ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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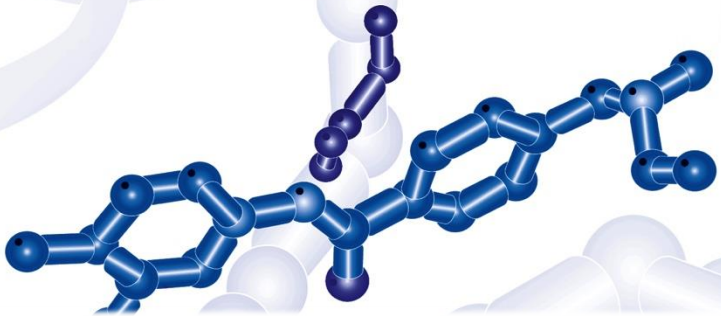


ZelebrudoMIDE (NX-2127) and bexobrutiDEG (NX-5948)

Alexey Danilov, MD, PhD

New Drugs in Hematology

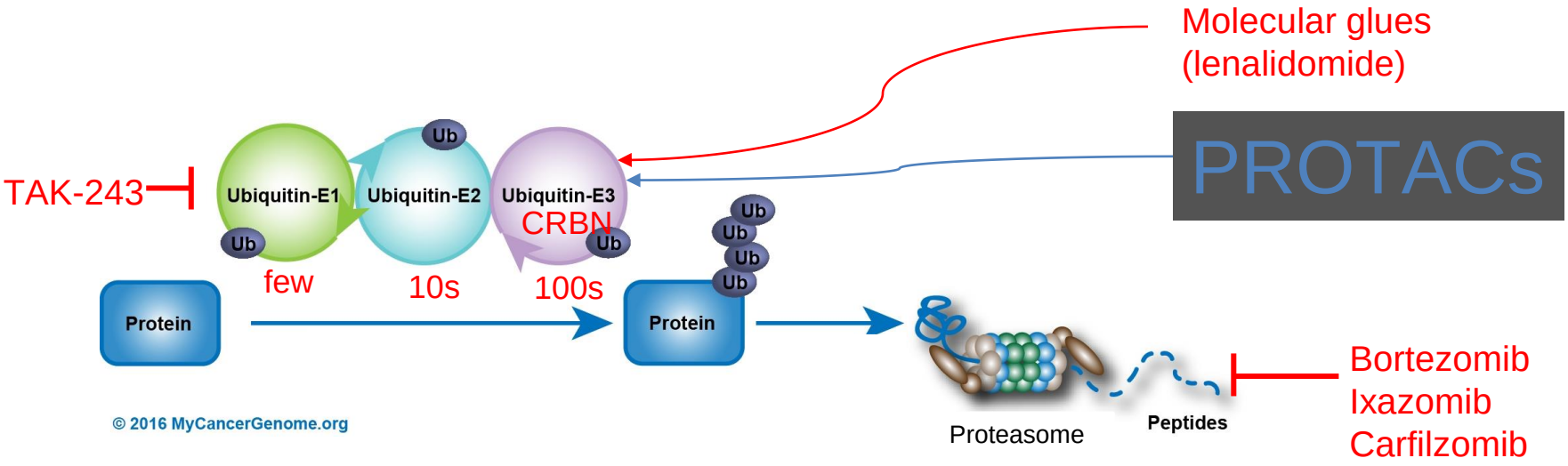
President: Pier Luigi Zinzani

Bologna,
Royal Hotel Carlton
May 18-19-20, 2026

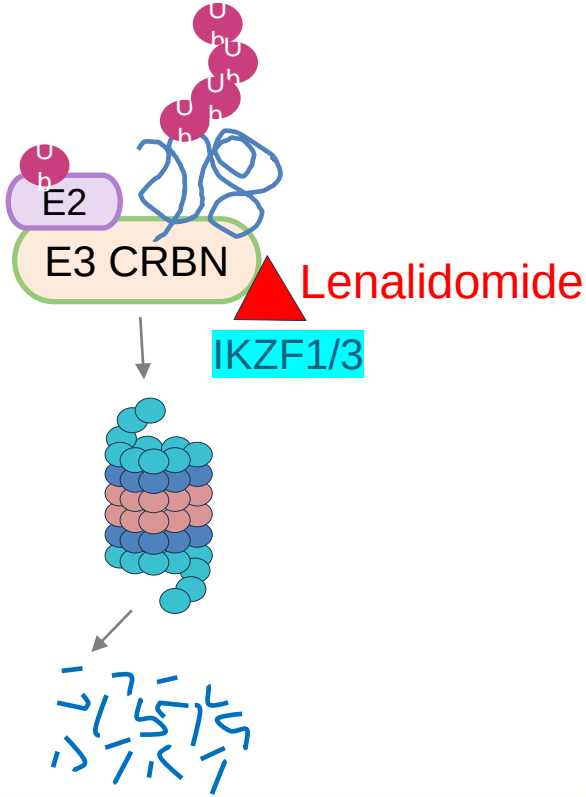
Disclosures of Name Surname

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

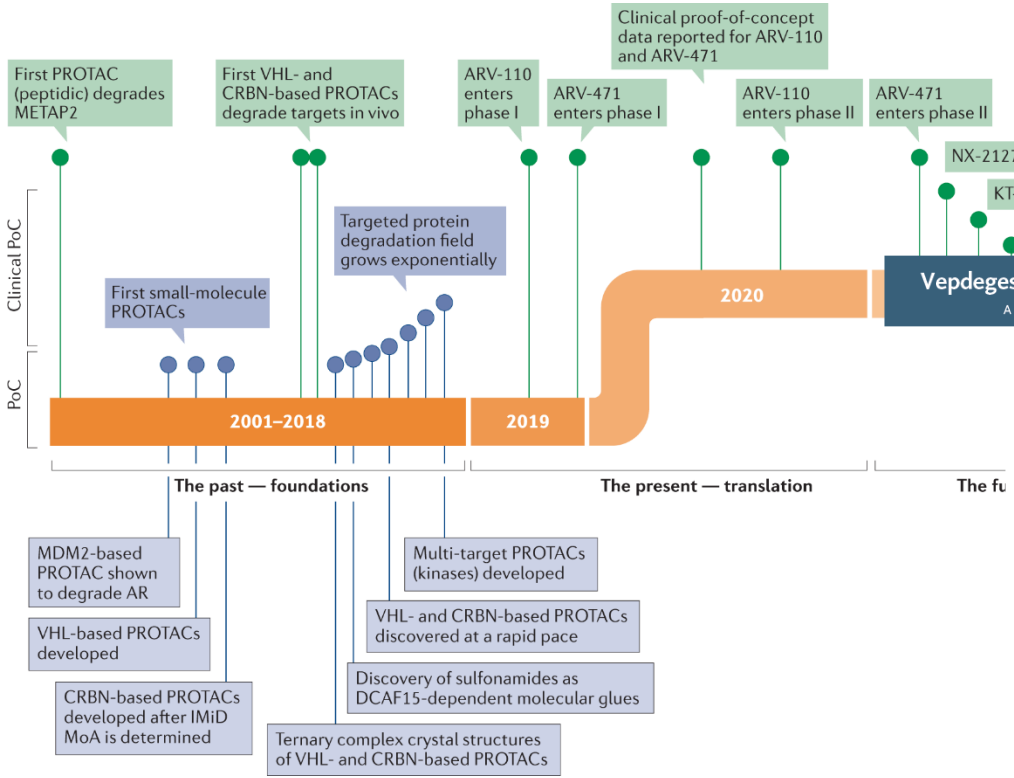
Drug Targets within the Ubiquitin-Proteasome System



Drug Targets within the Ubiquitin-Proteasome System

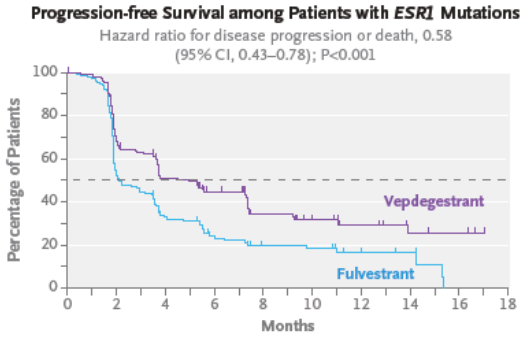


Timeline of PROTAC Development



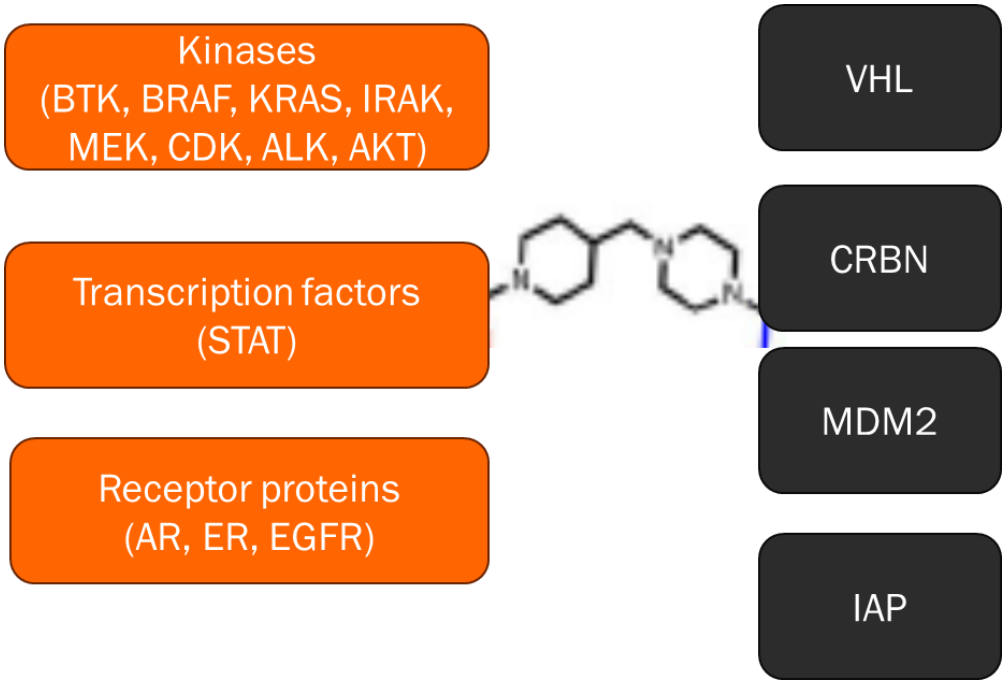
Vepdegestrant, a PROTAC Estrogen Receptor Degrader, in Breast Cancer

A Research Summary based on Campone M et al. | 10.1056/NEJMoa2505725 | Published on May 31, 2025



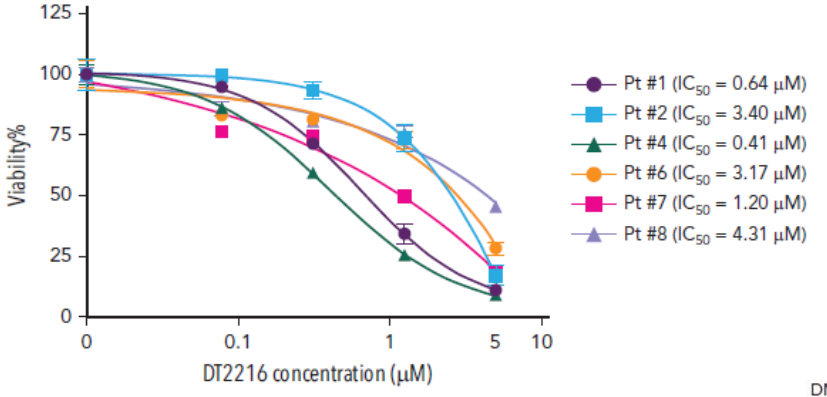
Bekes M, et al. Nat Rev Drug Discov. 2022;21(3):181-200.
Campone M, et al. N Engl J Med. 2025;393(6):556-568.

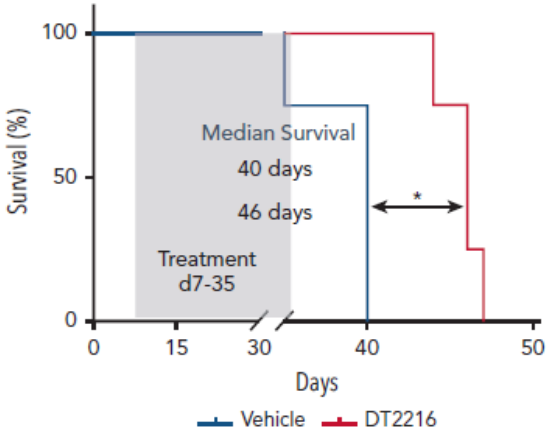
PROTACs: Hook and Harnesses

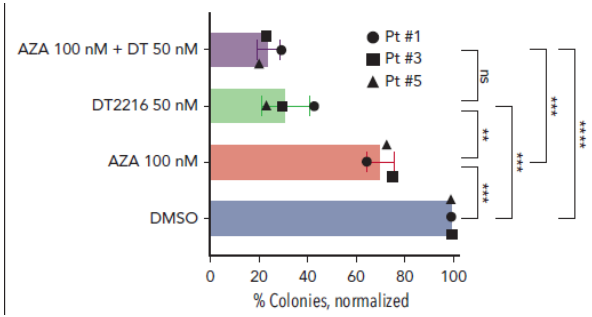


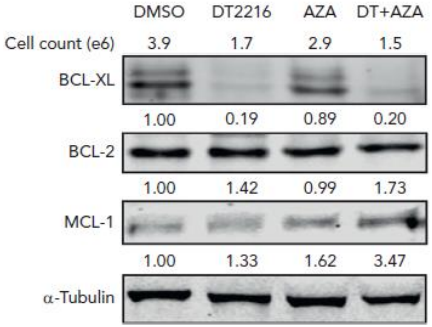
Huynh T, et al. Mol Cancer Ther. 2024;23(5):619-626.

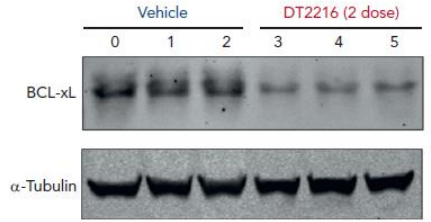
DT2216, a BCLX Degrader, Exhibits Anti-Leukemic Effect in AML Models





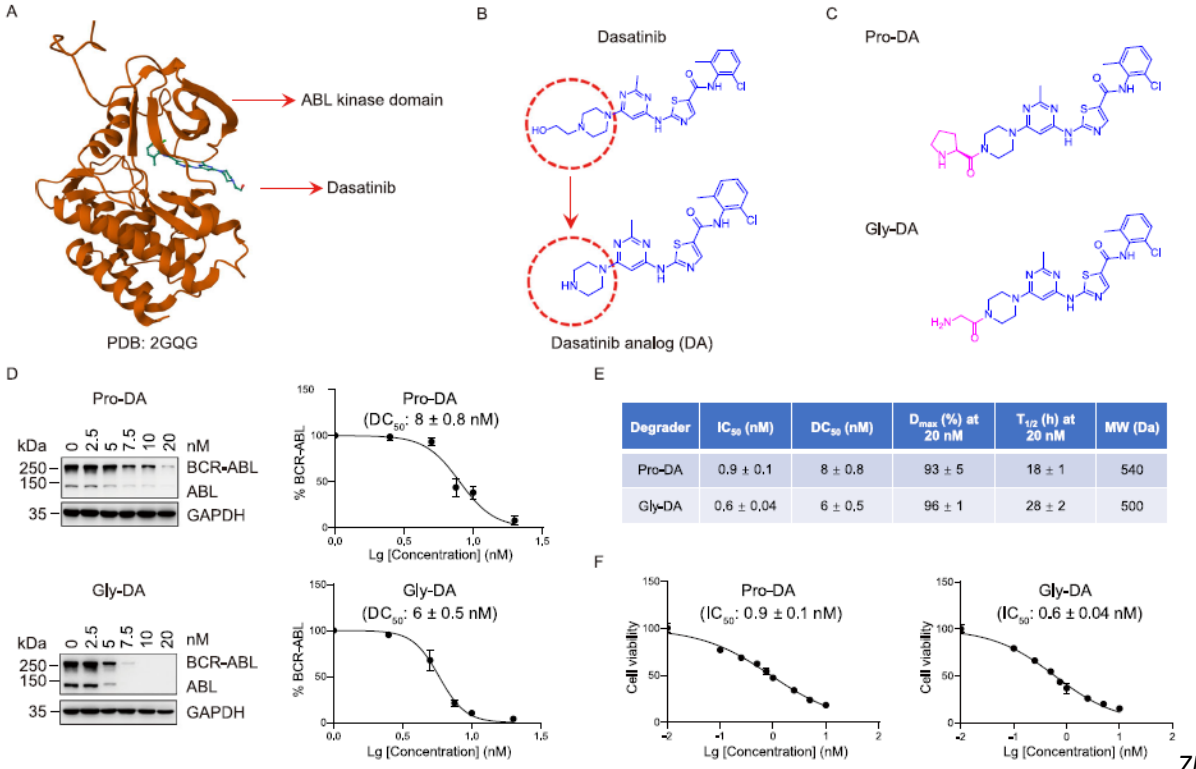






Wang Z, et al. Blood. 2025;146(3):341-355.

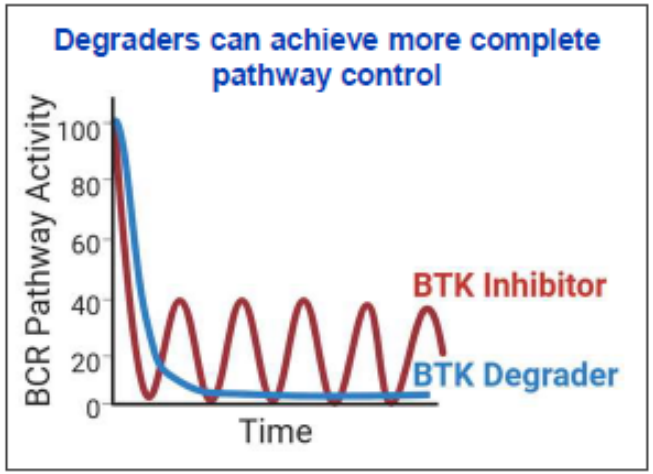
Dasatinib Analog, a Linker-free Bcr-Abl Degrader

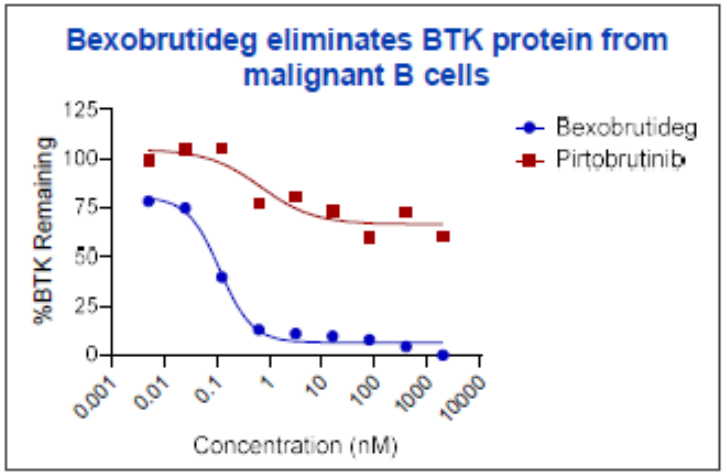


Degrader	IC_{50} (nM)	DC_{50} (nM)	D_{max} (%) at 20 nM	$T_{1/2}$ (h) at 20 nM	MW (Da)
Pro-DA	0.9 ± 0.1	8 ± 0.8	93 ± 5	18 ± 1	540
Gly-DA	0.6 ± 0.04	6 ± 0.5	96 ± 1	28 ± 2	500

Zhang J et al, Nature Comm 2025

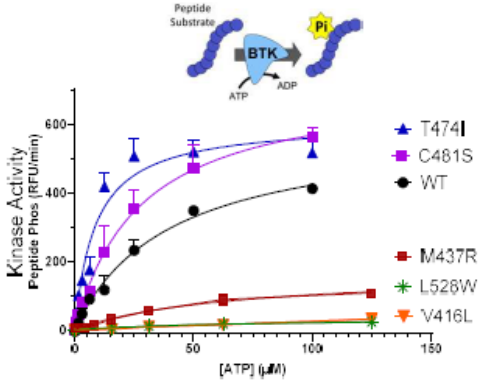
Why We Think Degraders are Cool?



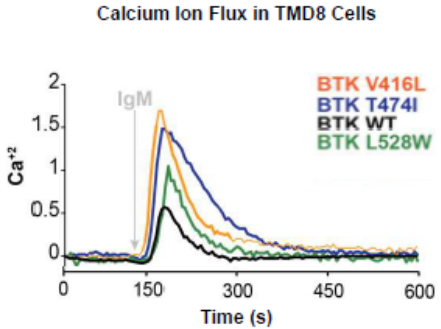


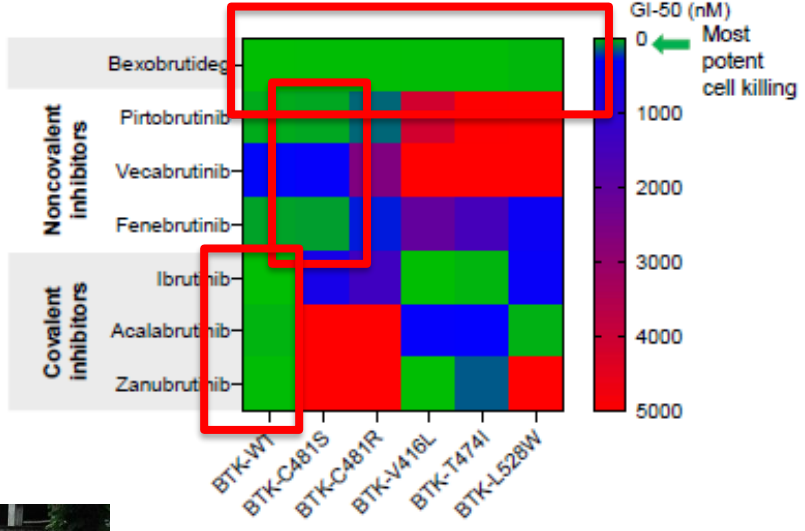
BTK Degraders: For All Your Anti-BTK Needs

BTKi-resistant mutations V416L and L528W lack kinase activity

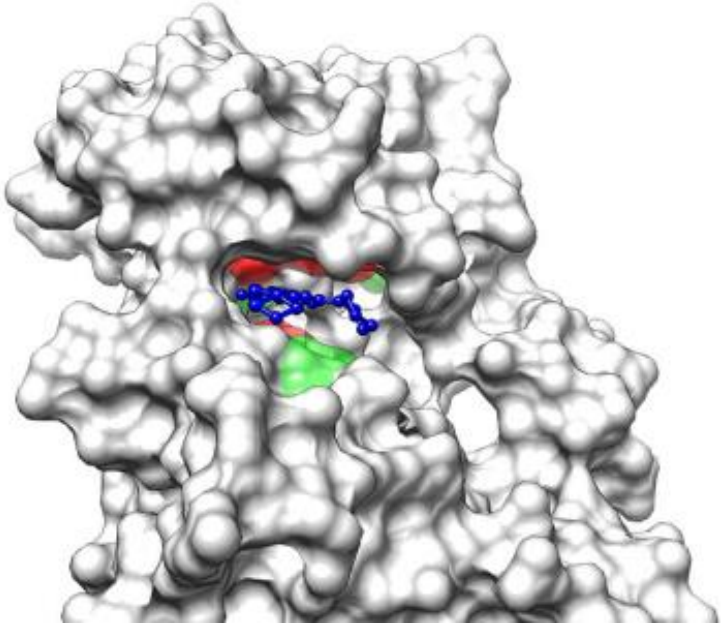


BTK kinase-dead mutations V416L and L528W propagate BCR signaling





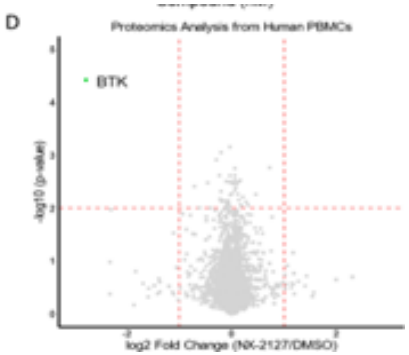
Bexobrutideg Binds in ATP Pocket Avoiding Interactions with Common Mutations



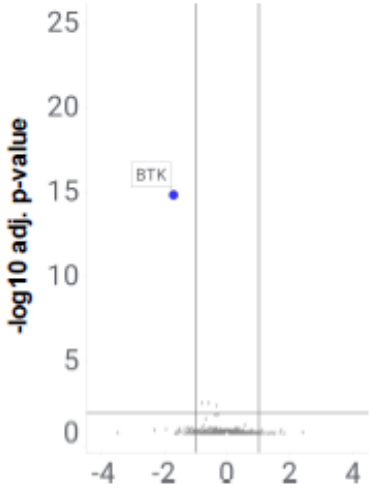
Slide credit: Nurix Therapeutics

BTK Degraders are Highly Selective Compounds

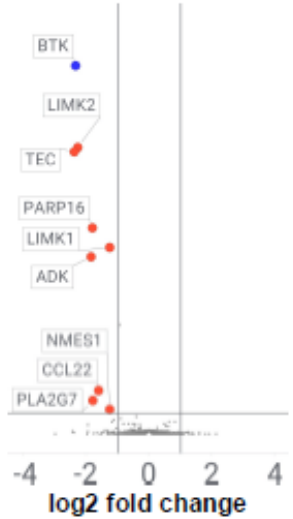
NX-2127



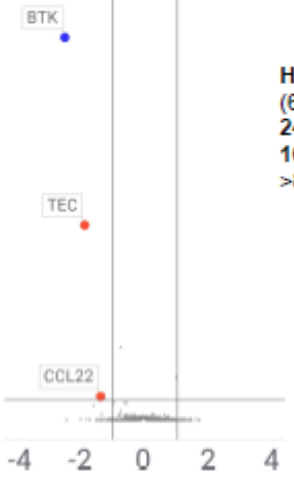
Bexobrutideg



BGB-16673



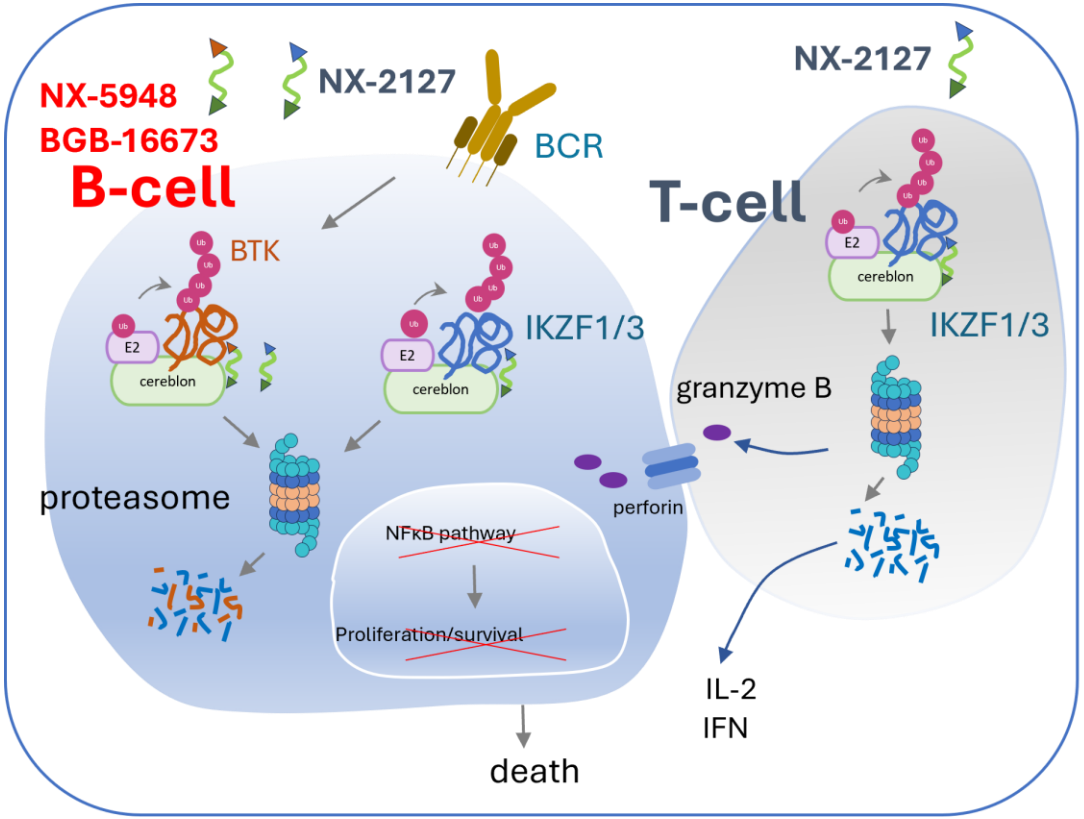
AbbVie cmpd. 1



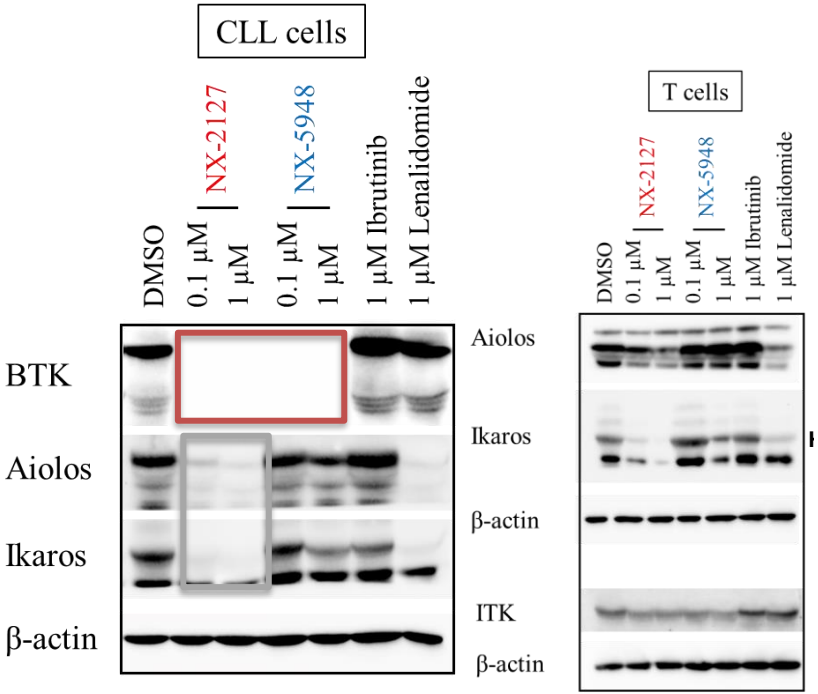
Human PBMCs
(6 healthy donors)
24-hour treatment
10xDC90
>8700 proteins detected

Robbins DW, et al. *J Med Chem*. 2024;67(4):2321-2336.
Noviski M, et al. Presented at: AACR; 2023. 2850.
Nurix Therapeutics

CRBN-recruiting dergaders NX-2127 (zelebrudomide), NX-5948 (bexobrutideg) and BGB-16673

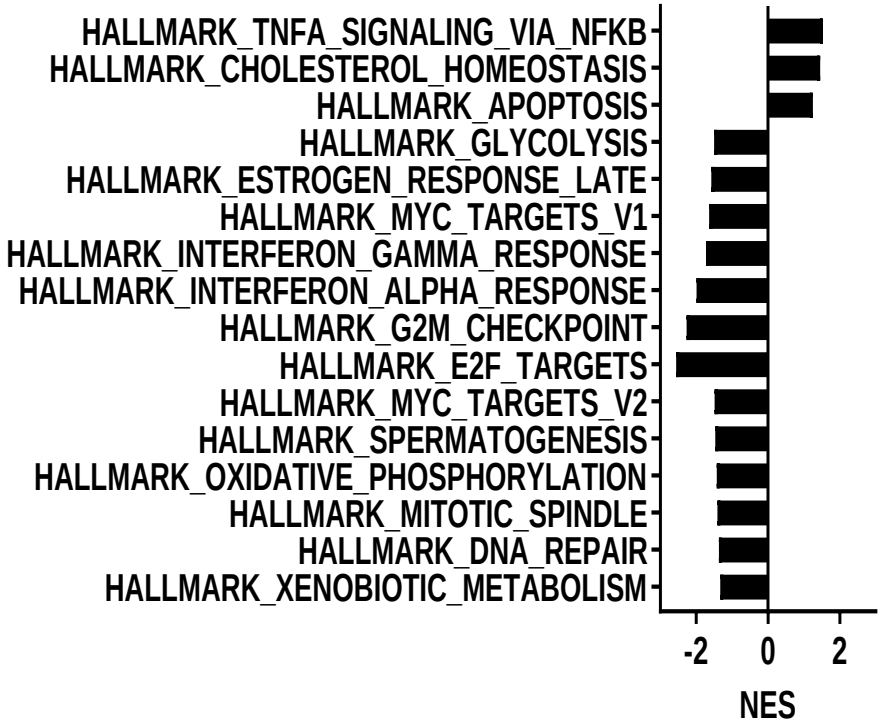


BTK and IKZF degradation by NX c



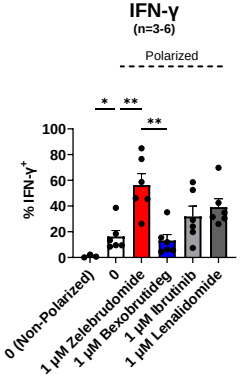
24 hour exposure

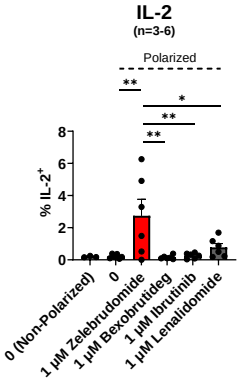
Bexobrutideg vs. DMSO (24h)

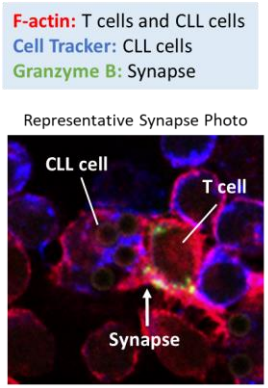


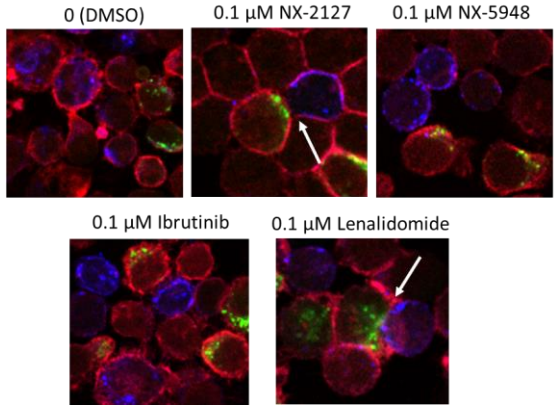
Huynh I et al, iwCLL 2025

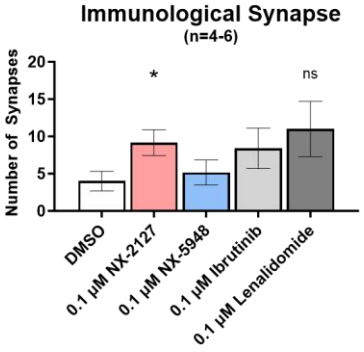
NX-2127 enhances synapse formation and cytotoxicity

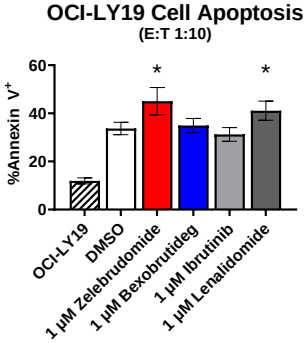








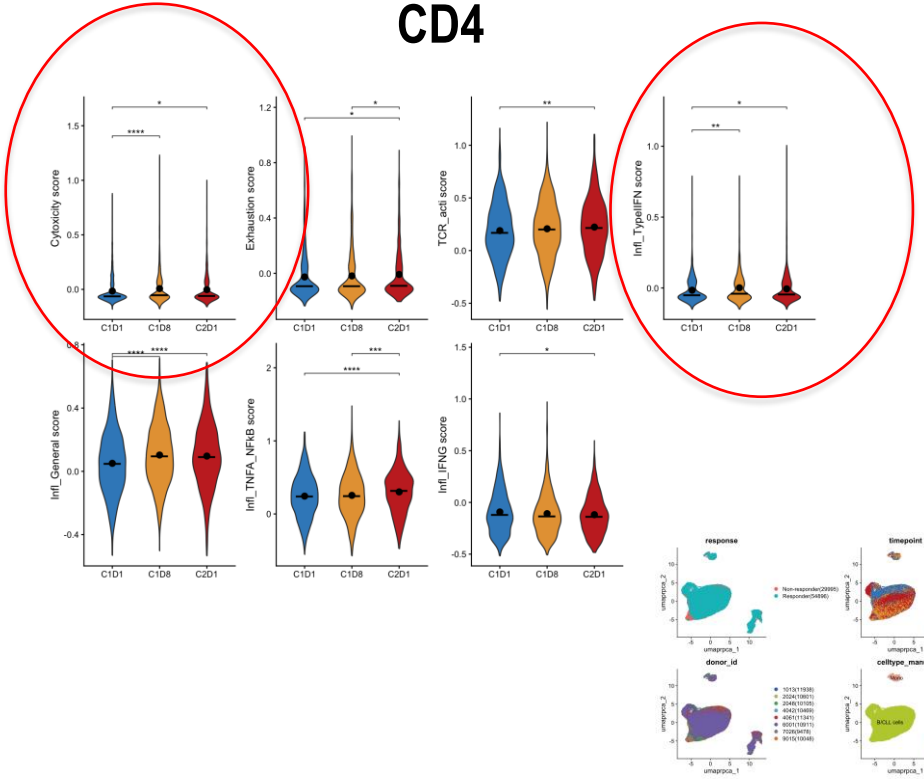




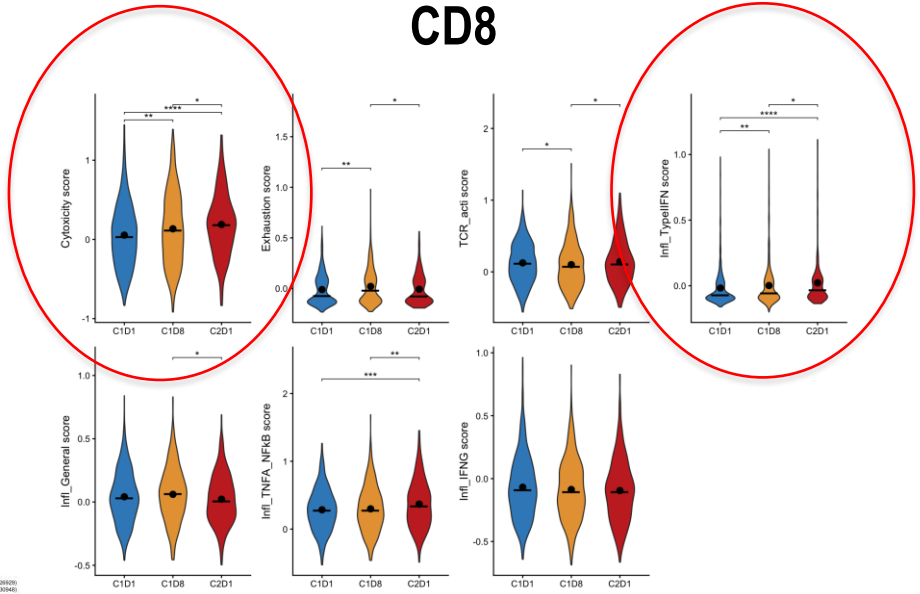
Huynh T et al, iwCLL 2025

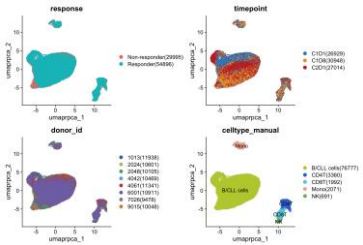
Increased Cytotoxicity and IFN-γ Score in T cells from patients treated with NX-2127

CD4

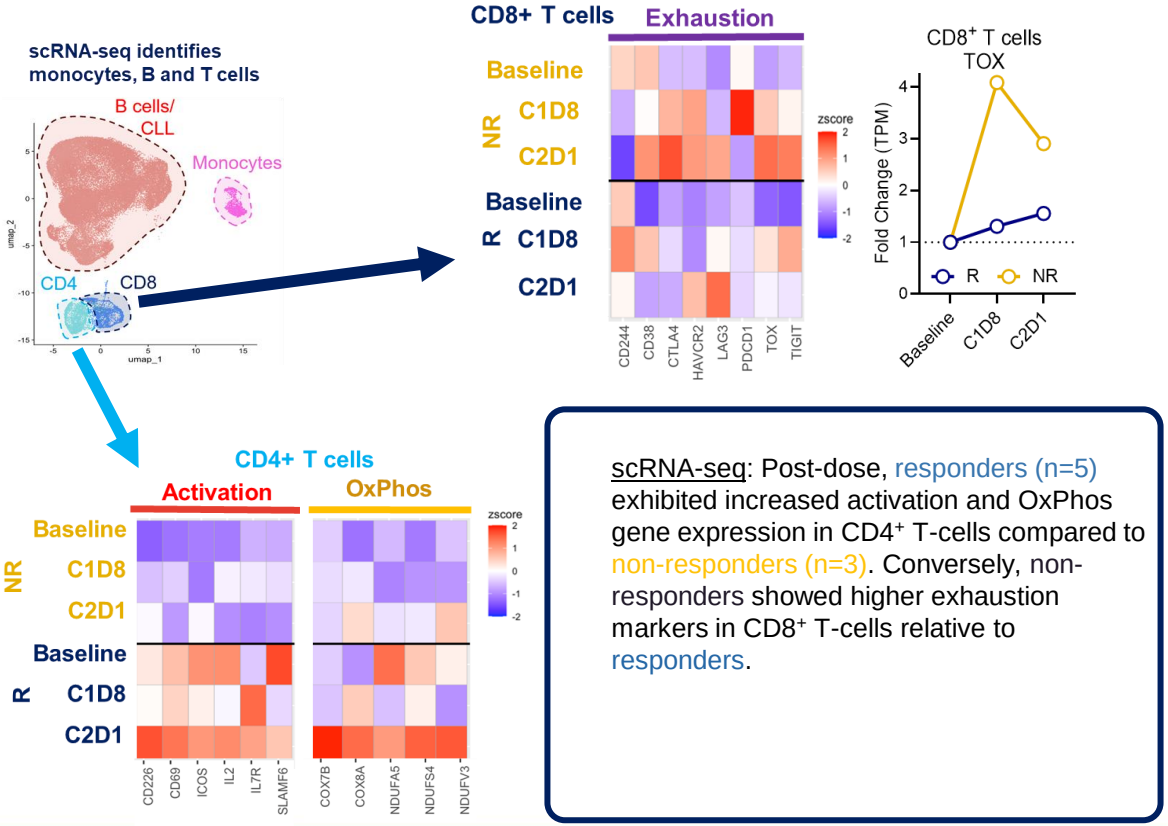


CD8





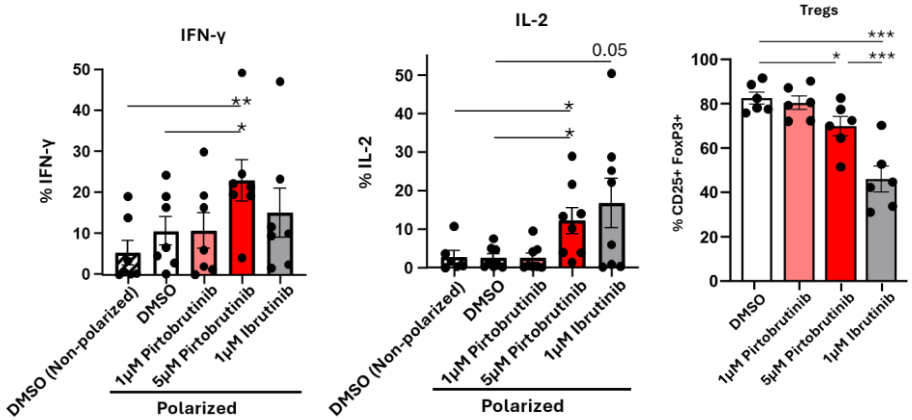
T cell signatures predict response to NX-2127



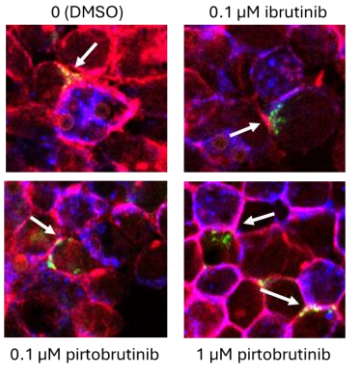
scRNA-seq: Post-dose, responders (n=5) exhibited increased activation and OxPhos gene expression in CD4⁺ T-cells compared to non-responders (n=3). Conversely, non-responders showed higher exhaustion markers in CD8⁺ T-cells relative to responders.

Pirtobrutinib may partially reverse the immunosuppressive TME

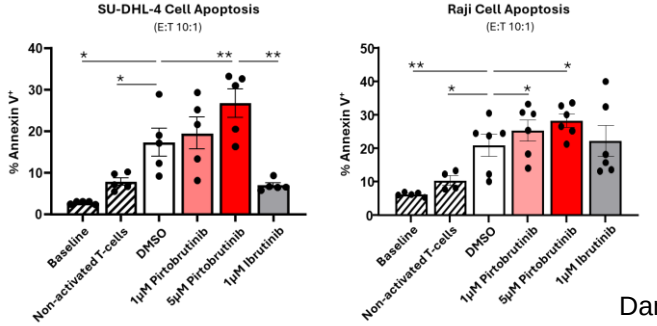
PIRTOBRUTINIB PROMOTES T_H1 POLARIZATION AND REDUCES T_{REG} DIFFERENTIATION



PIRTOBRUTINIB ENHANCES IMMUNOLOGICAL SYNAPSE AND PROMOTES CYTOTOXICITY



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

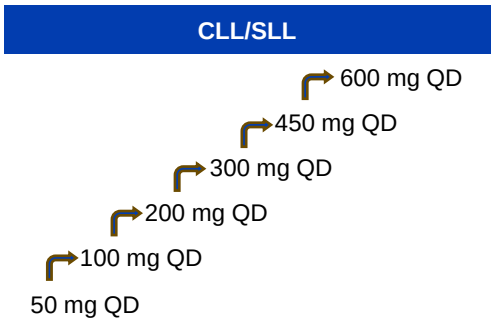


Danilov lab, ASH 2025

Bexobrutideg Phase 1a/b (NX-5948-301) Trial Design

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

Phase 1a dose escalation (fully enrolled)



CLL Phase 1b randomized cohort 1 (fully enrolled; 200 vs 600 mg)

- CLL/SLL 200 mg QD Prior BTKi and BCL2i
- CLL/SLL 600 mg QD Prior BTKi and BCL2i

CLL Phase 1b expansion, other cohorts (ongoing; all 600 mg)

- Non-C481S BTK mutations, prior BTKi and BCL2i
- Prior non-covalent BTKi, no BCL2i
- TP53 or 17p deletion, 2L, prior BTKi, no BCL2i
- 2L+, prior BTKi, no BCL2i
- BTKi-naïve
- With wAIHA, prior BTKi
- With CNS involvement, prior BTKi

NHL/WM Phase 1b expansion cohorts (600 mg)

- **MZL** Marginal zone lymphoma
- **FL** Follicular lymphoma
- **WM** Waldenström macroglobulinemia
- **MCL** Mantle cell lymphoma
- **DLBCL** Diffuse large B-cell lymphoma
- **PCNSL** Primary CNS lymphoma

***2L+**, second line +; **BCL2i**, B-cell lymphoma 2 inhibitor; **BTKi**, Bruton's tyrosine kinase inhibitor; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **NHL**, non-Hodgkin's lymphoma; **QD**, once daily; **SLL**, small lymphocytic lymphoma; **wAIHA**, warm autoimmune hemolytic anemia; **WM**, Waldenström macroglobulinemia*

Demographics in Overall Population (Phase 1a/b)

Population representative of CLL/SLL demographics

Characteristics	Phase 1a/b – all patients (n=126)
Median age, years (range)	69.0 (35–88)
Sex, n (%)	
Female	42 (33.3)
Male	84 (66.7)
Ethnicity, n (%)	
Hispanic or Latino	5 (4.0)
Not Hispanic or Latino	114 (90.5)
Not reported	5 (4.0)
Unknown	2 (1.6)
Race, n (%)	
Black or African American	8 (6.3)
White	110 (87.3)
Not reported	7 (5.6)
Other	1 (0.8)

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

Data cutoff: 19 Sep 2025

Baseline Disease Characteristics in Phase 1a/b and 1a

Multiple prior lines of therapy and a high prevalence of baseline mutations

Characteristics	Phase 1a/b – all patients (n=126)	Phase 1a (n=48)
ECOG PS, n (%)		
0	45 (35.7)	19 (39.6)
1	81 (64.3)	29 (60.4)
CNS involvement, n (%)	5 (4.0)	5 (10.4)
Median prior lines of therapy, n (range)	3.0 (1–17)	4.0 (2–12)
Previous treatments,[a] n (%)		
BTKi	108 (85.7)	47 (97.9)
cBTKi	106 (84.1)	47 (97.9)
ncBTKi	34 (27.0)	13 (27.1)
BCL2i	78 (61.9)	40 (83.3)
BTKi and BCL2i	75 (59.5)	39 (81.3)
CAR-T therapy	9 (7.1)	3 (6.3)
Bispecific antibody	5 (4.0)	1 (2.1)
PI3Ki	26 (20.6)	14 (29.2)
Chemo/chemo-immunotherapies	84 (66.7)	35 (72.9)
Mutation status,[b] n (%)	(n=111)	(n=47)
BTK	44 (39.6)	18 (38.3)
TP53	44 (39.6)	21 (44.7)
PLCG2	9 (8.1)	7 (14.9)
BCL2	8 (7.2)	6 (12.8)

[a]*Patients could have received multiple prior treatments;* [b]*Mutations presented here were centrally sequenced*

Data cutoff: 19 Sep 2025

***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;* ***CNS**, central nervous system;* ***ECOG PS**, Eastern Cooperative Oncology Group performance status;* ***ncBTKi**, non-covalent BTKi;* ***PI3Ki**, phosphoinositide 3-kinase inhibitor;* ***PLCG2**, phospholipase C gamma 2*

Overall Safety Summary in Phase 1a/b 600 mg Group vs All Patients

Tolerable safety profile, consistent between the RP2D 600 mg and overall study population

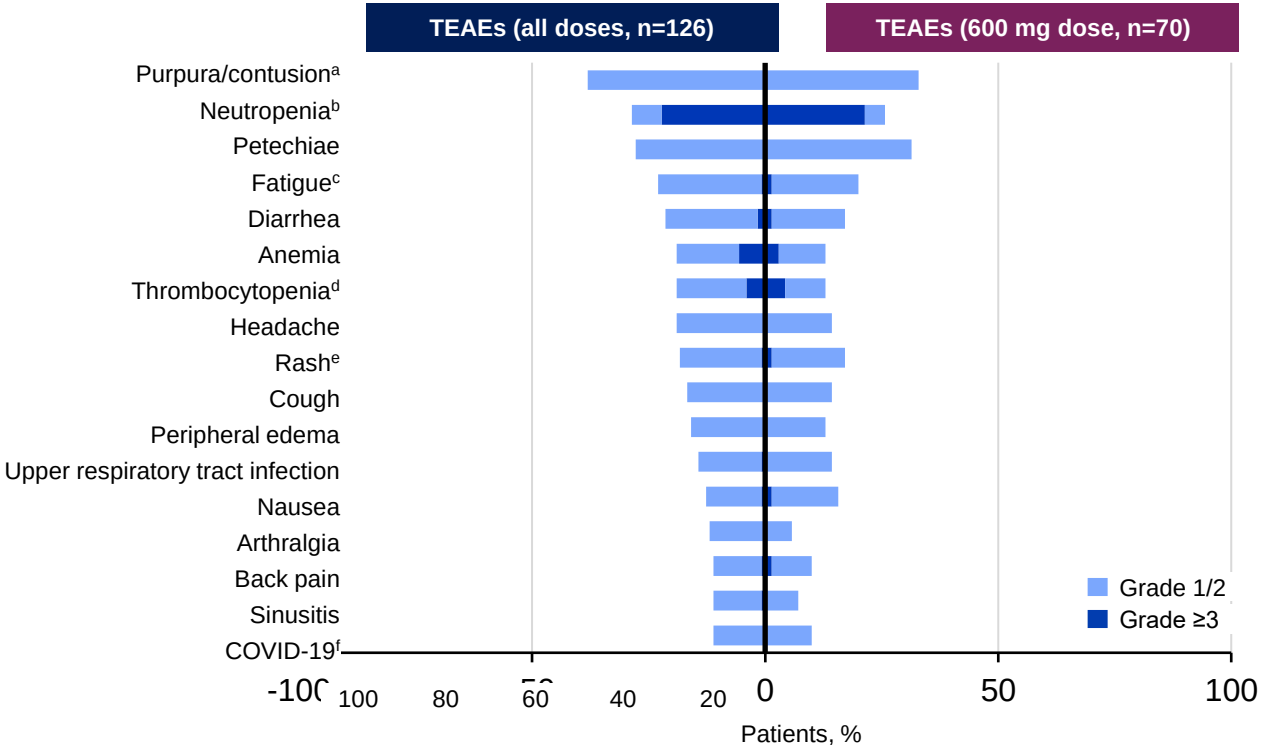
	Phase 1a/b – all patients (n=126)	Phase 1a/b 600 mg (n=70)
Any TEAE, n (%)	114 (90.5)	60 (85.7)
Treatment related	95 (75.4)	51 (72.9)
Grade ≥3	62 (49.2)	31 (44.3)
Treatment-related	31 (24.6)	18 (25.7)
SAE	27 (21.4)	10 (14.3)
Treatment-related	7 (5.6)	3 (4.3)
Grade 5[a]	3 (2.4)	1 (1.4)
Treatment-related	0	0
Leading to treatment discontinuation	8 (6.3)	4 (5.7)
Treatment-related	5 (4.0)	2 (2.9)
DLT	0	0
Median duration of treatment, months (range)	7.1 (0.0–32.3)	3.6 (0.0–18.0)

[a]*Grade 5 AEs: pulmonary embolism; death not otherwise specified; pneumonia*
***AE**, adverse event; **DLT**, dose-limiting toxicity; **RP2D**, recommended Phase 2 dose; **SAE**, serious AE; **TEAE**, treatment-emergent AE*

Data cutoff: 19 Sep 2025

TEAEs in ≥10% in Phase 1a/b 600 mg Group vs All Patients

Comparable AE profile for patients at the RP2D 600mg dose and overall population



- Tolerable safety profile consistent with prior disclosures
- No dose-limiting toxicities
- No systemic fungal infections or Grade 4 infections of any kind reported
- Single event of new onset atrial fibrillation in keeping with the rate in the age-matched general population
- 3 Grade 5 AEs (death not otherwise specified; pulmonary embolism; pneumonia; all deemed not related to bexobrutideg)

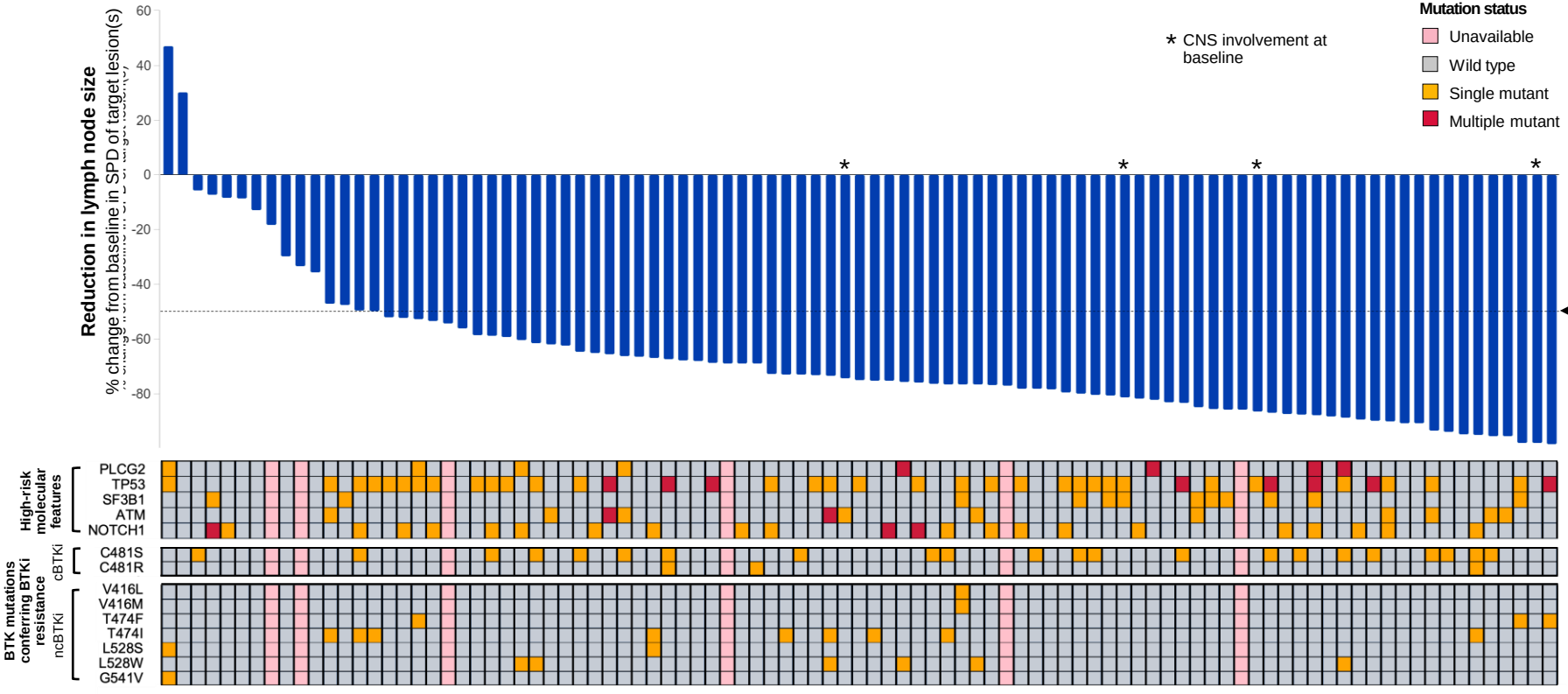
[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [c]Fatigue was transient; [d]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [e]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [f]Aggregate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

***AE**, adverse event; **NOS**, not otherwise specified; **RP2D**, recommended Phase 2 dose; **TEAE**, treatment-emergent adverse event*

Data cutoff: 19 Sep 2025

Reduction in Lymph Node Size in Phase 1a/b Overall Population[a]

Clinical activity across patients with BTK mutations,[b] high-risk molecular features and/or CNS involvement



[a]*Waterfall plot includes patients with measurable lymph node status (n=93); mutations were reported at VAF >5%;* [b]*Patients could have no mutations, a single mutation, or multiple mutations*

***ATM**, ataxia-telangiectasia mutated; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **iwCLL**, International Workshop on CLL; **ncBTKi**, non-covalent BTKi; **NOTCH1**, neurologic locus notch homolog protein 1; **PLCG2**, phospholipase C gamma 2; **SPD**, sum of products diameters*

Data cutoff: 19 Sep 2025

Overall Response Rate in Phase 1a Across All Dose Levels (n=47)

Encouraging ORR and long median duration of response

Response-evaluable patients	Phase 1a (n=47)
Objective response rate (ORR),[a] % (95% CI)	**83.0 (69.2–92.4)**
Disease control rate (DCR),[b] % (95% CI)	95.7 (85.5–99.5)
Best response,[c] n (%)	
Complete response (CR)	2 (4.3)
Nodal partial response (nPR)	1 (2.1)
Partial response (PR/PR-L)	36 (76.6)
Stable disease (SD)	6 (12.8)
Progressive disease (PD)	2 (4.3)
Median follow-up,[d] months (range)	19.0 (13.5–32.3)
Median duration of response, months (95% CI)	20.1 (12.2–NE) (n=39)

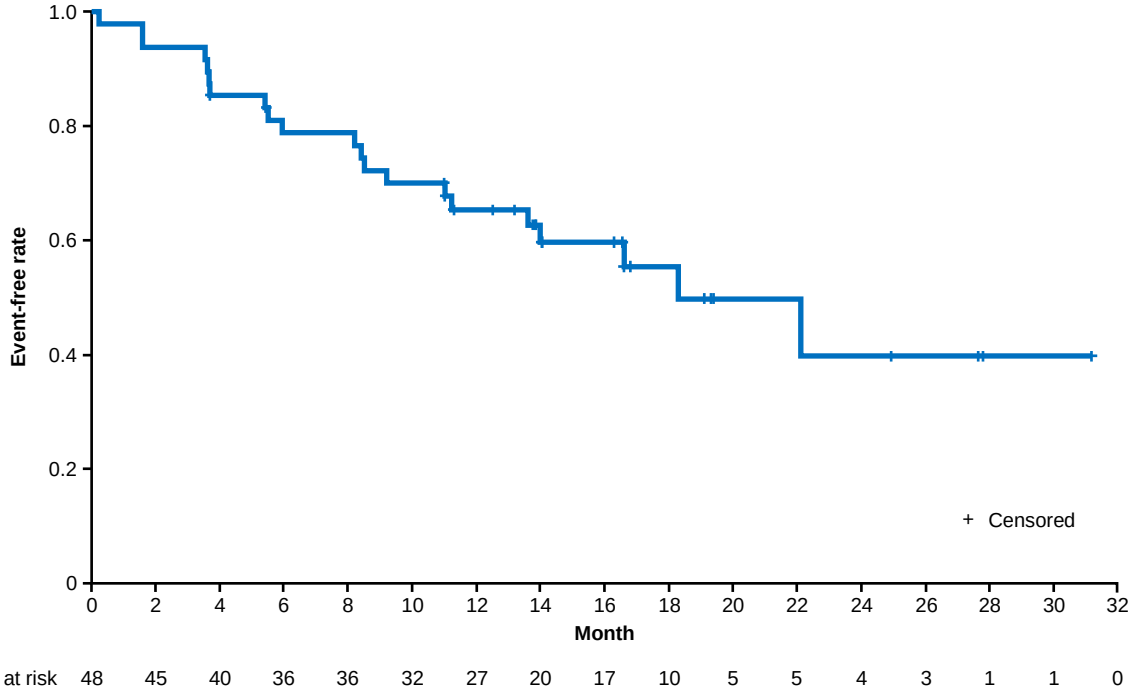
[a]Objective response rate includes CR + nPR + PR + PR-L; [b]Disease control rate includes CR + nPR + PR/PR-L + SD; [c]Percentages are based on the number of patients dosed who had at least one post-baseline disease assessment or documented clinical PD; [d]Time from treatment start to data cutoff

Data cutoff: 19 Sep 2025

***CI**, confidence interval; **CR**, complete response; **DCR**, disease control rate; **NE**, not evaluable; **nPR**, nodal partial response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **PR-L**, partial response with lymphocytosis; **SD**, stable disease*

PFS in Phase 1a Across All Dose Levels (n=48)

Median PFS of 22.1 months in study population with longest follow-up



PFS summary	
	n=48
Median PFS, months (95% CI)	22.1 (11.2–NE)
Median PFS follow-up, months (95% CI)	16.6 (14.0–19.3)

Median for PFS by Kaplan–Meier method; median PFS follow-up is by reverse Kaplan–Meier method; PFS data currently immature

Data cutoff: 19 Sep 2025

***CI**, confidence interval; **NE**, not evaluable; **PFS**, progression-free survival*

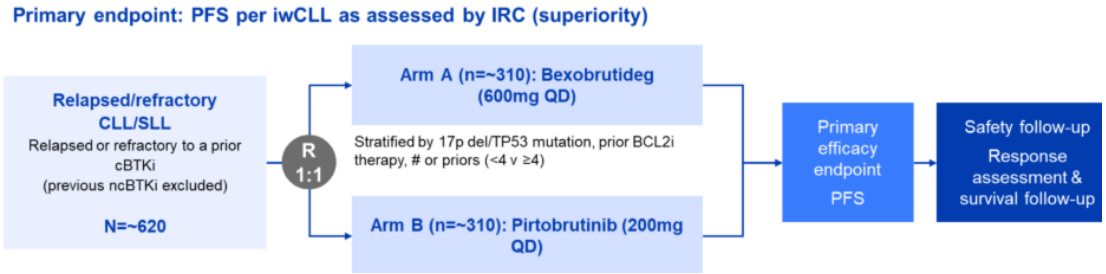
Upcoming studies with BEXOBRUTIDEG

DAYBreak CLL-201

A Single-arm, Phase 2, Open-label Multicenter Study to evaluate NX-5948 in Adults with Relapsed/Refractory CLL/SLL Previously exposed to a BTKi and a BCL2i (NCT07221500)

Eligibility: prior cBTKi, ncBTKi and BCL2i
Primary Endpoint: ORR
Dose: bexobrutideg 600 mg po daily

Phase 3 confirmatory study (CLL-306): Bexobrutideg vs. Pirtobrutinib in 2L+ R/R CLL



Conclusions

Not all BTK degraders are created equal
They are highly effective in multiple-refractory patient population
Combinations are coming

THANK YOU!

- **Sonia Rodriguez-Rodriguez PhD**
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- **Tiana Huynh MS**
- **Andrew Chen**
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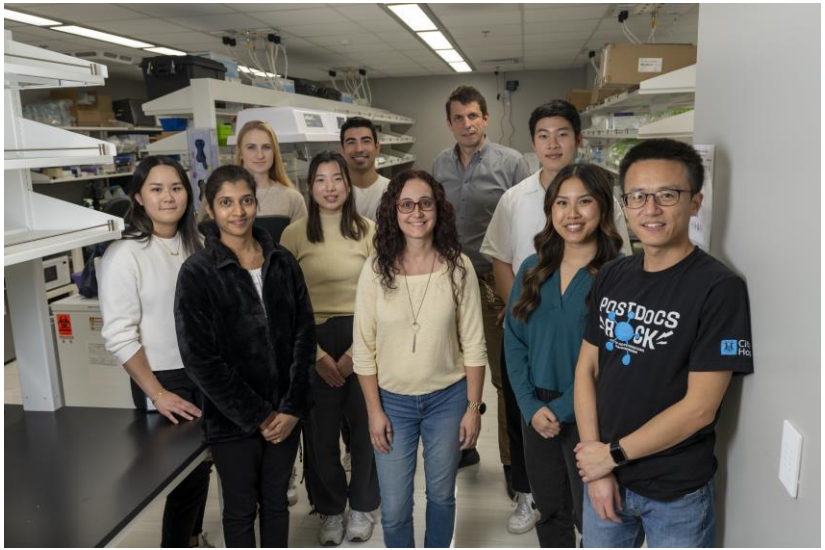
- **Lily Nixon**



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