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UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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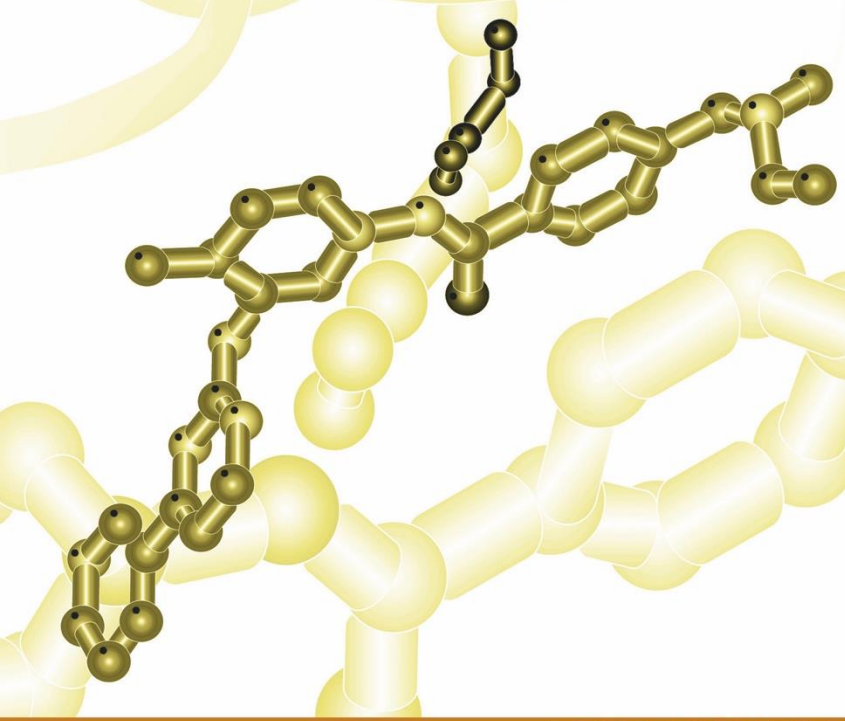


# New Drugs in Hematology

**President:** Pier Luigi Zinzani
**Co-President:** Michele Cavo

**Bologna,**
**Royal Hotel Carlton**
**January 15-17, 2024**

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

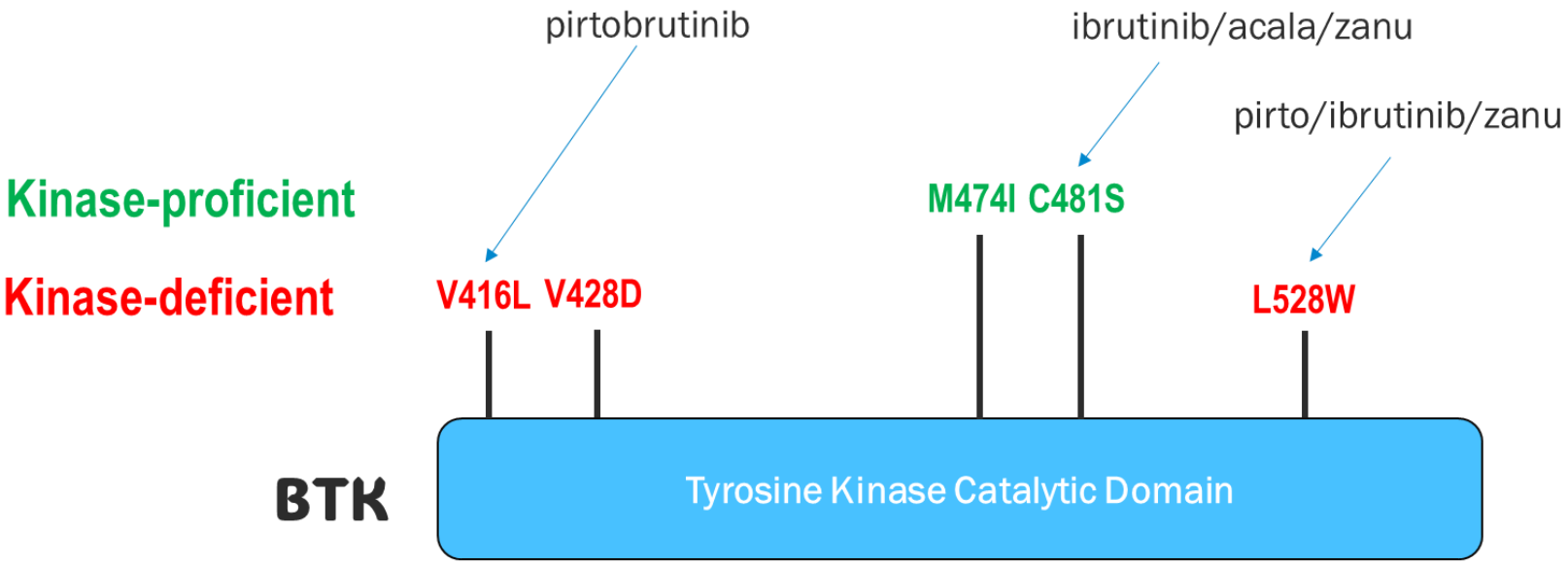
# Disclosures of Alexey Danilov

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Abbvie | X | | X | | | | |
| AstraZeneca | X | | X | | | | |
| Beigene | X | | X | | | | |
| Bristol Meyers Squibb | X | | X | | | | |
| Bayer Oncology | X | | | | | | |
| Genentech | | | X | | | | |
| GenMab | X | | X | | | | |
| Incyte | X | | X | | | | |
| Janssen | | | X | | | | |
| Lilly Oncology | X | | X | | | | |
| MEI Pharma | X | | X | | | | |
| Merck | | | X | | | | |
| Nurix | X | | X | | | | |
| Takeda | X | | | | | | |
| Prelude | | | X | | | | |
| Morphosys | X | | | | | | |

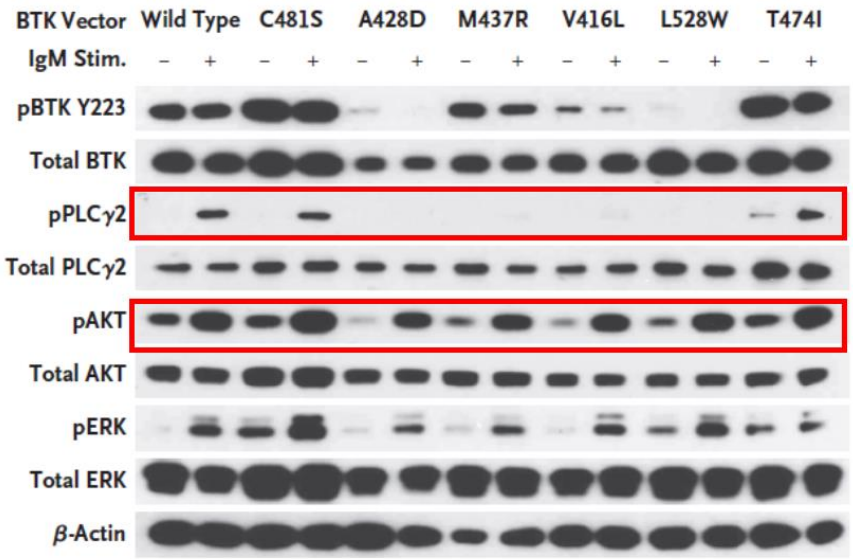
# PROTAC therapies: NX-2127 & NX-5948

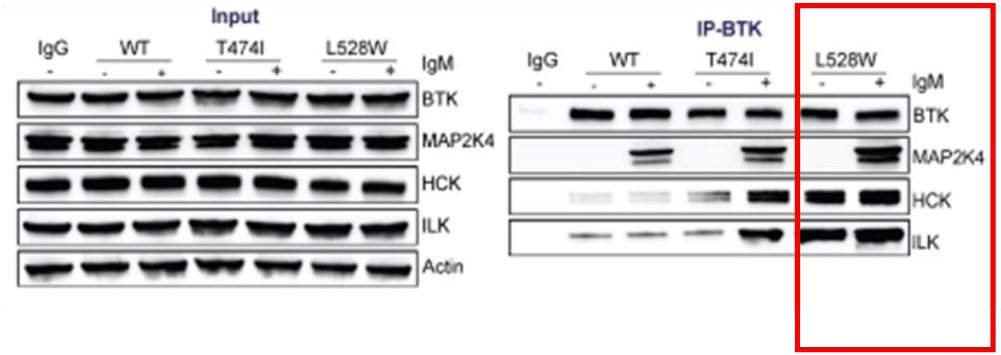
**Alexey Danilov, MD, PhD**
**Professor, Department of Hematology & Hematopoietic Cell Transplantation**
**Co-Director, Toni Stephenson Lymphoma Center**
**City of Hope Comprehensive Cancer Center**


# Emerging mutations in the BTK catalytic domain



# BTK inhibitory and scaffolding effects of BTK mutants

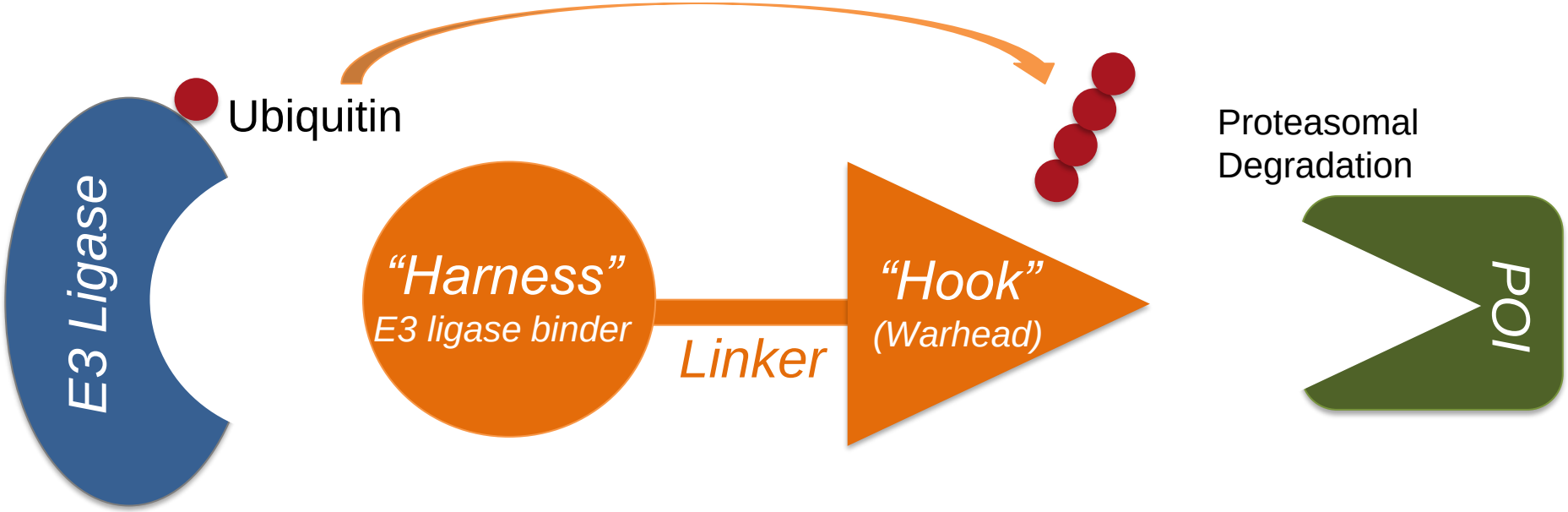



Wang et al, NEJM 2022
Montoya S et al, ICML 2023

# General structure of PROTAC (Proteolysis-targeting chimera)

***Catalytic ubiquitination and degradation of target***

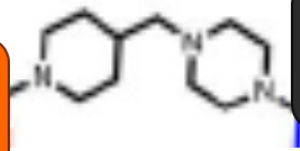


# Hooks and harnesses

Kinases
(BTK, BRAF, KRAS, IRAK,
MEK, CDK, ALK, AKT)

Transcription factors
(STAT)

Receptor proteins
(AR, ER, EGFR)



VHL

CRBN

MDM2

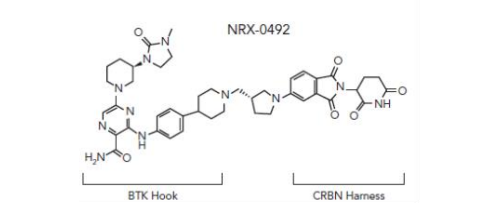
IAP

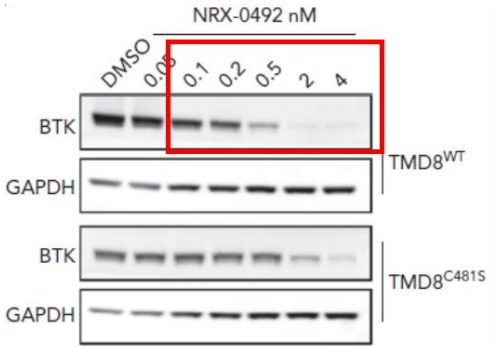
# BTK degraders in pre-clinical development

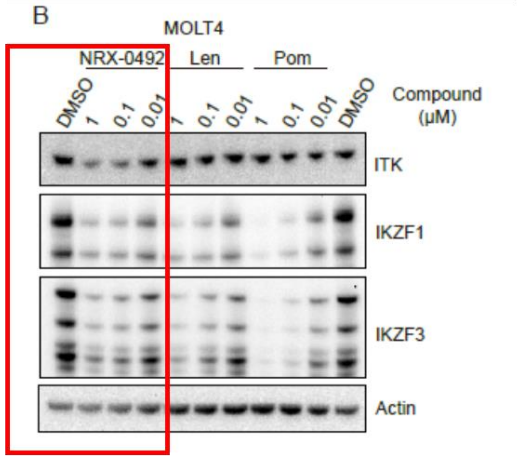
| Compound | Hook (Target) | Harness (E3 ligase) | Chemistry | Reference |
|---|---|---|---|---|
| CJH-005-067 | Bosutinib | Pomalidomide CRBN | Non-covalent | 21 (Huang, 2018) |
| DD-04-015 | RNA486 | Pomalidomide CRBN | Non-covalent | 21 (Huang, 2018) |
| MT-802 | Ibrutinib | Pomalidomide CRBN | Non-covalent | 22 (Buhimschi, 2018) |
| SJF620 | Ibrutinib | Lenalidomide CRBN | Non-covalent | 24 (Jaime-Figueroa, 2020) |
| P13I | Ibrutinib | Pomalidomide CRBN | Non-covalent | 25 (Sun, 2018) |
| L181 | Ibrutinib | Lenalidomide CRBN | Non-covalent | 26 (Sun, 2019) |
| Compound 9 | PF-06250112 / Phenyl-pyrazol | Pomalidomide CRBN | Non-covalent | 27 (Zorba, 2018) |
| Compound 10 | PF-06250112 / Phenyl-pyrazol | Pomalidomide CRBN | Non-covalent | 27 (Zorba, 2018) |
| DD-03-171 | CGI1746 / vecabrutinib | Thalidomide CRBN | Non-covalent | 28 (Dobrovolsky, 2019) |
| DD-03-007 | CGI1746 / vecabrutinib | Thalidomide CRBN | Non-covalent | 28 (Dobrovolsky, 2019) |
| PROTAC 2 | Ibrutinib | IAP | Covalent Irreversible | 29 (Tinworth, 2019) |
| PROTAC 3 | Ibrutinib | IAP | Covalent Reversible | 29 (Tinworth, 2019) |
| NC-1 | Ibrutinib | Thalidomide CRBN | Non-covalent | 30 (Gabizon, 2020) |
| IR-2 | Ibrutinib | Thalidomide CRBN | Covalent Irreversible | 30 (Gabizon, 2020) |
| RC-3 | Ibrutinib | Thalidomide CRBN | Covalent Reversible | 30 (Gabizon, 2020) |
| RC-1 | Ibrutinib | Pomalidomide CRBN | Covalent Reversible | 32 (Guo, 2020) |
| RNC-1 | Ibrutinib | Pomalidomide CRBN | Non-covalent | 32 (Guo, 2020) |
| IRC-1 | Ibrutinib | Pomalidomide CRBN | Covalent Irreversible | 32 (Guo, 2020) |
| PS-2 | Poseltinib | Pomalidomide CRBN | Covalent Reversible | 33 (Yu, 2022) |
| Compound 7 | Ibrutinib | VHL | Covalent Reversible | 34 (Xue, 2020) |
| SPB5208 | Ibrutinib | Thalidomide CRBN | ? | 35 (Liu, 2020) |
| Compound 6e | ARQ531 / nemtabrutinib | Pomalidomide CRBN | Non-covalent | 36 (Zhao, 2021) |
| Compound 3e | ARQ531 / nemtabrutinib | Pomalidomide CRBN | Non-covalent | 37 (Chen, 2023) |
| PTD10 | GDC-0853 / fenebrutinib | Pomalidomide CRBN | ? | 38 (Li, 2023) |
| C13 | Ibrutinib | Thalidomide CRBN | Non-covalent | 39 (Zhang, 2022) |
| UBX-382 | Novel BTK binder | Thalidomide CRBN | Non-covalent | 40 (Lim, 2023) |
| Compound 15 | Ibrutinib | Pomalidomide CRBN | Non-covalent | 41 (Huang, 2023) |
| NRX-0492 | Pyrazine-carboxamide | Thalidomide CRBN | Non-covalent | ASH (Zhang, 2023) |

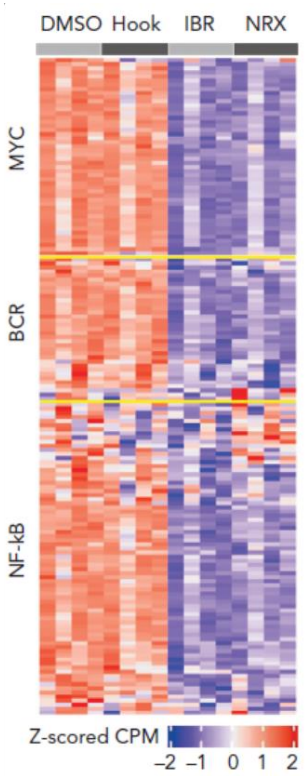
Huynh T et al., in revision

# NX-0942 degrades BTK, ITK and IKZF



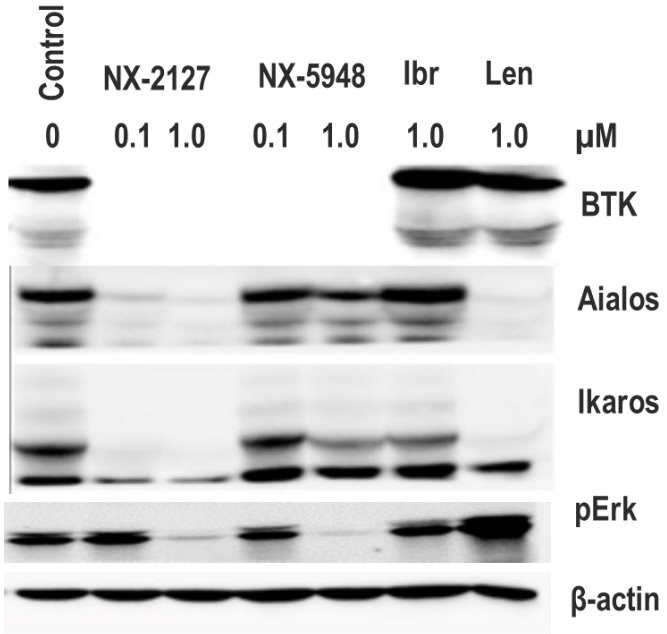



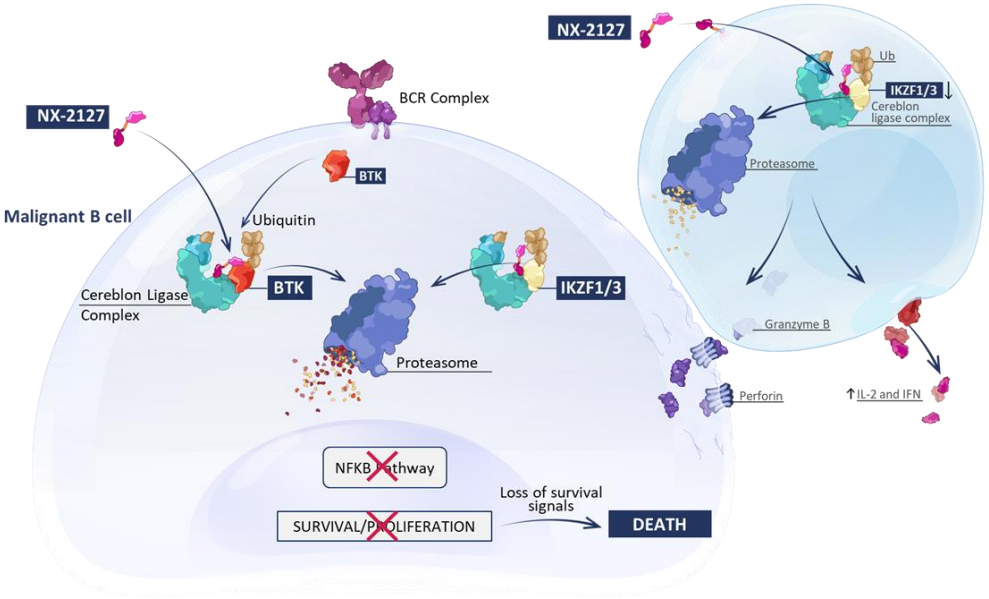




Zhang et al, Blood 2023

# IMID-capable vs. IMID-deficient degraders

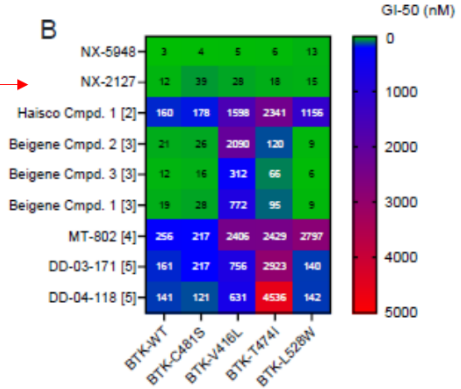



Huynh et al, iwCLL 2023

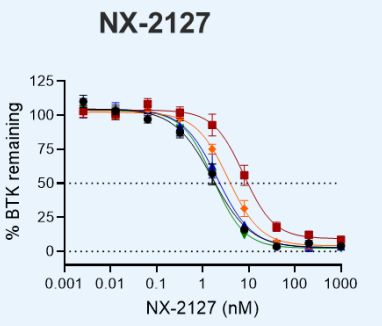
# BTK degradation and BTK mutations

- NX-2127 degrades wild-type and mutant *BTK*
- NX-2127 kills DLBCL tumor cells harboring BTK and mutant *BTK*

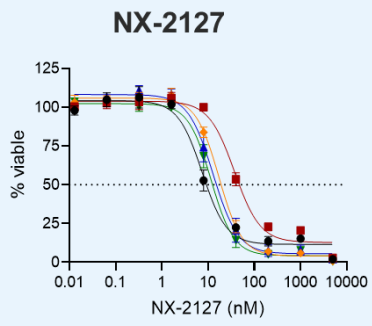


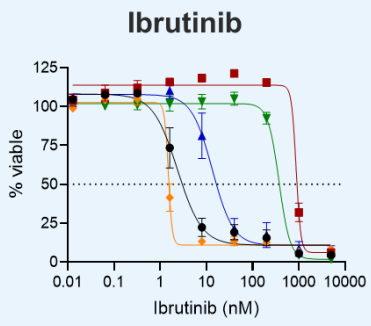

BTK-WT
BTK-C481S
BTK-V416L
BTK-T474I
BTK-L528W

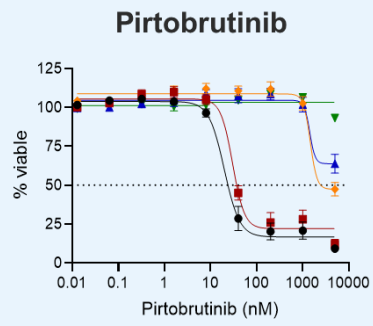
## BTK degradation




## Cell viability



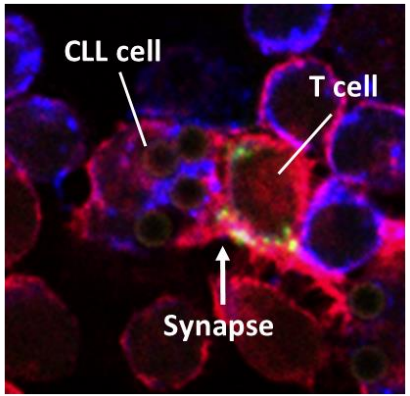



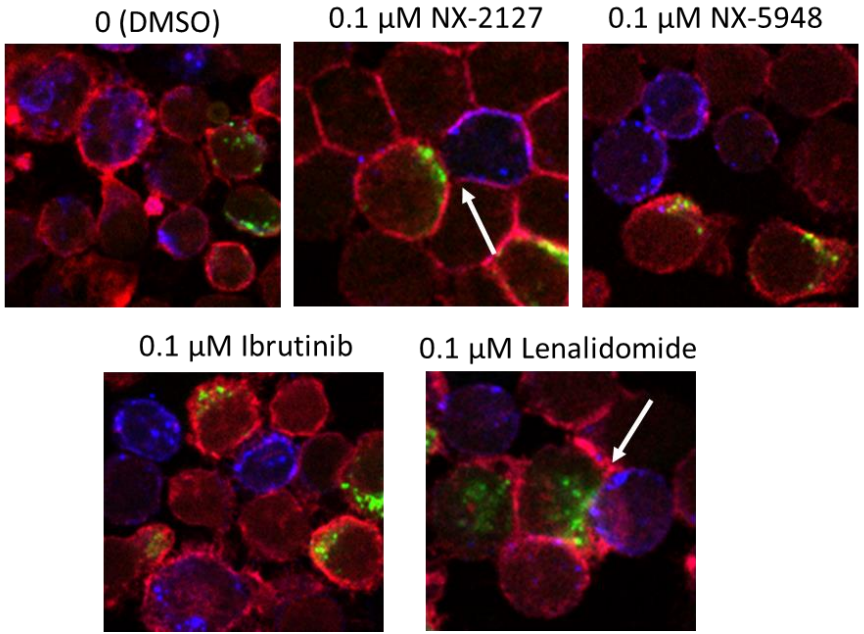

Montoya S, et al. ASH 2022 (abstract #750)
Noviski M et al, AACR 2023 (abstract #2850)

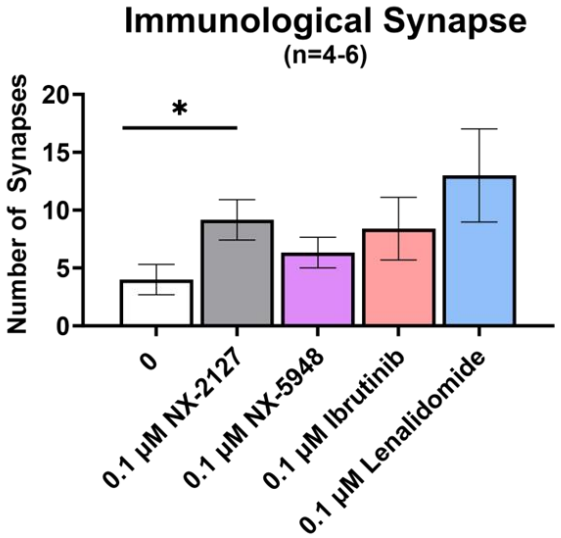
# IMID-capable vs. IMID-deficient degraders

**F-actin:** T cells and CLL cells
**Cell Tracker:** CLL cells
**Granzyme B:** Synapse

Representative Synapse Photo

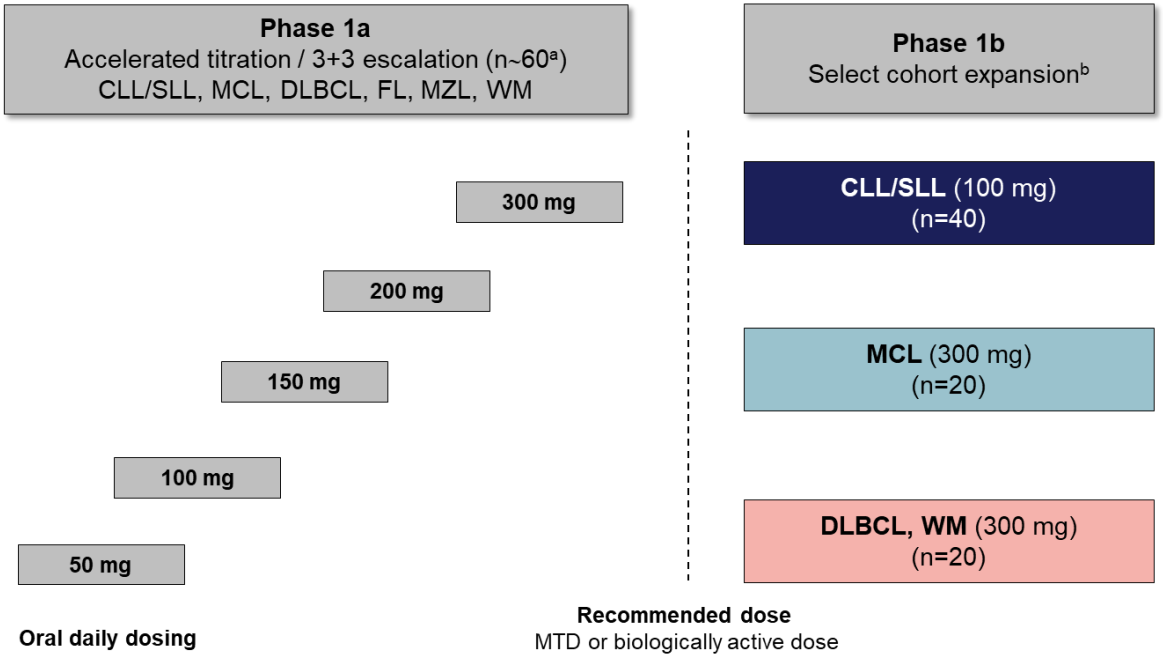



Huynh et al, iwCLL 2023

# NX-2127: 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 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)

**CLL**, chronic lymphocytic leukemia; **DLBCL**, diffuse large B-cell lymphoma; **DLT**, dose-limiting toxicity; **FL**, follicular lymphoma; **MCL**, mantle cell lymphoma; **MTD**, maximum tolerated dose; **MZL**, marginal zone lymphoma; **PD,** pharmacodynamics; **PK,** pharmacokinetics; **PCNSL,** primary central nervous system lymphoma; **SLL,** small lymphocytic lymphoma; **WM**, Waldenstrom's macroglobulinemia

Danilov et al, ASH 2023

# NX-2127: patient 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) |
| **Lines of prior therapy**[a], median (range) | 4 (2–10) | 5 (2–11) | 4 (2–11) |
| BTKi, n (%) | 15 (71.4) | 33 (100.0) | 48 (88.9) |
| Pirtobrutinib, n (%) | 5 (23.8) | 9 (27.3) | 14 (25.9) |
| BTKi and BCL2i, n (%) | 1 (4.8) | 26 (78.8) | 27 (50.0) |
| cBTKi, ncBTKi, and BCL2i, n (%) | 0 (0.0) | 8 (24.2) | 8 (14.8) |
| CAR-T/NK therapy, n (%) | 3 (14.3) | 1 (3.0) | 4 (7.4) |
| Bispecific antibody, n (%) | 2 (9.5) | 0 (0.0) | 2 (3.7) |
| IMiD (lenalidomide), n (%) | 4 (19.0) | 4 (12.1) | 8 (14.8) |

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# NX-2127: patient characteristics

| Mutations[a] | NHL/WM (n=21) | CLL/SLL (n=33) | Overall population (N=54) |
|---|---|---|---|
| ***BTK***, n (%) | 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 (12.0) | 4 (7.4) |

[a]Patients could have multiple *BTK* mutations; Mutations were tested at baseline by NGS centrally. ≥5% allelic frequency is reported
[b]*L845F, D334H, D1140N, T961M, S707F*

Danilov et al, ASH 2023

# 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

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

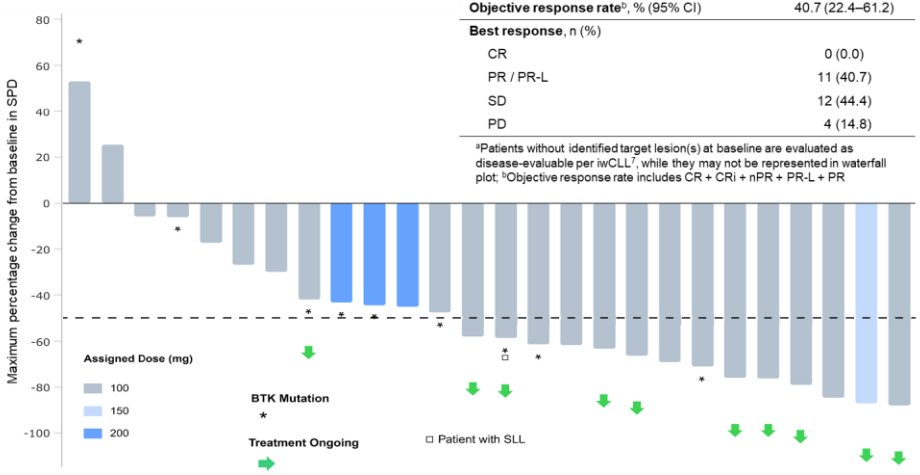
Data cutoff: 15 Sep 2023

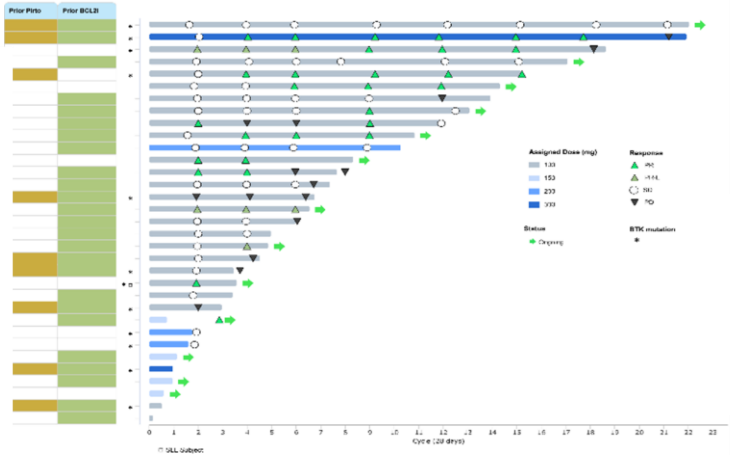
Danilov et al, ASH 2023

# NX-2127 efficacy – patients with CLL

| 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



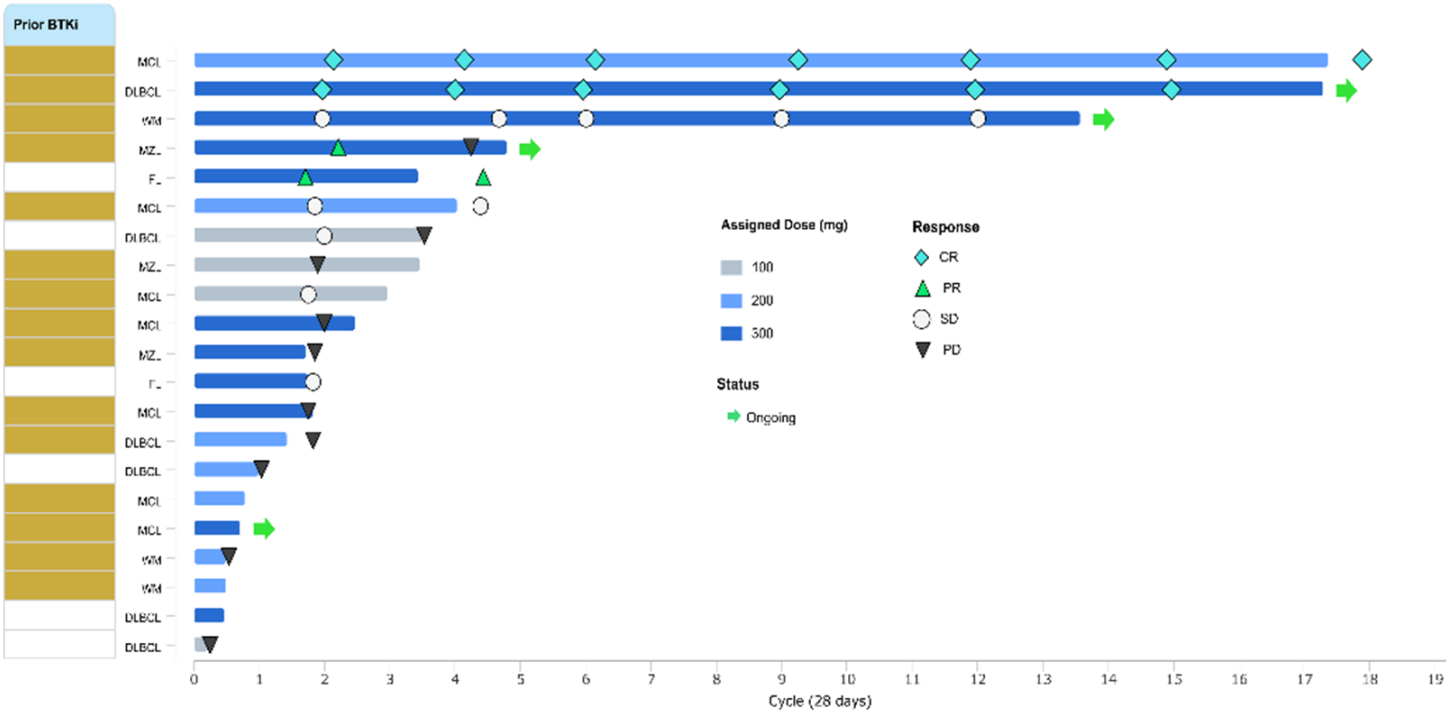

**BCL2i,** B-cell lymphoma-2 inhibitor; **BTK,** Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **PD**, progressive disease; **PR**, partial response; **PR-L**, partial response with lymphocytosis; **SD**, stable disease; *Mutations were tested at baseline by NGS centrally in those patients with available samples (cutoff ≥5% VAF)

**CI**, confidence interval; **CR**, complete response; **DLBCL,** diffuse large B-cell lymphoma; **FL**, follicular lymphoma; **MCL,** mantle cell lymphoma; **MZL,** marginal zone lymphoma; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **SPD**, sum of product diameters; **WM,** Waldenstrom's macroglobulinemia

Data cutoff: 15 Sep 2023

Danilov et al, ASH 2023

# NX-2127 efficacy: patients with NHL

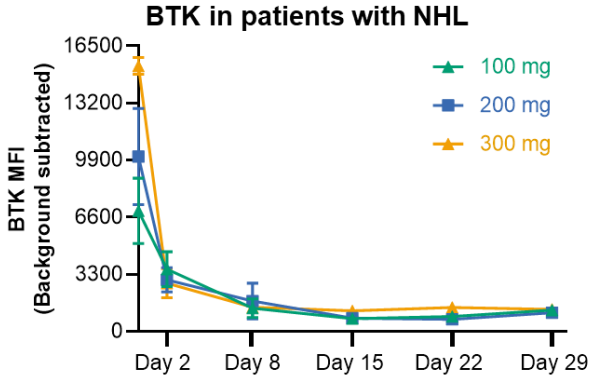



**CR**, complete response; **DLBCL,** diffuse large B-cell lymphoma; **FL**, follicular lymphoma; **MCL,** mantle cell lymphoma; **MZL,** marginal zone lymphoma; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **WM,** Waldenstrom's macroglobulinemia

Data cutoff: 15 Sep 2023

Danilov et al, ASH 2023

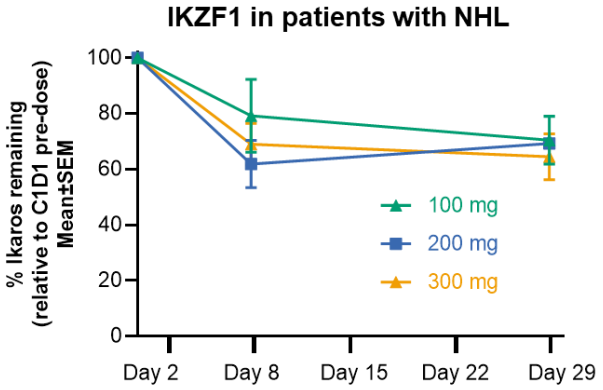
# NX-2127: BTK degradation




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 |

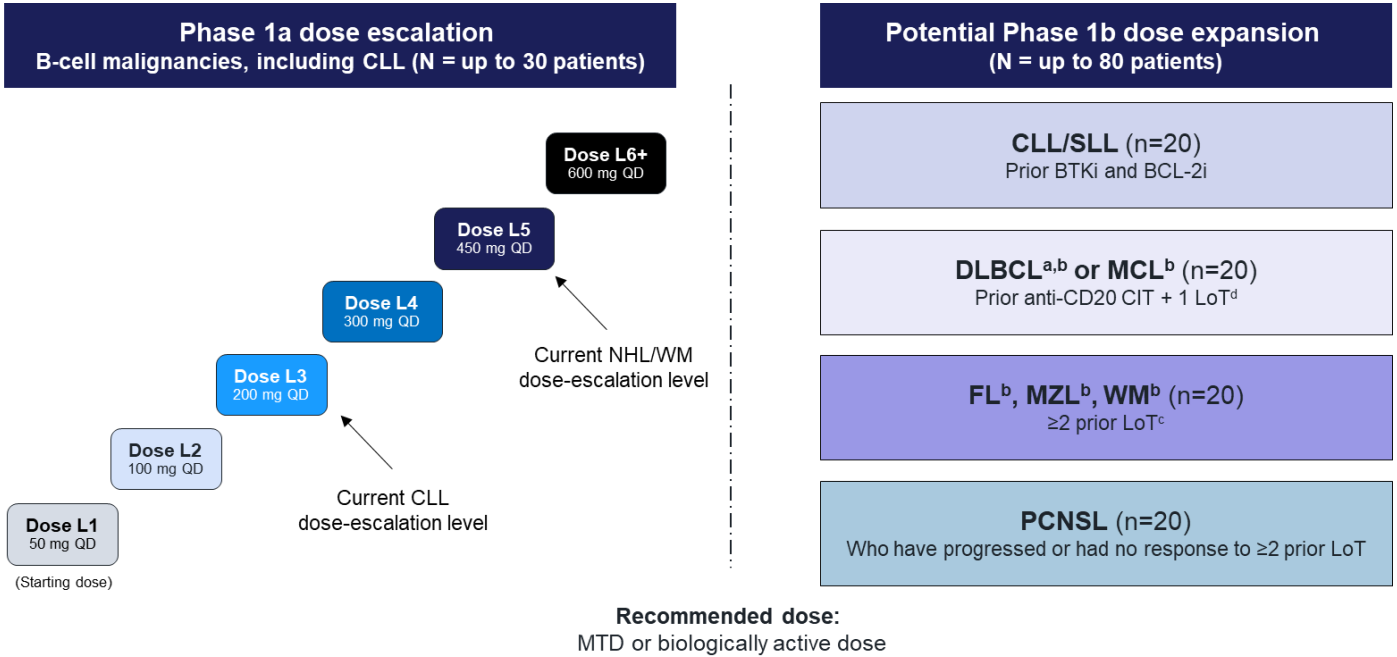
**BTK**, Bruton's tyrosine kinase




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

Danilov A et al, ICML 2023 (abstract #426)

# NX-5948: trial design




[a]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; [b]Includes patients with secondary CNS involvement; [c]Additional lines of therapy include anthracycline for non-GCB DLBCL and BTKi for MCL

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# NX-5948: patient 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) |

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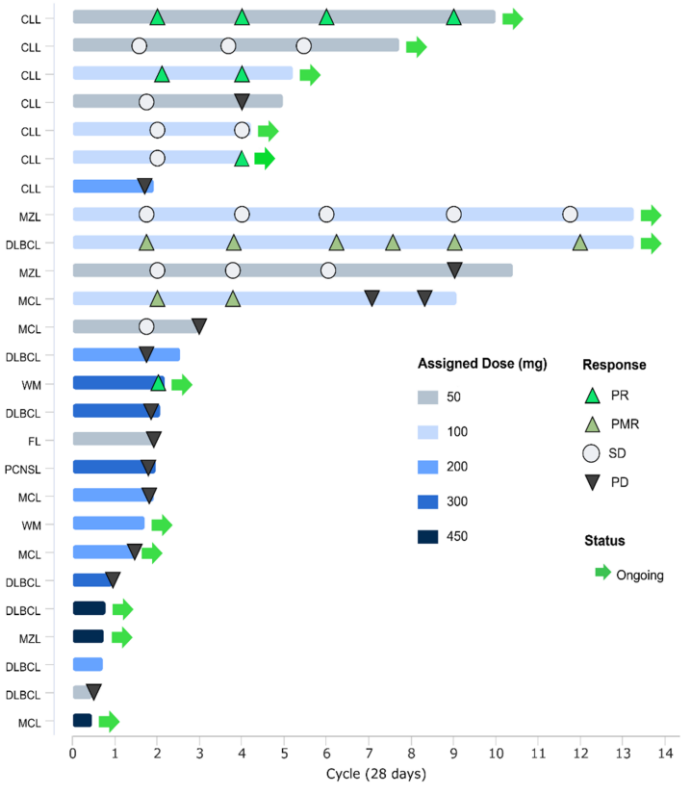
# NX-5948: safety and efficacy




| TEAEs, n (%) | 50 mg (n=7) | 100 mg (n=6) | 200 mg (n=6) | 300 mg (n=4) | 450 mg (n=3) | All doses (N=26) |
|---|---|---|---|---|---|---|
| Purpura/contusion[a] | 5 (71.4) | 2 (33.3) | 1 (16.7) | 2 (50.0) | 2 (66.7) | 12 (46.2) |
| Thrombocytopenia[b] | 2 (28.6) | 3 (33.3) | 2 (33.3) | 3 (75.0) | 1 (33.3) | 10 (38.5) |
| Neutropenia[c] | 1 (14.3) | 3 (50.0) | 0 (0.0) | 4 (100.0) | 0 (0.0) | 8 (30.8) |
| Anemia | 2 (28.6) | 2 (33.3) | 0 (0.0) | 1 (25.0) | 1 (33.3) | 6 (23.1) |
| Cough | 0 (0.0) | 2 (33.3) | 1 (16.7) | 2 (50.0) | 0 (0.0) | 5 (19.2) |
| Headache | 2 (28.6) | 0 (0.0) | 2 (33.0) | 1 (25.0) | 0 (0.0) | 5 (19.2) |
| Nausea | 3 (42.9) | 0 (0.0) | 2 (33.3) | 0 (0.0) | 0 (0.0) | 5 (19.2) |
| Rash | 2 (28.6) | 2 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (15.4) |

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# NX-2127 & NX-5948: summary

- BTK degraders had a manageable safety profile that was consistent with previous reports for BTK-targeted therapies

- Treatment with NX-2127 resulted in encouraging and durable responses in a heavily pre-treated patient population including patients with *BTK* resistance mutations

  - **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

- Treatment with NX-5948 has shown preliminary efficacy in CLL/NHL and no DLTs so far. Dose escalation is ongoing