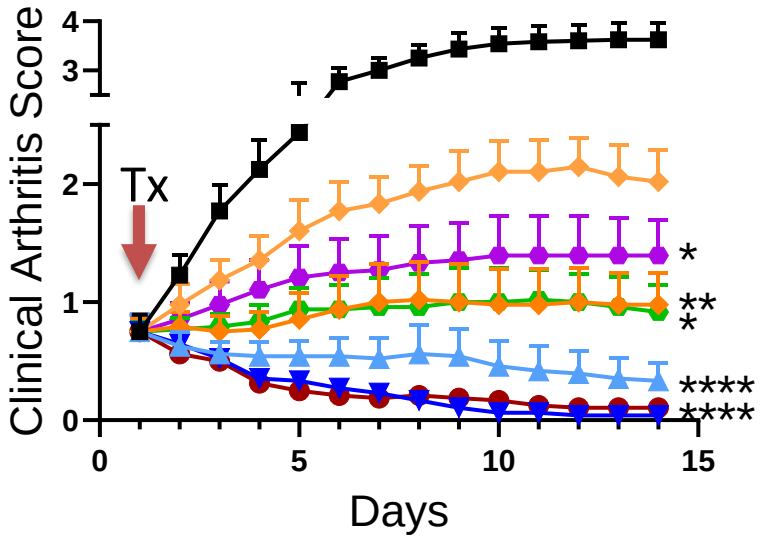
CLL, chronic lymphocytic leukemia; **NHL**, non-Hodgkin's lymphoma; **PD**, progressive disease; **PR**, partial response; **PMR**, partial metabolic response; **SD**, stable disease

Activity across multiple disease types may reflect scaffolding activity

Data cutoff: 17 Oct 2023

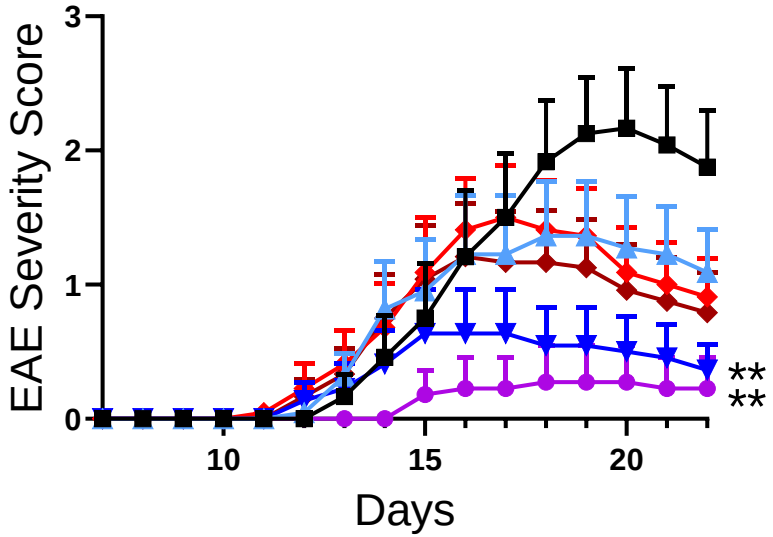
Beyond Hematology/Oncology: NX-5948 Is Highly Effective in Models of Rheumatoid Arthritis and Multiple Sclerosis

Rheumatoid Arthritis Model



- Vehicle
- Rilzabrutinib 10 mg/kg
- Rilzabrutinib 30 mg/kg
- Enbrel 10 mg/kg
- Tofacitinib 30 mg/kg BID
- Ibrutinib 30 mg/kg
- NX-5948 10 mg/kg
- NX-5948 30 mg/kg

Multiple Sclerosis Model



- Vehicle
- Ibrutinib 10 mg/kg
- Ibrutinib 30 mg/kg
- NX-5948 10 mg/kg
- NX-5948 30 mg/kg
- FTY720 3 mg/kg

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001 compared with vehicle control

Source: Rountree et al., 3rd B&T-cell Summit 2022

Conclusions

- NX-2127 and NX-5948 have demonstrated clinical activity in patients with B-cell malignancies including CLL and NHL:
  - PK exposure resulted in rapid, robust, and sustained BTK degradation
  - Sustained disease control including partial and complete responses was seen in patients who relapsed after BTK inhibitor therapies and had *BTK* mutations
  - Tolerable, albeit different, safety profiles were observed
- The NX-5948-301 study is actively enrolling patients in the US, UK and the Netherlands. Additional data with higher dose levels and longer treatment duration are expected later in 2024
- In 2024, Nurix will complete preclinical studies to enable an investigational new drug (IND) application for NX-5948 in autoimmune indications