9th POSTGRADUATE

Lymphoma Conference

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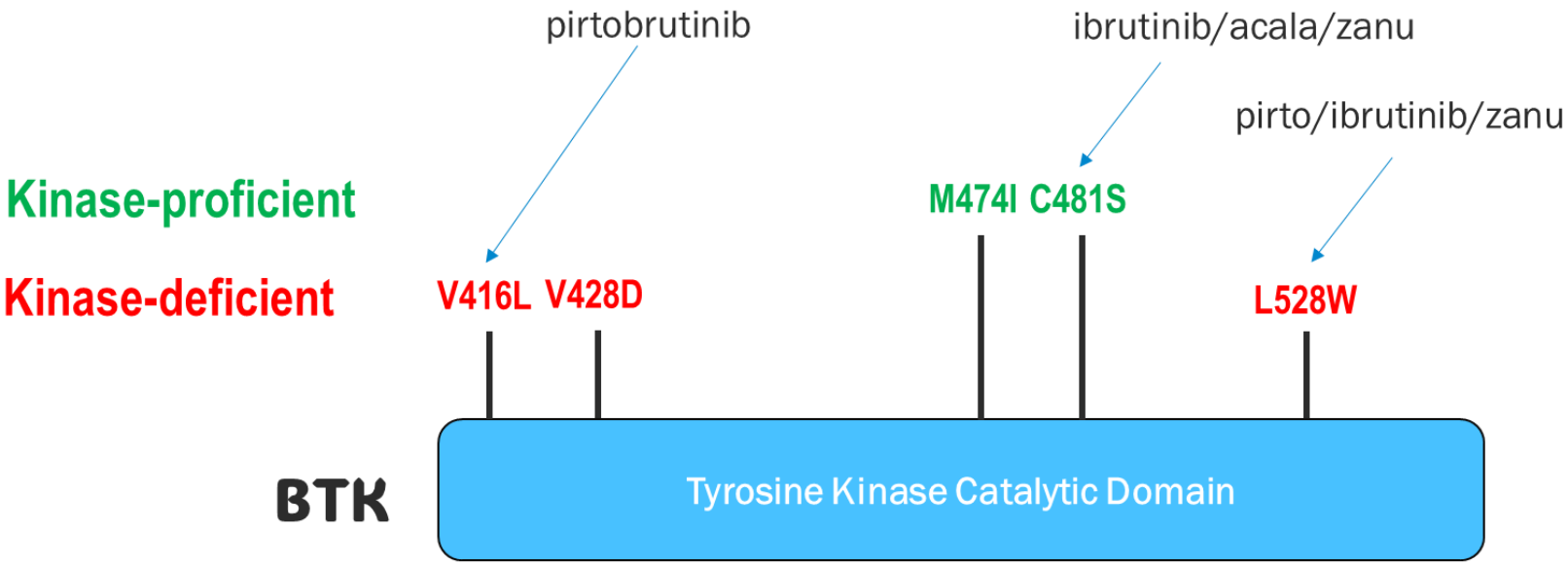
President:
P.L. Zinzani

Disclosures

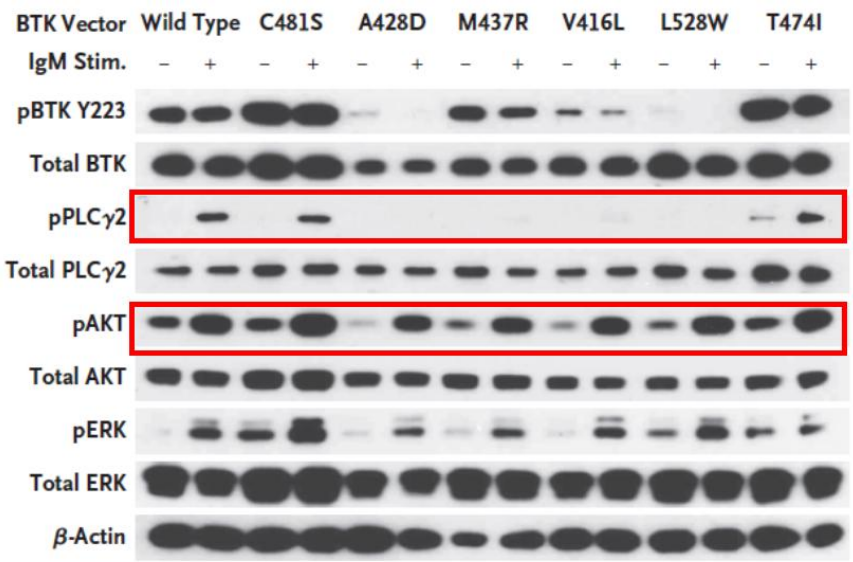
Disclosures of Alexey Danilov

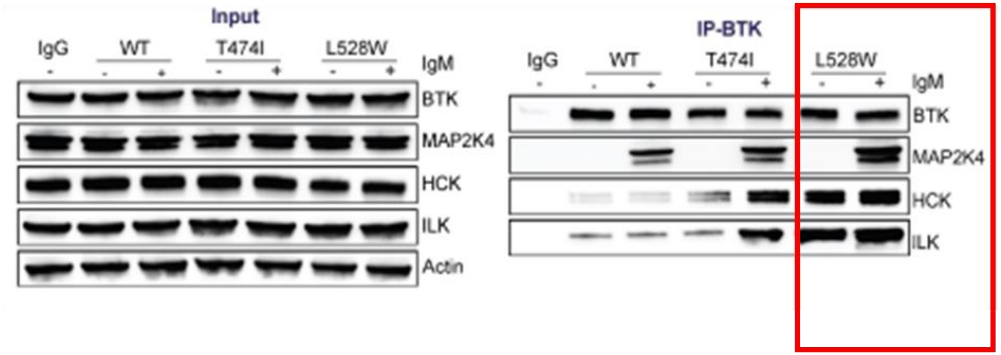
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	X		x				
ADCT			x				
AstraZeneca	x		x				
Beigene	x		x				
BMS	x		x				
GenMab	x		x				
Janssen			x				
Lilly Oncology	x		x				
Merck	x		x				
Nurix	X		X				
Regeneron	X		X				
Roche			X				

Emerging mutations in the BTK catalytic domain



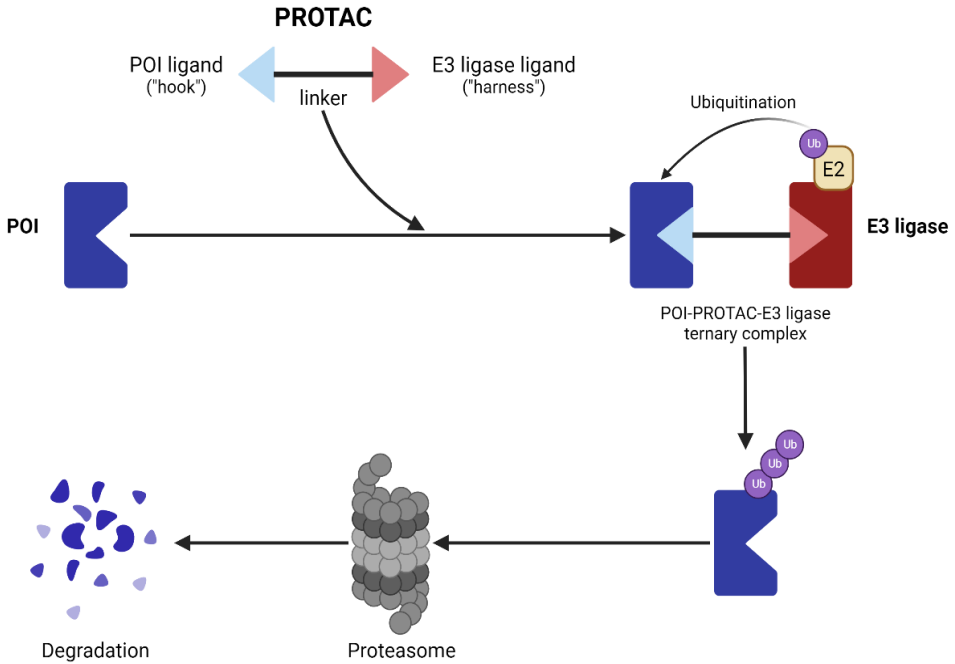
BTK activating and scaffolding effects of BTK mutants





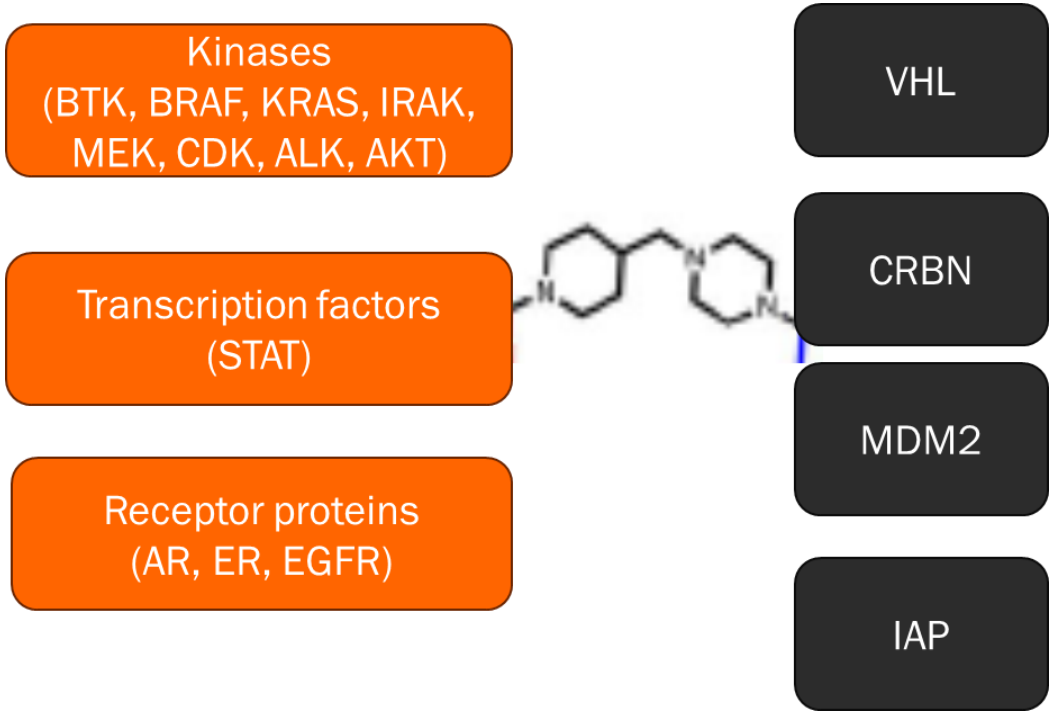
Wang et al, NEJM 2022
Montoya S et al, Science 2024

The place of Proteolysis-targeted chimeras (PROTACs) in the UPS pathways



Huynh T et al, Mol Cancer Ther 2024

Hooks and harnesses



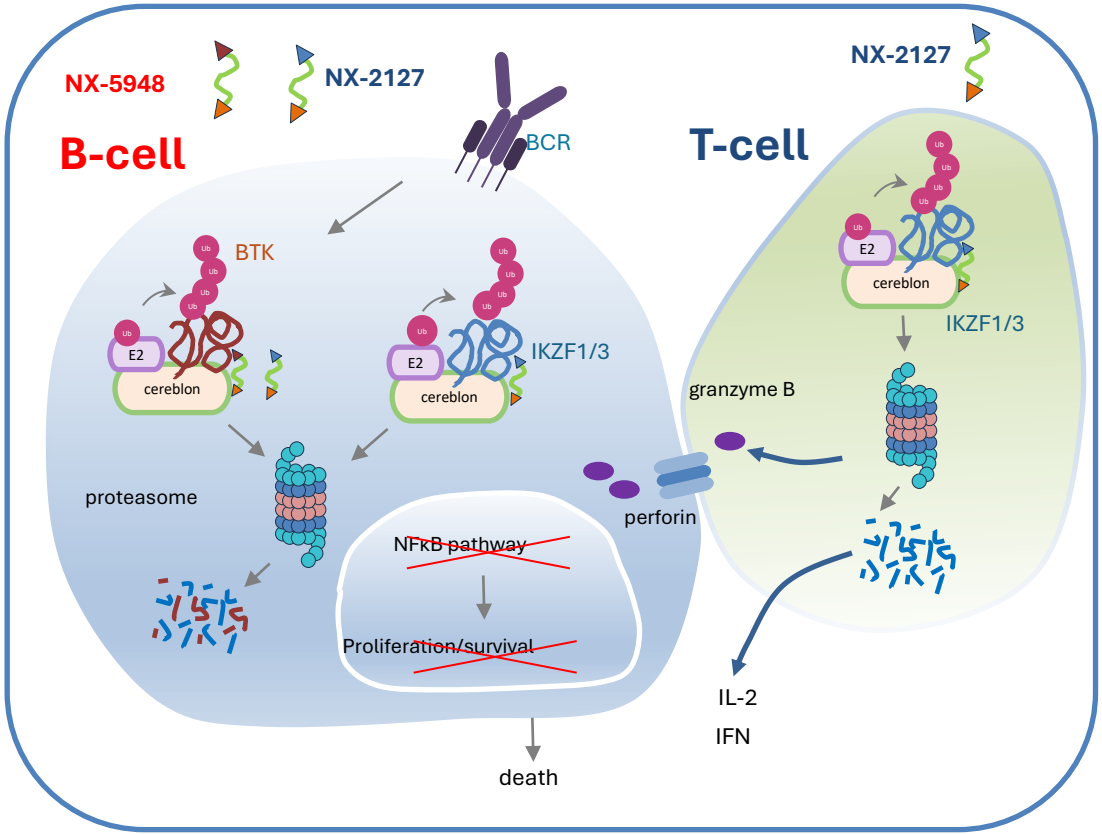
Huynh T et al, Mol Cancer Ther 2024

BTK degraders in pre-clinical development

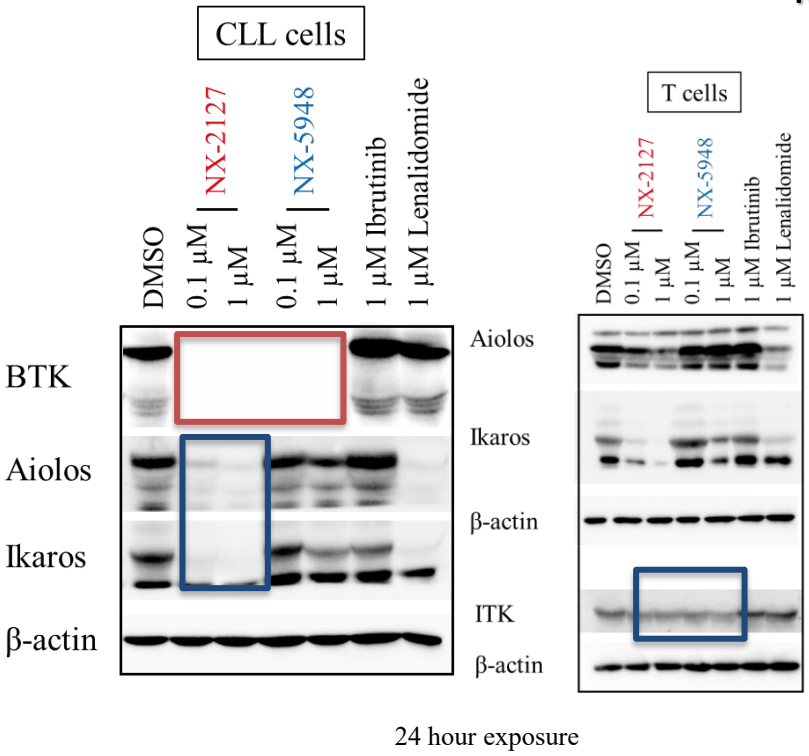
Compound	Hook (Target)	Harness (E3 ligase)	Chemistry	Reference
CJH-005-067	Bosutinib	Pomalidomide CRBN	Non-covalent	21 (Huang, 2018)
DD-04-015	RNA486	Pomalidomide CRBN	Non-covalent	21 (Huang, 2018)
MT-802	Ibrutinib	Pomalidomide CRBN	Non-covalent	22 (Buhimschi, 2018)
SJF620	Ibrutinib	Lenalidomide CRBN	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, Mol Cancer Ther 2024

CRBN-recruiting degraders: NX-2127 and NX-5948

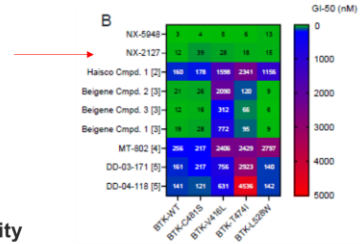


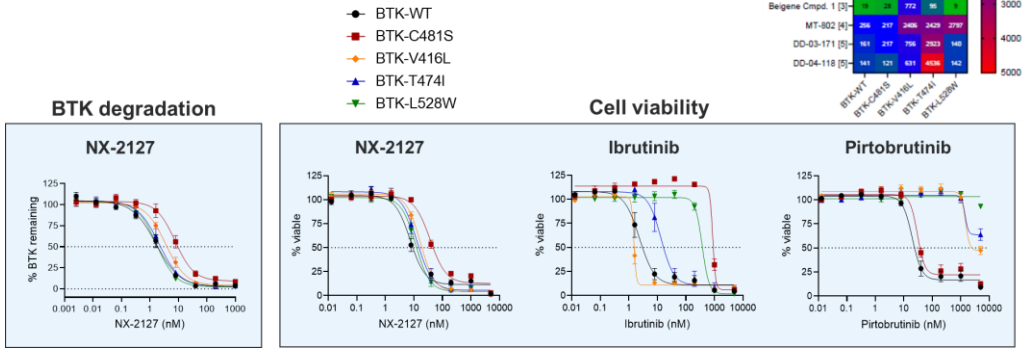
NX-2127 and NX-5948 degrade BTK in primary CLL cells, but only NX-2127 degrades Ikaros/Aialos



24 hour exposure

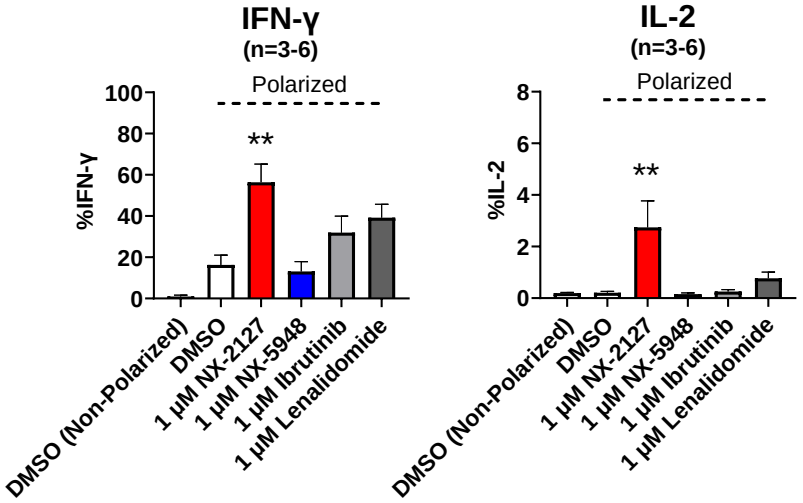
- NX-2127 degrades wild-type and mutant *BTK*
- NX-2127 kills DLBCL tumor cells harboring BTK and mutant *BTK*

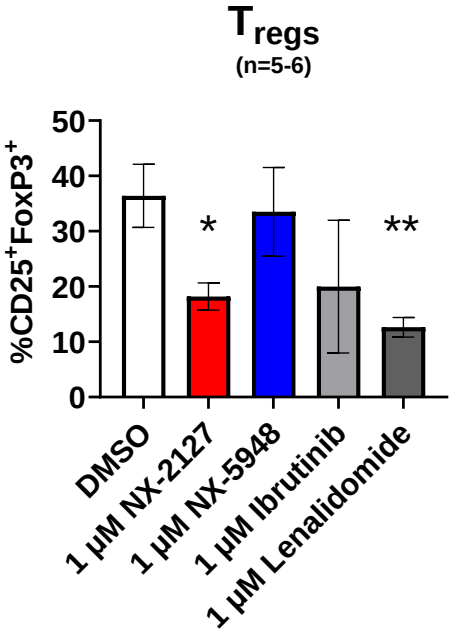




Huynh T et al, ASH 2024
Noviski M et al, AACR 2023 (abstract #2850)

NX-2127 promotes T_{H1} polarization and reduces Tregs





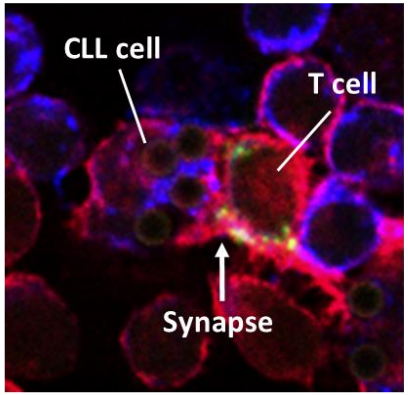
Naïve CD4+ T cells from primary CLL samples were stimulated with αCD3/CD28 mAbs, treated with NX-2127 or NX-5948, and supplemented with human cytokines to promote T_H1 polarization for 7 days.

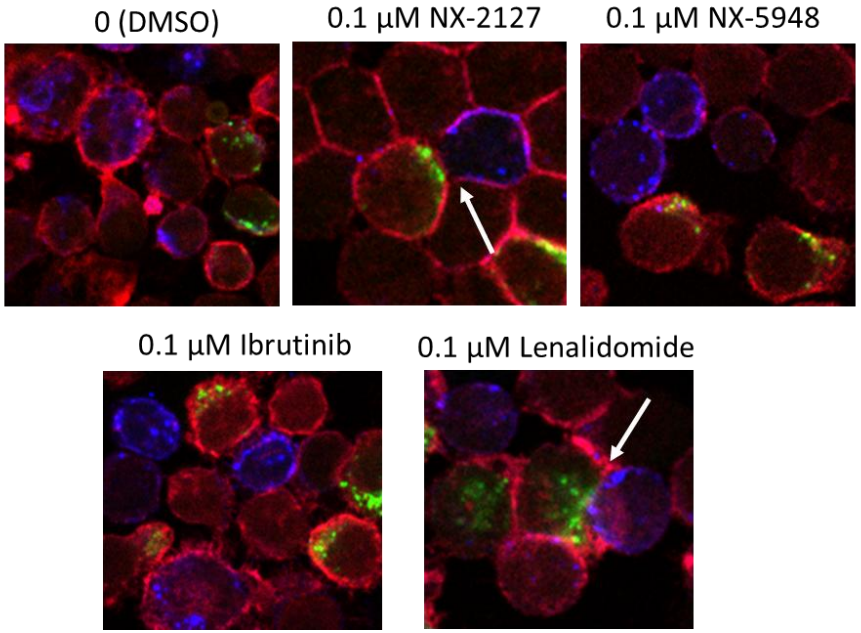
Huynh T et al, ASH 2024

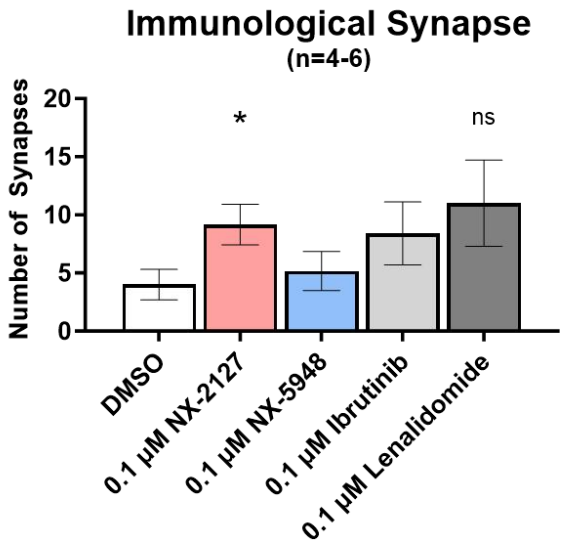
NX-2127 enhances synapse formation

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

Representative Synapse Photo

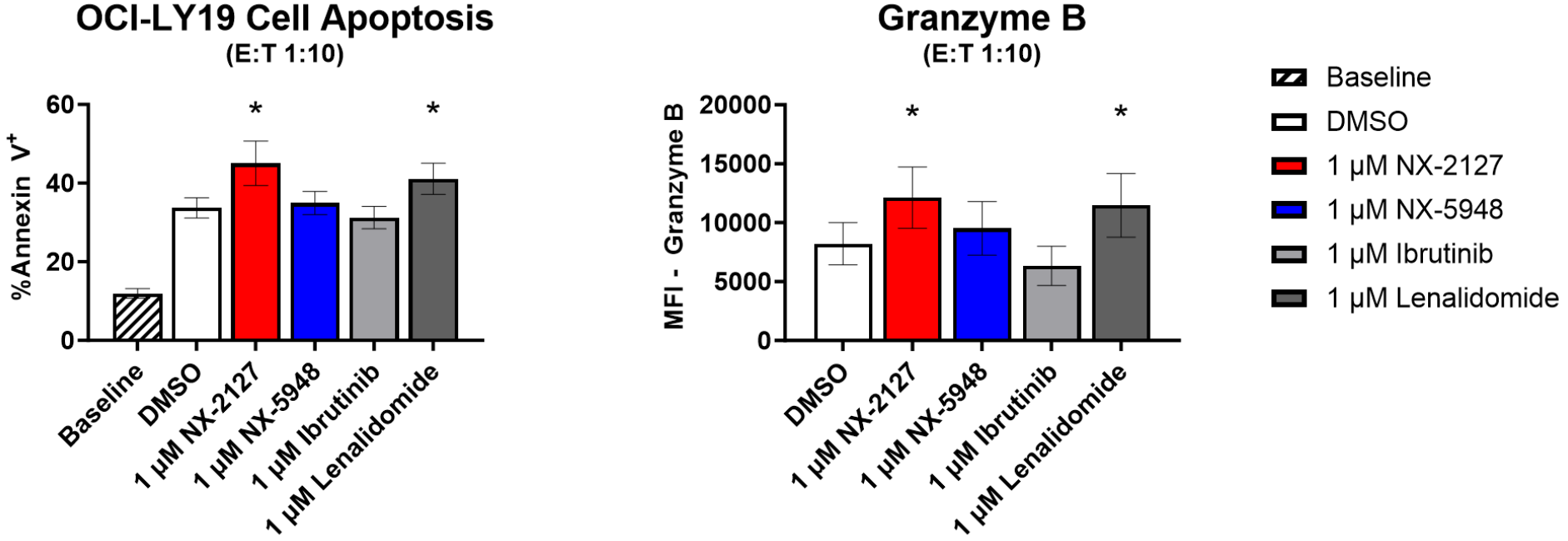






Huynh T et al, ASH 2024

NX-2127 enhances cytotoxicity



Huynh T et al, ASH 2024

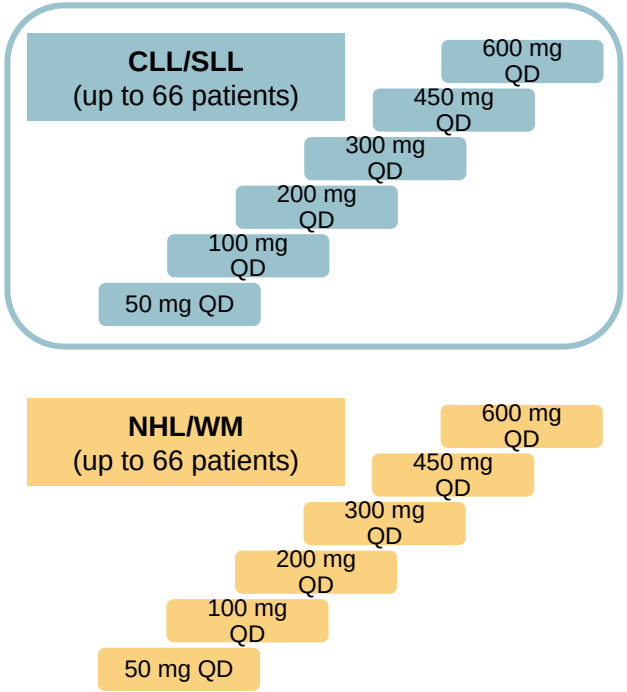
NX-5948-301: Trial Design

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

Phase 1a dose escalation (completed enrollment)

Key eligibility criteria

- Age ≥18 years
- Relapsed/refractory disease
- ≥2 prior lines of therapy (≥1 for PCNSL)
- ECOG PS 0–1 (ECOG PS 0–2 for PCNSL)



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

CLL/SLL 200 mg QD Prior BTKi and BCL2i	**CLL/SLL 600 mg QD** Prior BTKi and BCL2i
WM 3L+ post-BTKi	**WM** 2L post-BTKi

MCL
Prior BTKi and anti-CD20 CIT

MZL
Prior anti-CD20 CIT and ≥2 prior LoT

DLBCL
Prior anthracycline, anti-CD20 CIT + 1 LoT

FL
Prior anti-CD20 CIT + 1 LoT

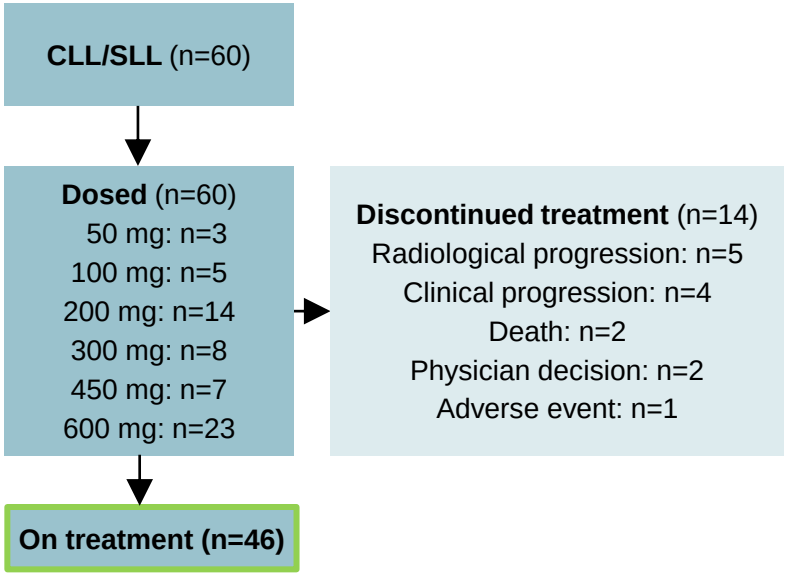
PCNSL/SCNSL
Patients who have progressed or had no response to ≥1 prior LoT

Shah et al, ASH 2024

CLL Patient Disposition and Demographics

Phase 1a and 1b

Patient disposition



Patient demographics

Characteristics	Patients[a] (n=60)
Median age, years (range)	67.0 (35–88)
Sex, n (%)	
Male	38 (63.3)
Ethnicity, n (%)	
Hispanic or Latino	4 (6.7)
Race, n (%)	
Black or African American	5 (8.3)
White	51 (85.0)
Other	4 (6.7)

[a]Population demographics in CLL cohort were comparable to those in the overall population

CLL, chronic lymphocytic leukemia; **SLL**, small lymphocytic lymphoma

Shah et al, ASH 2024

Baseline Disease Characteristics

Multiple prior lines of therapy and high prevalence of baseline mutations

Characteristics	Patients with CLL/SLL[a] (n=60)
ECOG PS, n (%)	
0	24 (40.0)
1	36 (60.0)
CNS involvement, n (%)	5 (8.3)
Median prior lines of therapy (range)	4.0 (1–12)
Previous treatments[b], n (%)	
BTKi	59 (98.3)
cBTKi	59 (98.3)
ncBTKi[c]	17 (28.3)
BCL2i	50 (83.3)
BTKi and BCL2i	49 (81.7)
CAR-T therapy	3 (5.0)
Bispecific antibody	4 (6.7)
PI3Ki	18 (30.0)
Chemo/chemo-immunotherapies (CIT)	43 (71.7)
Mutation status[d] (n=57), n (%)	
TP53	23 (40.4)
BTK	22 (38.6)
PLCG2	7 (12.3)
BCL2	6 (10.5)

[a]Baseline disease characteristics in CLL cohort were comparable to those in the overall population; [b]Patients could have received multiple prior treatments; [c]All patients who received ncBTKi have also previously received cBTKi; [d]Mutations presented here were centrally sequenced.

BCL2, B-cell lymphoma 2; **BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CAR-T**, chimeric antigen receptor T-cell; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group (ECOG) performance status; **ncBTKi**, non-covalent BTKi; **PI3Ki**, phosphoinositide 3-kinase inhibitor; **PLCG2**, phospholipase C gamma 2; **SLL**, small lymphocytic lymphoma

Shah et al, ASH 2024

NX-5948 Safety Profile

TEAEs in ≥10% of overall population or Grade ≥3 TEAEs or SAEs in >1 patient

TEAEs, n (%)	**Patients with CLL/SLL (n=60)**			**Overall population (N=125)**		
	Any grade	**Grade ≥3**	**SAEs**	**Any grade**	**Grade ≥3**	**SAEs**
Purpura/contusion[a]	22 (36.7)	–	–	42 (33.6)	–	–
Fatigue[b]	16 (26.7)	–	–	29 (23.2)	2 (1.6)	–
Petechiae	16 (26.7)	–	–	28 (22.4)	–	–
Thrombocytopenia[c]	10 (16.7)	1 (1.7)	–	26 (20.8)	7 (5.6)	–
Rash[d]	14 (23.3)	1 (1.7)	1 (1.7)	24 (19.2)	2 (1.6)	1 (0.8)
Neutropenia[e]	14 (23.3)	11 (18.3)	–	23 (18.4)	18 (14.4)	–
Anemia	11 (18.3)	4 (6.7)	–	21 (16.8)	10 (8.0)	–
Headache	10 (16.7)	–	–	21 (16.8)	1 (0.8)	1 (0.8)
COVID-19[f]	10 (16.7)	–	–	19 (15.2)	2 (1.6)	2 (1.6)
Diarrhea	12 (20.0)	1 (1.7)	–	18 (14.4)	1 (0.8)	–
Cough	9 (15.0)	–	–	16 (12.8)	1 (0.8)	–
Pneumonia[g]	4 (6.7)	2 (3.3)	2 (3.3)	10 (8.0)	6 (4.8)	6 (4.8)
Lower respiratory tract infection	3 (5.0)	1 (1.7)	1 (1.7)	9 (7.2)	3 (2.4)	2 (1.6)
Fall	1 (1.7)	1 (1.7)	1 (1.7)	8 (6.4)	2 (1.6)	2 (1.6)
Hypertension	2 (3.3)	1 (1.7)	–	7 (5.6)	5 (4.0)	–
Hyponatremia	–	–	–	3 (2.4)	2 (1.6)	–
Pulmonary embolism	1 (1.7)	1 (1.7)	1 (1.7)	2 (1.6)	2 (1.6)	2 (1.6)
Subdural hematoma	1 (1.7)	–	1 (1.7)	2 (1.6)	1 (0.8)	2 (1.6)

- Tolerable safety profile consistent with prior disclosures
- 1 case of Grade 1 AFib in a CLL patient with pre-existing AFib
- 6 TEAEs resulted in drug discontinuation (1 CLL; 5 NHL)
- 2 Grade 5 AEs (1 pulmonary embolism; 1 case pending) deemed not related to NX-5948

[a]Purpura/contusion includes episodes of contusion or purpura; [b]Fatigue was transient; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [d]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [e]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [f]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'; [g]Aggregate of 'pneumonia' and 'pneumonia klebsiella'

Afib, atrial fibrillation; **CLL**, chronic lymphocytic leukemia; **SAE**, serious adverse event; **SLL**, small lymphocytic lymphoma; **TEAE**, treatment emergent adverse event

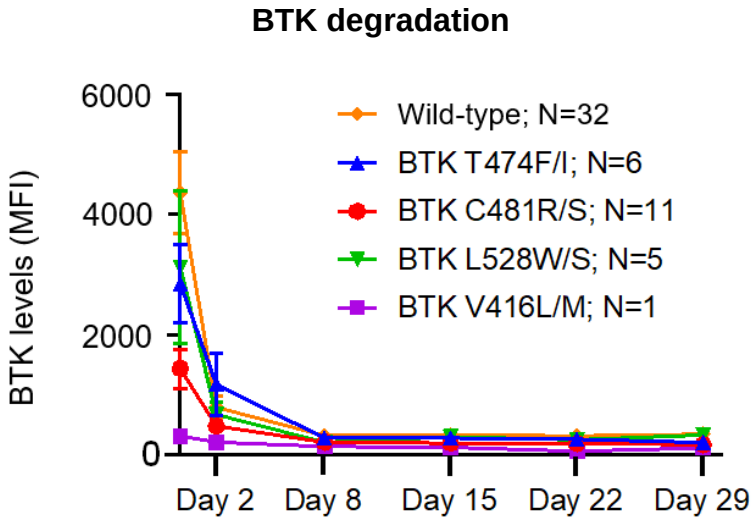
Shah et al, ASH 2024

NX-5948 Degrades Wild-Type and Mutated *BTK*

NX-5948 degrades gatekeeper, kinase-proficient and kinase-dead *BTK* mutations

	Patients with CLL/SLL (n=57)[c]
Baseline mutation status, n (%)	
BTK mutations[1,a,b]	22 (38.6)
C481S	12 (21.1)
C481R	2 (3.5)
L528W	4 (7.0)
L528S	1 (1.8)
T474I	5 (8.8)
T474F	1 (1.8)
V416M	1 (1.8)
V416L	1 (1.8)
G541V	1 (1.8)

[a]Patients could have multiple prior treatments and *BTK* mutations; *BTK* mutations were tested at baseline by NGS centrally. ≥5% allelic frequency is reported
[b]Patients can have more than one resistance mutation
[c]Patients with available mutation status



Note: Some patients have multiple *BTK* mutations

Shah et al, ASH 2024

Reference
1. Montoya et al. Science 2024;383

BTK, Bruton's tyrosine kinase; **CLL**, chronic lymphocytic leukemia; **MFI**, mean fluorescence intensity **SEM**, standard error of the mean **SLL**, small lymphocytic lymphoma

NX-5948 Overall Response Assessment

Response rate deepens with longer time on treatment

CLL response-evaluable patients	**Primary ORR analysis[b]** ≥1 response assessment(s) at 8 weeks (n=49)[c]	**Exploratory ORR analysis[b]** ≥2 response assessments at 16 weeks (n=38)[c]
Objective response rate (ORR),[a] % (95% CI)	75.5 (61.1–86.7)	84.2 (68.7–94.0)
Best response, n (%)		
CR	0 (0.0)	0 (0.0)
PR	36 (73.5)	32 (84.2)
PR-L	1 (2.0)	0 (0.0)
SD	10 (20.4)	4 (10.5)
PD	2 (4.1)	2 (5.3)

[a]Objective response rate includes CR + PR + PR-L

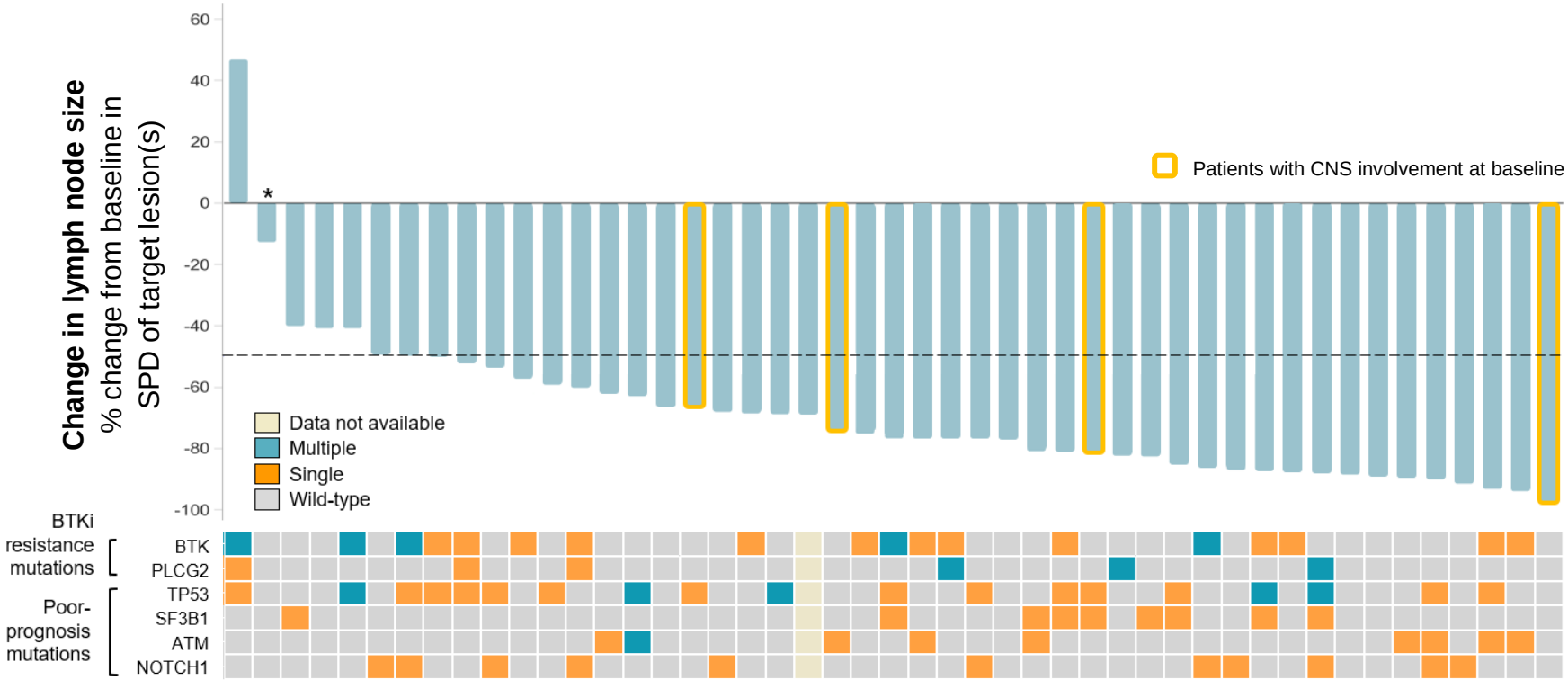
[b]Patients who progressed prior to their first response assessment and patients who discontinued for any reason after their first response assessment are included in the denominators

[c]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL, while they may not be represented in waterfall plot

Shah et al, ASH 2024

Lymph Node Assessment and High-Risk Molecular Features

Clinical activity in patients with CLL including those with baseline mutations and CNS involvement



*Patient with Richter's transformation to Hodgkin's on biopsy; Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL, while they may not be represented in waterfall plot

ATM, Ataxia-telangiectasia mutated; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **CR**, complete response; **ncBTKi**, non-covalent BTKi; **NOTCH1**, neurologic locus notch homolog protein 1; **PD**, progressive disease; **PLCG2**, phospholipase C gamma 2; **PR**, partial response; **PR-L**, partial response with rebound lymphocytosis; **RR**, relapsed/refractory; **RT**, Richter's Transformation; **SD**, stable disease; **SPD**, sum of products diameters

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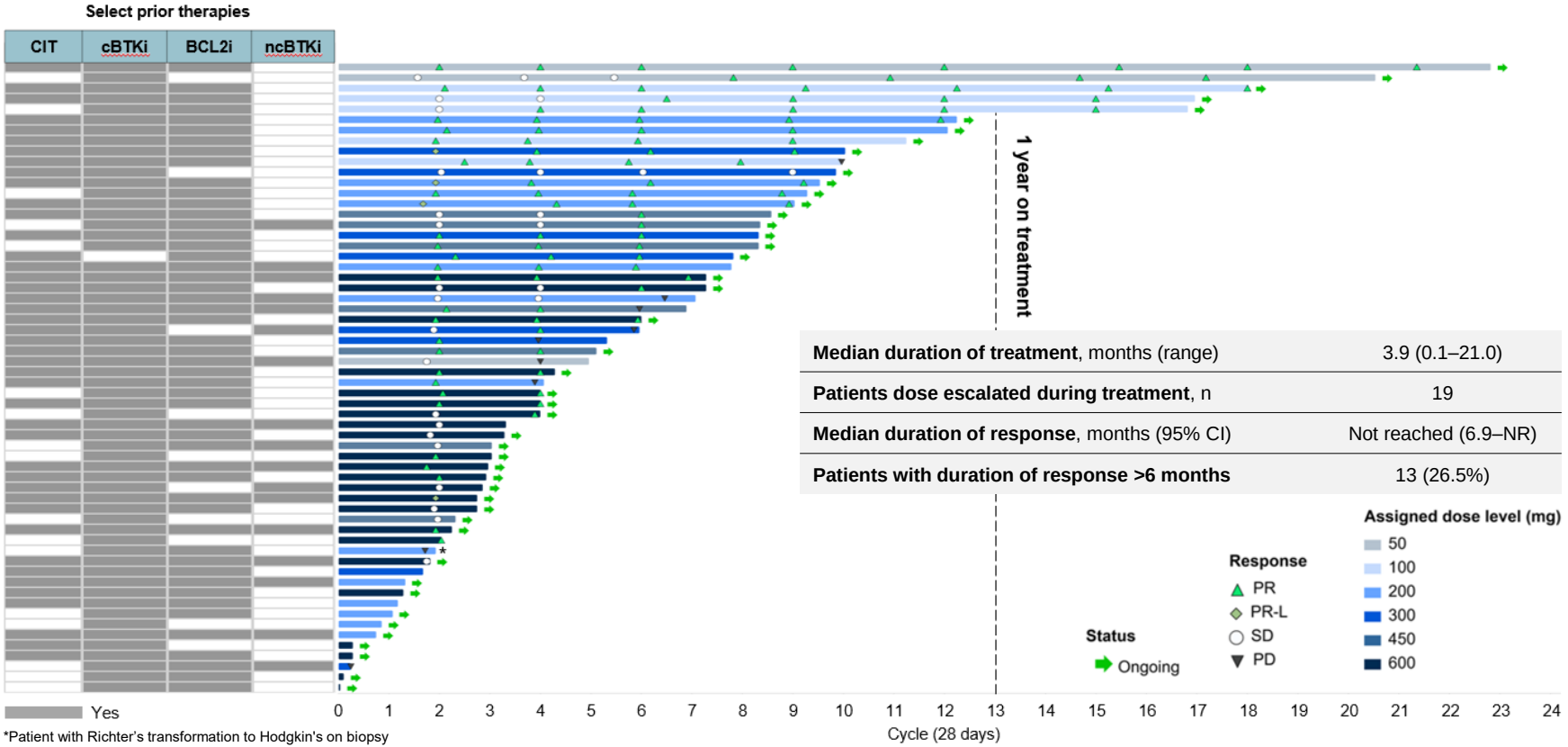
NX-5948 Duration of Treatment

Durable responses regardless of prior therapy



Median duration of treatment, months (range)	3.9 (0.1–21.0)
Patients dose escalated during treatment, n	19
Median duration of response, months (95% CI)	Not reached (6.9–NR)
Patients with duration of response >6 months	13 (26.5%)

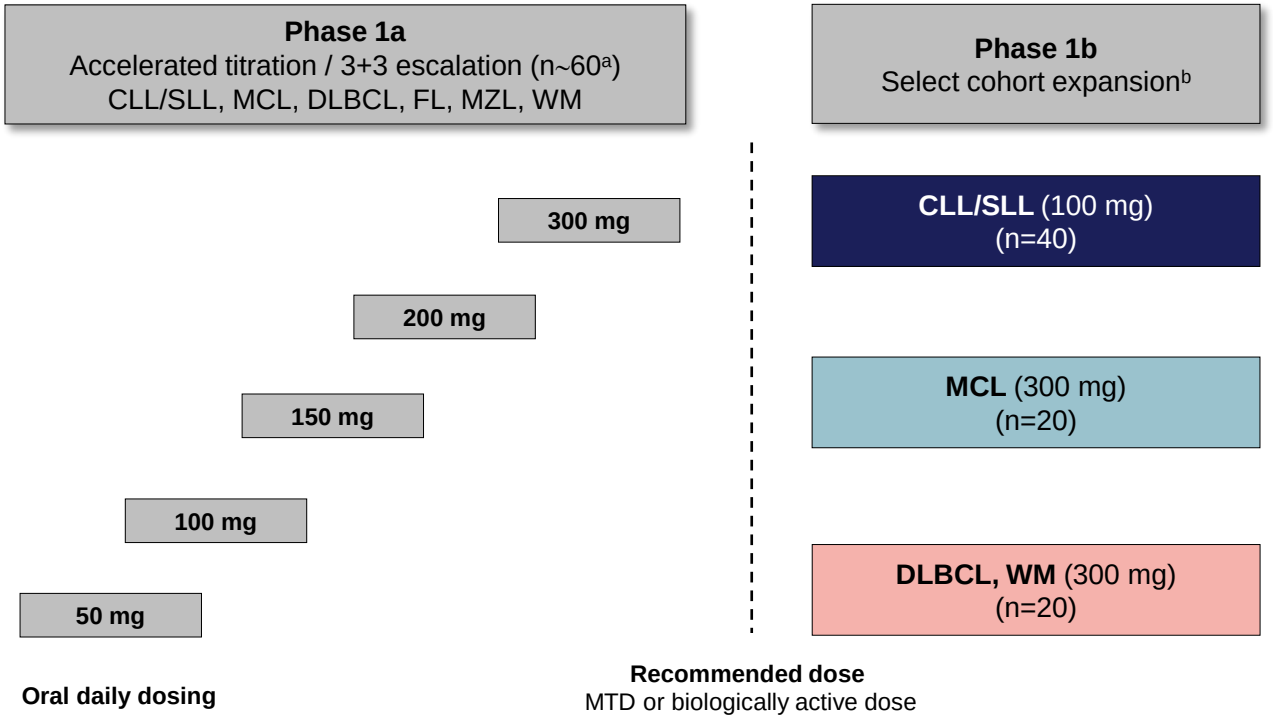
*Patient with Richter's transformation to Hodgkin's on biopsy

BCL2i, BCL2 inhibitor; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CIT**, chemo/chemo-immunotherapies; **ncBTKi**, non-covalent BTKi; **NR**, not reached; **PD**, progressive disease; **PR**, partial response; **PR-L**, PR with rebound lymphocytosis; **SD**, stable disease

Data cutoff: 10 Oct 2024

NX-2127-001: trial design

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



- 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)

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)

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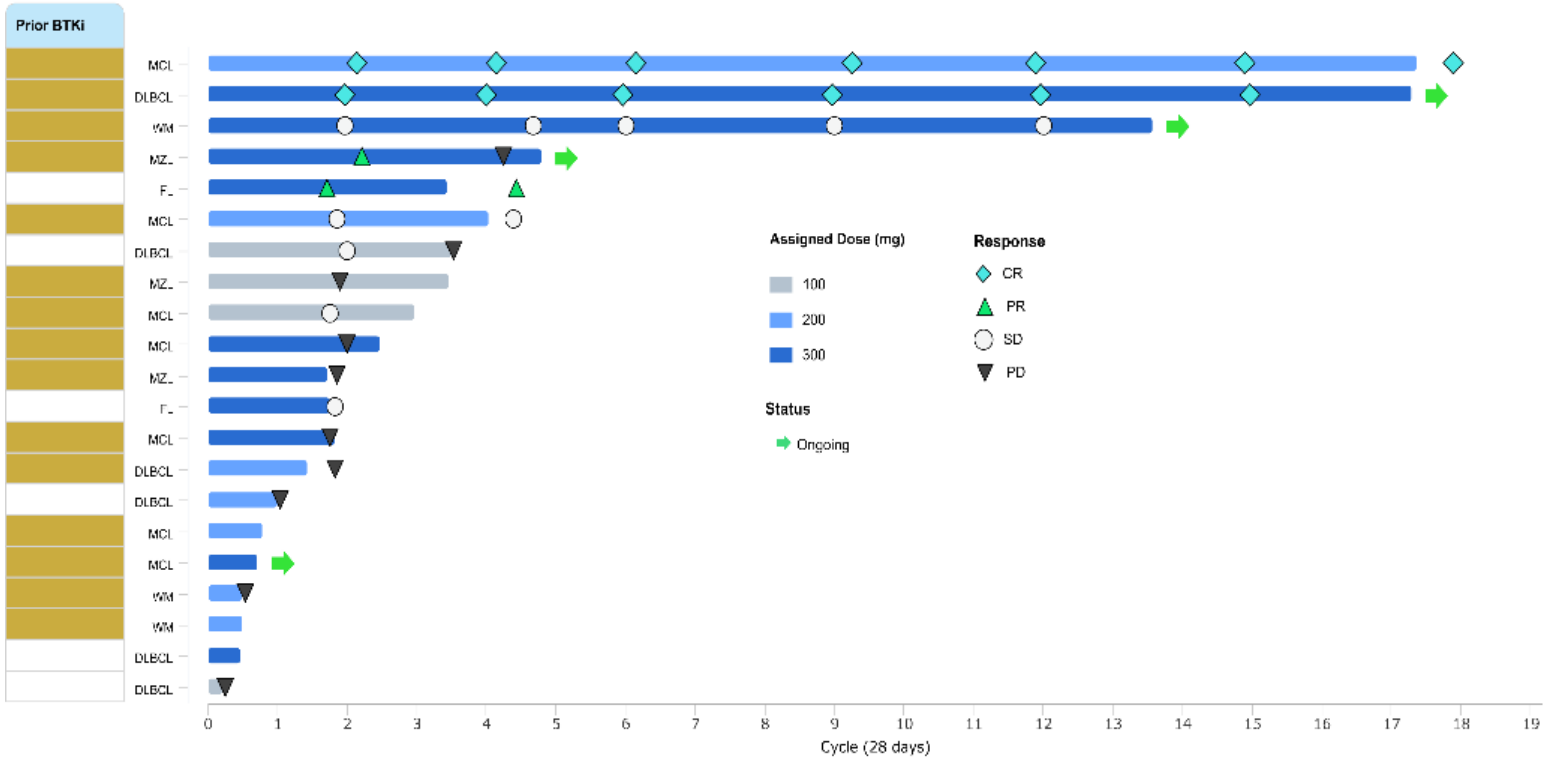
Duration of treatment and best response to NX-2127 (patients with NHL/WM)



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

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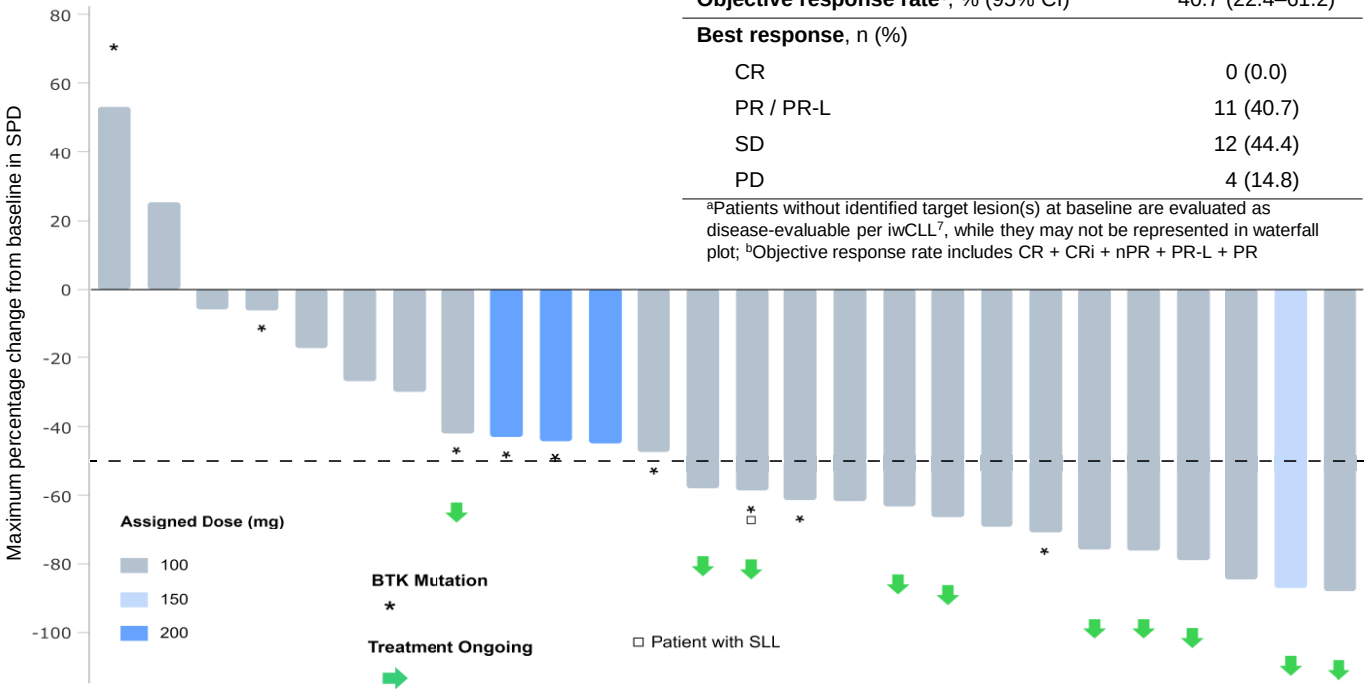
NX-2127 efficacy (patients with CLL/SLL)

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; **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

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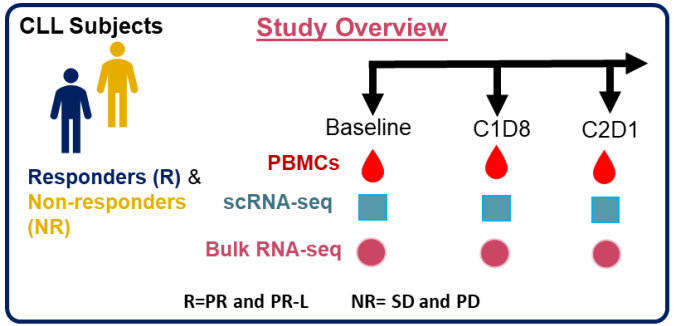
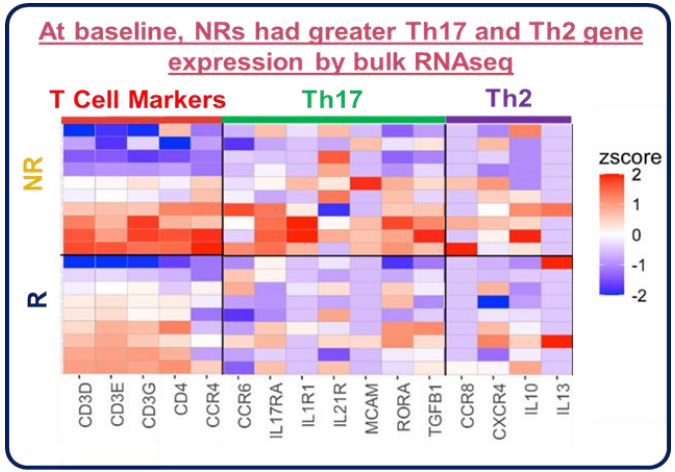
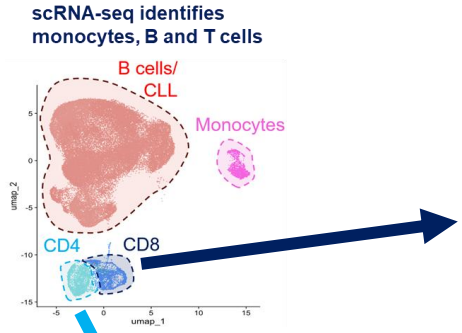
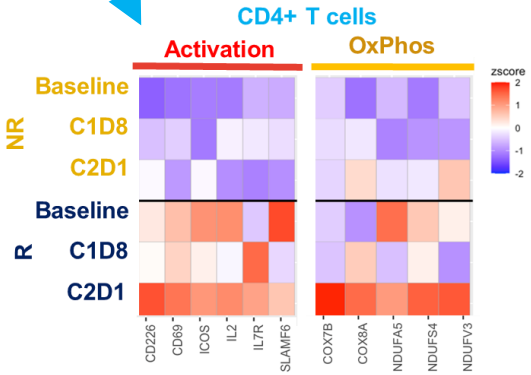
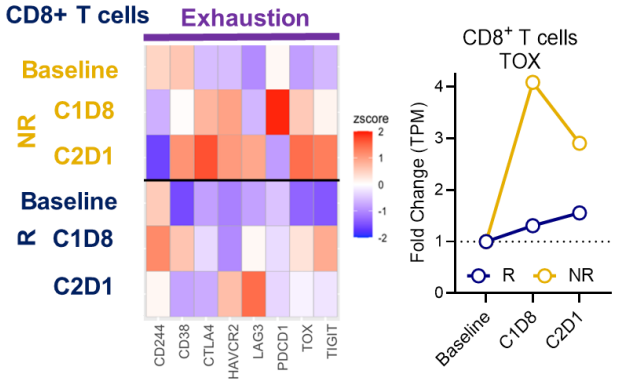
NX-2127 modulates patient T cells











Key Points:

Bulk RNA-seq: At baseline, **non-responders** exhibited higher Th17/Th2 gene expression levels compared to **responders.**

scRNA-seq: Post-dose, **responders (n=5)** exhibited increased activation and OxPhos gene expression in CD4+ T cells compared to **non-responders (n=3)**. Conversely, **non-responders** showed higher exhaustion markers in CD8+ T cells relative to **responders**.

CaDAnCe-101: Phase 1/2, Open-Label, Dose-Escalation/ Expansion Study in R/R B-Cell Malignancies

CaDAnCe-101 (BGB-16673-101, NCT05006716)

Key eligibility criteria for CLL/SLL

- Meets iwCLL 2018 criteria for treatment
- ≥2 prior therapies, including cBTKi if approved for disease
- ECOG PS 0-2 & adequate end-organ function

Key study objectives for part 1

- **Primary:** safety[c] and tolerability, MTD, and RP2D
- **Secondary:** PK, PD, and preliminary antitumor activity[d]

Part 1: Monotherapy dose finding[a]

Part 1a: Dose escalation
Selected R/R B-cell malignancies
(MZL, FL, MCL, **CLL/SLL**, WM, DLBCL, RT)
n≤72
Oral, QD, 28-day cycle[b]
Doses: 50 mg, 100 mg, 200 mg, 350 mg, 500 mg, 600 mg

Part 1b: Safety expansion
Selected R/R B-cell malignancies
(MZL, MCL, **CLL/SLL**, WM)
n≤120

Part 1c: Additional safety expansion
Selected R/R B-cell malignancies
(MZL, WM, RT, DLBCL, FL)
n≤100

Part 1d: Additional safety expansion
R/R CLL/SLL
n≤30

Part 1e: Additional safety expansion
Selected R/R B-cell malignancies (Japan only)
(MZL, FL, MCL, CLL/SLL, WM)
n=6-9

Part 1f: Monotherapy safety expansion
Selected BTK inhibitor–naive B-cell malignancies
(MZL, MCL, CLL/SLL, WM, RT)
n≤40

Determination of BGB-16673 RDFE

Phase 2

- **Cohort 1**: Post BTK inhibitor, R/R CLL/SLL
- **Cohort 2**: Post BTK inhibitor, R/R MCL
- **Cohort 3**: Post BTK inhibitor, R/R WM
- **Cohort 4**: Post BTK inhibitor, R/R MZL
- **Cohort 5**: R/R FL
- **Cohort 6**: R/R non-GCB DLBCL
- **Cohort 7**: Post BTK inhibitor, R/R RT

Baseline Patient Characteristics

Heavily pretreated, with high-risk CLL features

	Total (N=60)
Age, median (range), years	70 (50-91)
Male, n (%)	39 (65.0)
ECOG PS, n (%)	
0	34 (56.7)
1	25 (41.7)
2	1 (1.7)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	27/56 (48.2)
Unmutated IGHV	38/46 (82.6)
del(17p) and/or *TP53* mutation	40/60 (66.7)
Complex karyotype (≥3 abnormalities)	19/38 (50.0)

	Total (N=60)
Mutation status, n/N (%)	
BTK mutation present	18/54 (33.3)
PLCG2 mutation present	8/54 (14.8)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	43 (71.7)
cBTK inhibitor	56 (93.3)
ncBTK inhibitor	13 (21.7)
BCL2 inhibitor	50 (83.3)
cBTK + BCL2 inhibitors	38 (63.3)
cBTK + ncBTK + BCL2 inhibitors	12 (20.0)
Discontinued prior BTK inhibitor due to PD, n/N (%)[a]	50/56 (89.3)

Data cutoff: September 2, 2024.

[a] Remaining 6 patients discontinued prior BTK inhibitor due to toxicity (n=3), treatment completion (2), and other (n=1).

cBTK, covalent BTK; ncBTK, noncovalent BTK.

Safety Summary and All-Grade TEAEs in ≥10% of All Patients

- No atrial fibrillation
- No pancreatitis
- Major hemorrhage[b]: 3.3% (n=2; grade 1 subarachnoid hemorrhage [n=1] and grade 3 subdural hemorrhage [n=1])
- Febrile neutropenia: 1.7% (n=1; in the context of COVID-19 pneumonia and norovirus diarrhea)

	Total (N=60)	
Patients, n (%)	All Grade	Grade ≥3
Fatigue	18 (30.0)	1 (1.7)
Contusion (bruising)	17 (28.3)	0
Neutropenia[c]	15 (25.0)	13 (21.7)
Diarrhea	14 (23.3)	1 (1.7)
Anemia	11 (18.3)	0
Lipase increased[a]	10 (16.7)	2 (3.3)
Cough	9 (15.0)	0
Pneumonia	8 (13.3)	5 (8.3)
Pyrexia	8 (13.3)	0
Arthralgia	7 (11.7)	0
COVID-19	7 (11.7)	0
Dyspnea	7 (11.7)	0
Peripheral edema	7 (11.7)	0
Thrombocytopenia[d]	7 (11.7)	2 (3.3)
Amylase increased[a]	6 (10.0)	0
Nausea	6 (10.0)	0
Sinusitis	6 (10.0)	0

Median follow-up: 10.2 months (range, 0.3-26.4+).

[a] All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [b] Grade ≥3, serious, or any central nervous system bleeding. [c] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [d] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

Overall Response Rate

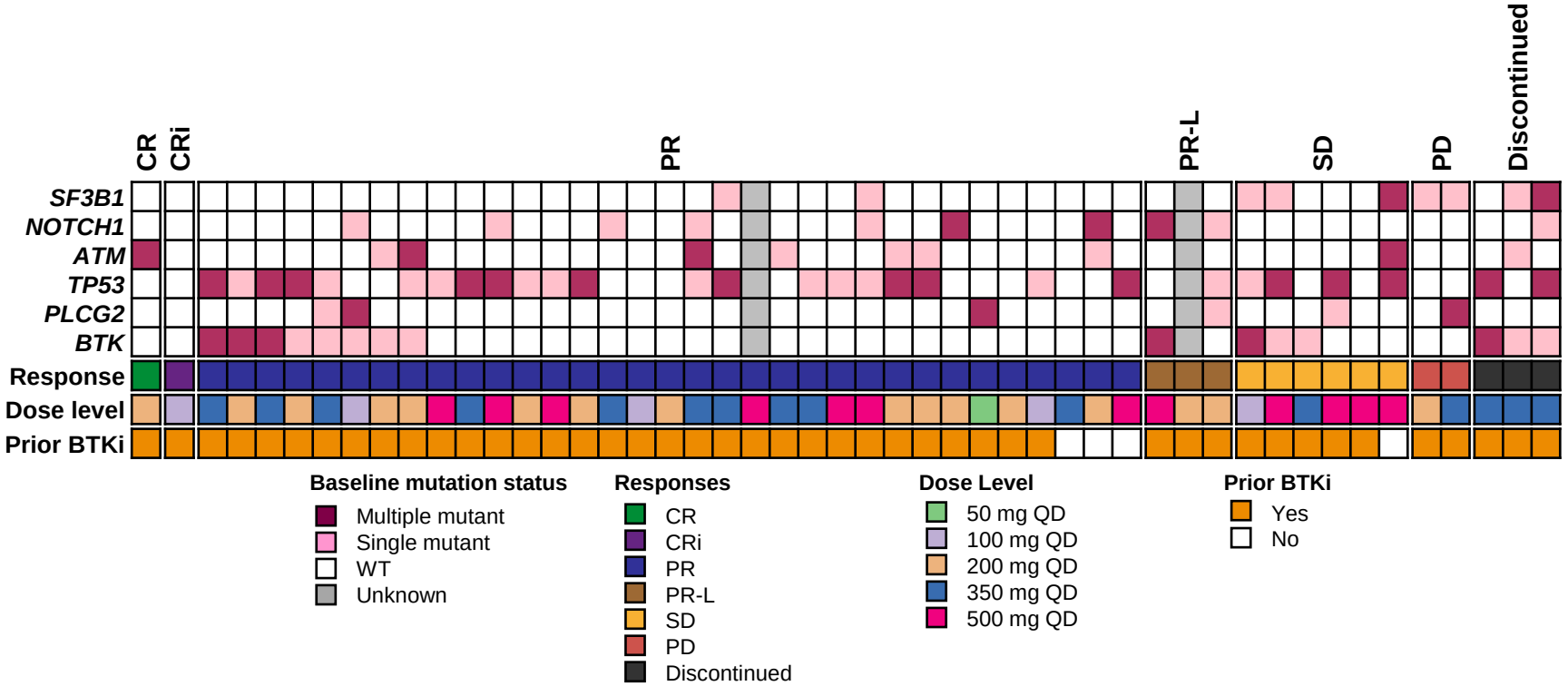
Significant Responses, Particularly at 200 mg Dose Level

	50 mg (n=1)	100 mg (n=5)	200 mg (n=16)	350 mg (n=15)	500 mg (n=12)	Total[a] (N=49)
Best overall response, n (%)						
CR/CRi	0	1 (20.0)	1 (6.3)	0	0	**2 (4.1)**
PR[b]	1 (100)	3 (60.0)	12 (75.0)	10 (66.7)	7 (58.3)	33 (67.3)
PR-L	0	0	2 (12.5)	0	1 (8.3)	3 (6.1)
SD	0	1 (20.0)	0	1 (6.7)	4 (33.3)	6 (12.2)
PD	0	0	1 (6.3)	1 (6.7)	0	2 (4.1)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (6.1)
ORR, n (%)[c]	1 (100)	4 (80.0)	**15 (93.8)**	10 (66.7)	8 (66.7)	**38 (77.6)**
Disease control rate, n (%)[d]	1 (100)	5 (100)	15 (93.8)	11 (73.3)	12 (100)	44 (89.8)
Time to first response, median (range), months[e]	2.9 (2.9-2.9)	4.2 (2.8-6.2)	2.9 (2.6-8.3)	2.8 (2.6-8.3)	2.8 (2.6-8.3)	2.8 (2.6-8.3)
Time to best response, median (range), months	2.9 (2.9-2.9)	5.6 (2.8-11.1)	3.4 (2.6-13.8)	5.6 (2.6-8.3)	4.2 (2.6-8.6)	3.6 (2.6-13.8)
Duration of exposure, median (range), months	26.4 (26.4-26.4)	13.8 (13.6-18.6)	10.6 (2.9-18.9)	10.3 (0.2-16.8)	9.3 (6.8-15.4)	10.4 (0.2-26.4)

[a] Efficacy-evaluable population. [b] Out of 33 patients with PR, 8 achieved all nodes normalized. [c] Includes best overall response of PR-L or better. [d] Includes best overall response of SD or better. [e] In patients with a best overall response of PR-L or better.
CRi, complete response with incomplete marrow recovery; PR-L, partial response with lymphocytosis.

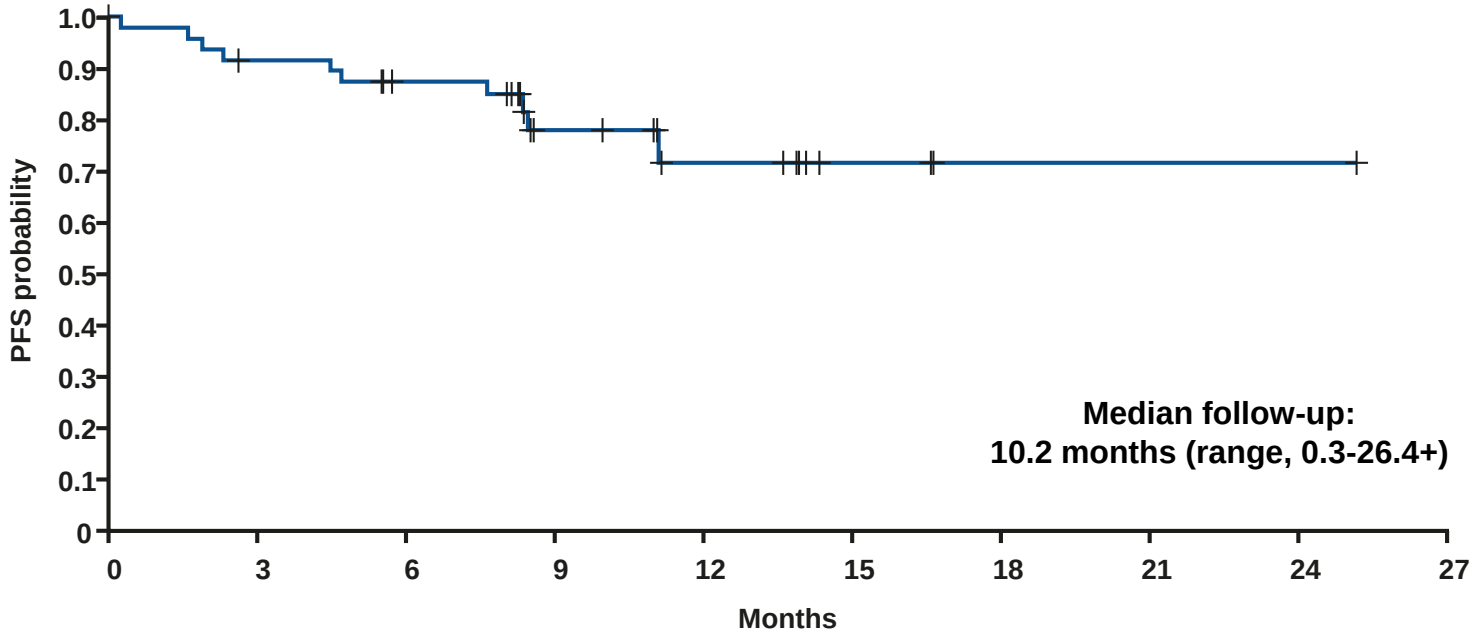
Responses Occurred Regardless of Specific Mutations

Best Overall Response vs. Baseline Mutation



BTKi, Bruton tyrosine kinase inhibitor; CRi, complete response with incomplete marrow recovery; PR-L, partial response with lymphocytosis; WT, wild type.

Progression-Free Survival



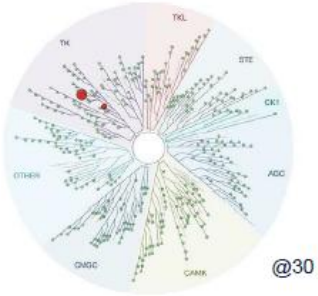
No. at risk:	60	43	37	20	10	4	1	1	1	0

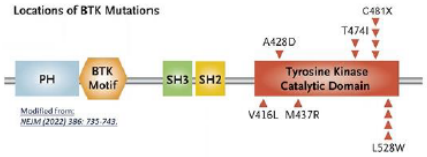
Data cutoff: September 2, 2024.

ABBV-101 is a highly potent and selective BTK degrader

BTK Degradation (6h)	DC_{50} (dMax)
TMD8-BTK^{WT}	0.7 nM (100%)
TMD8-BTK^{C481S}	0.8 nM (100%)
Human Whole Blood	4 nM (100%)

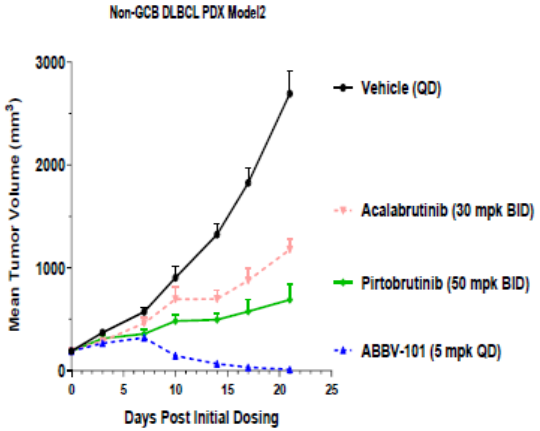
DiscoverX KINOMEscan





- TMD8 cells expressing BTK mutations were engineered using CRISPR technology (mutations confirmed by ddPCR)
- Compound potency in wildtype and mutant TMD8 cells (IC_{50}) was determined in a 72-hour Cell Titer Glo viability assay

3d IC_{50} (nM)]	WT	C481S	T474I	L528W	V416L
ABBV-101	0.5	1.1	2.8	0.1	29.8
Acalabrutinib	3.9	2970	43.3	3.5	106.3
Zanubrutinib	0.7	2320	11.7	3000	0.6
Pirtobrutinib	8.2	12.6	2730	3000	1900



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Conclusions

- PROTAC is a novel molecular approach to target oncogenic proteins
- BTK degraders with IMID function have clear T-cell immunomodulatory effects in preclinical setting
- BTK degraders show early efficacy in clinical trials with a manageable safety profile that was consistent with previous reports for BTK-targeted therapies
- BTK degraders overcome resistance to kinase inhibitors