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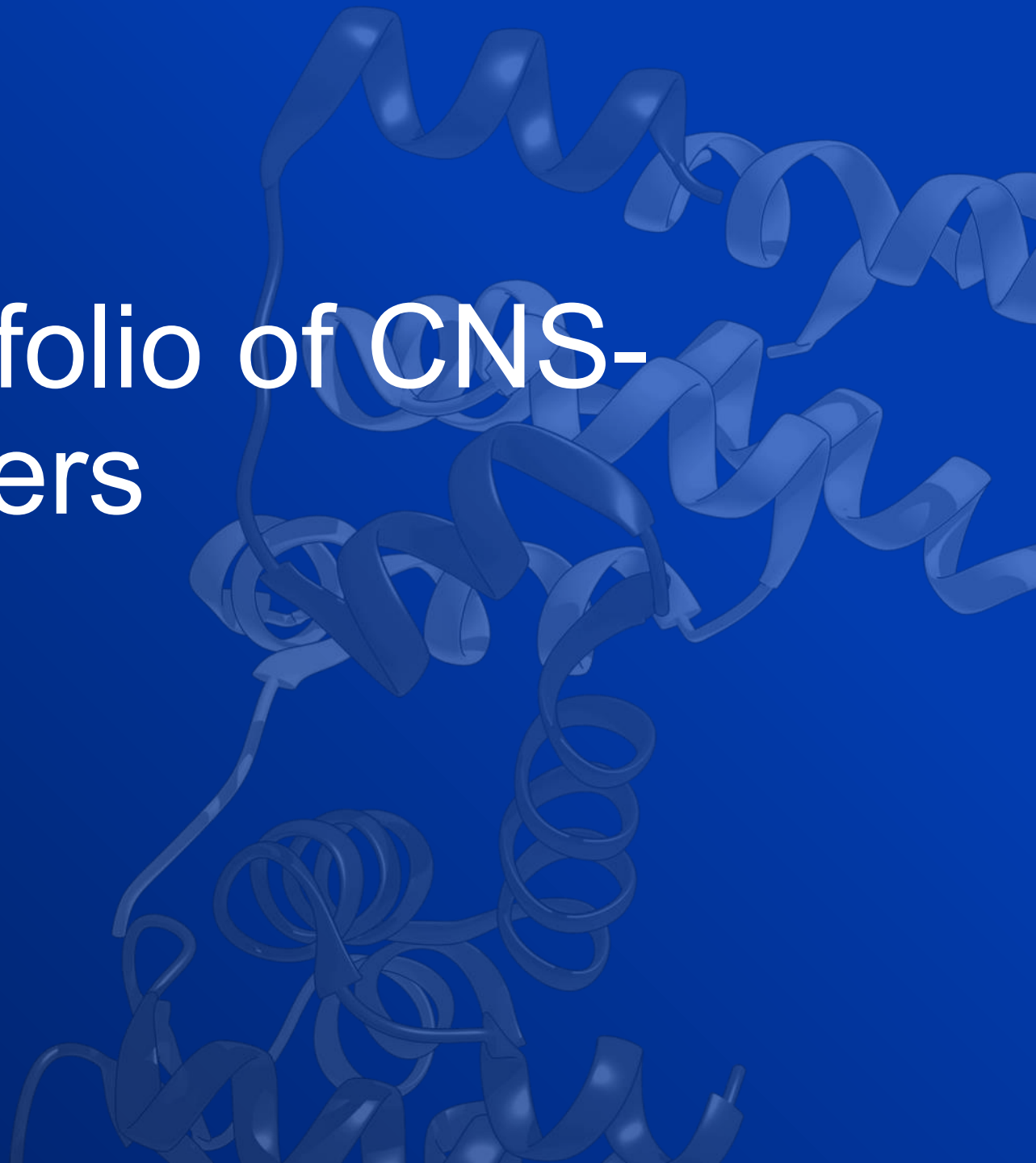
Developing a Portfolio of CNS-Penetrant Degraders



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8th TPD & Induced Proximity Summit
Boston, MA
October 29, 2025

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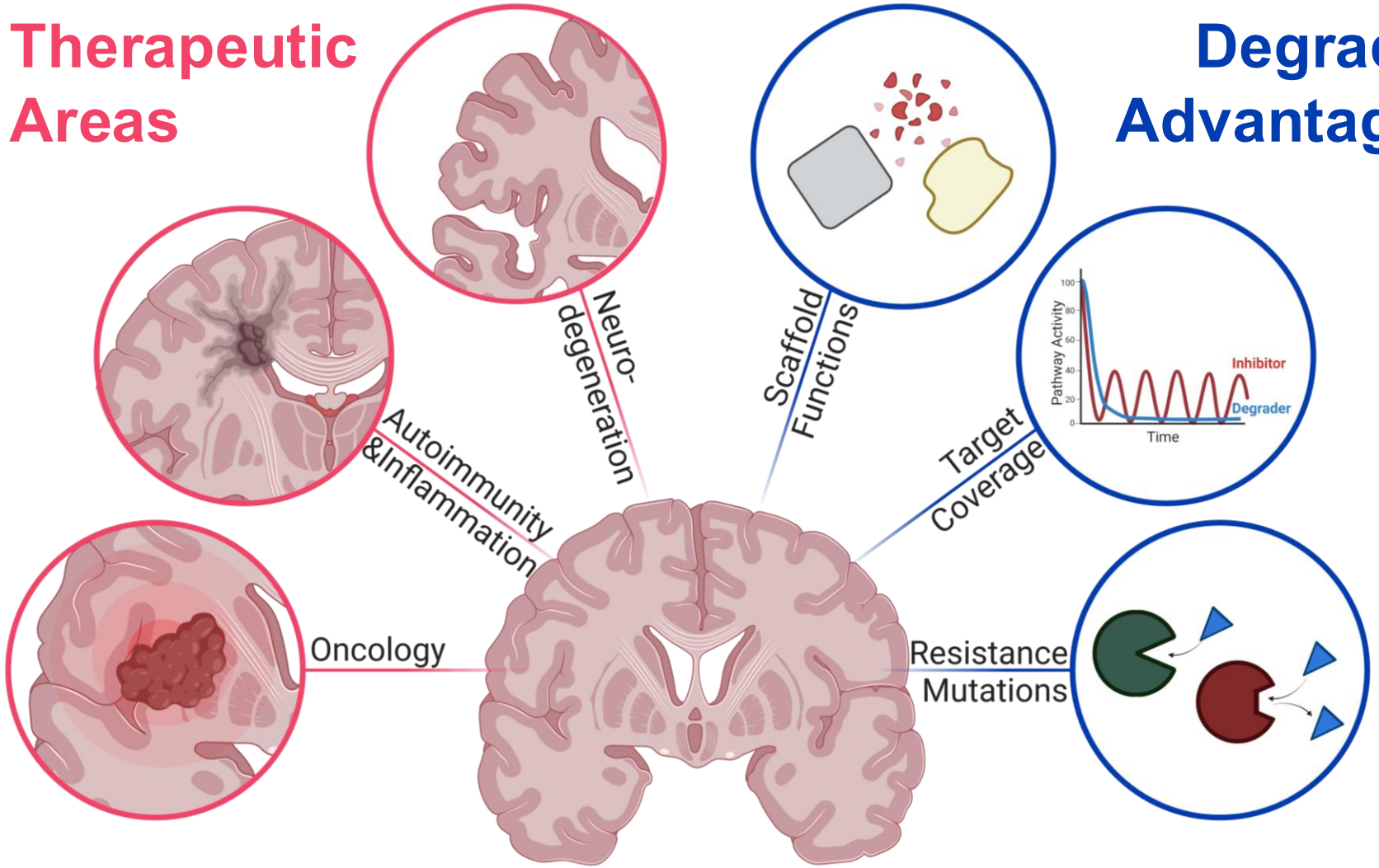
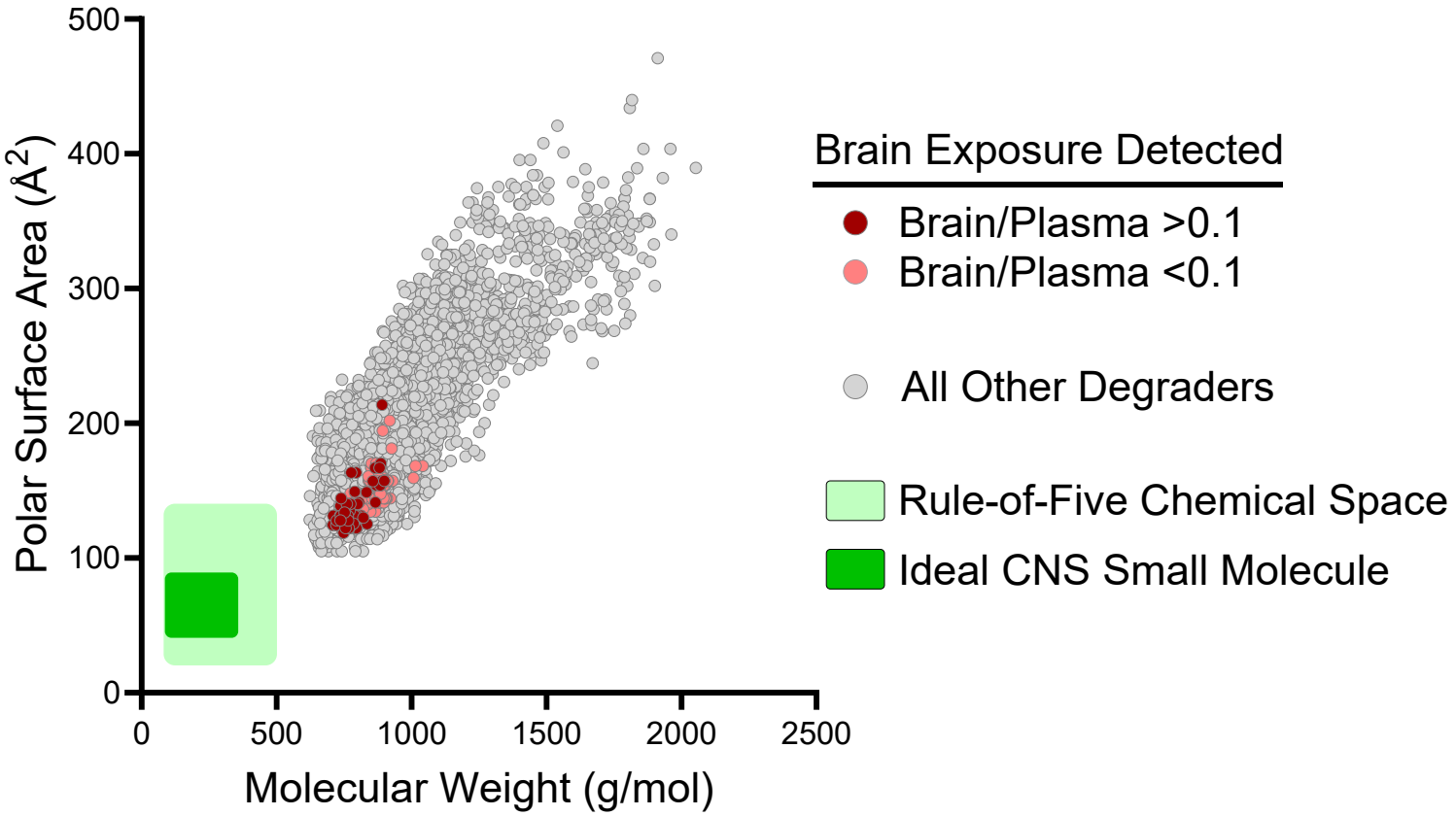
Why Create CNS-Penetrant Degraders?



Graphic created with BioRender

Nurix Targeted Protein Degraders have Achieved Brain Exposure at Meaningful Frequencies Across Diverse Programs

Targeted protein degraders occupy chemical space far outside the parameter space of typical CNS small molecules



64% of compounds screened have achieved brain exposure

Compounds Tested

	Percent w/ Exposure	Highest Exposure (ng/g)
Program 1	80%	663
Program 2	49%	377
Program 3	63%	1280
Program 4	15%	1570
Program 5	60%	247
Program 6	50%	64
Program 7	100%	216

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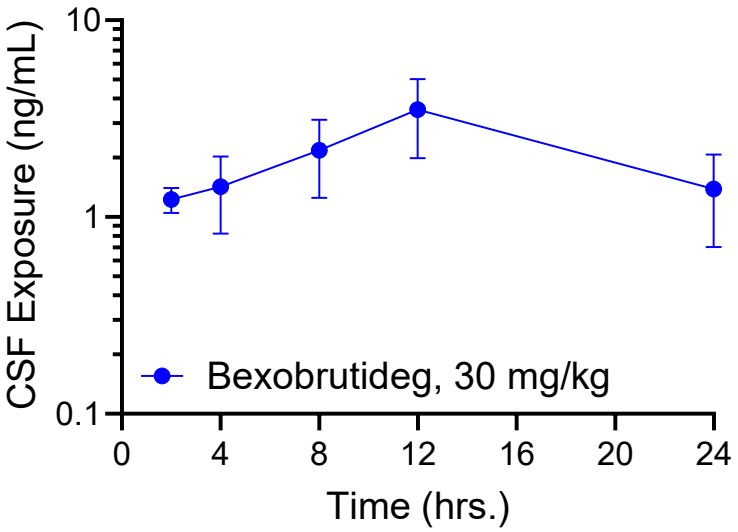
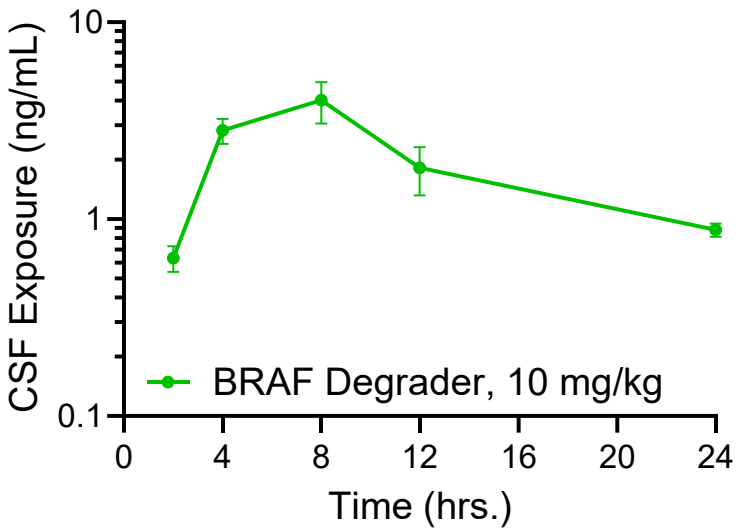
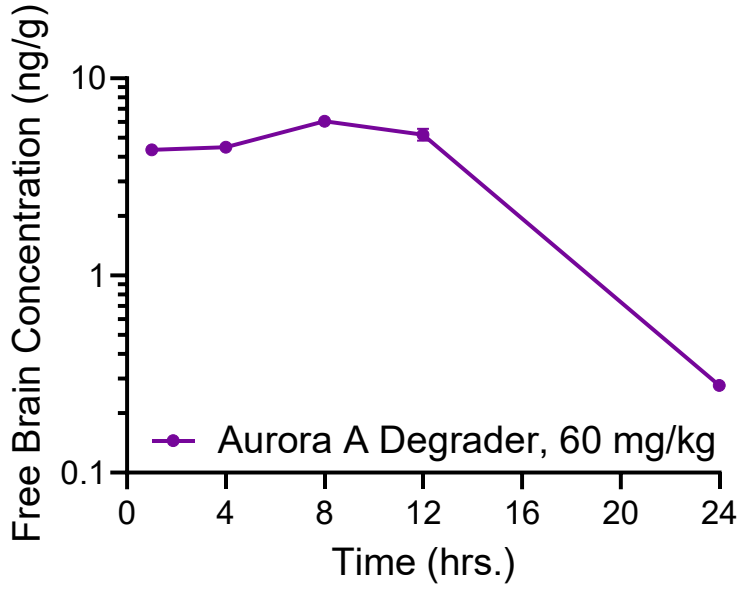
Kinetics of CNS Exposure Differ Between Degraders from Different Chemical Series







Nurix performs detailed characterization of CNS exposure to identify degrader pharmacokinetic profiles that best fit disease biology

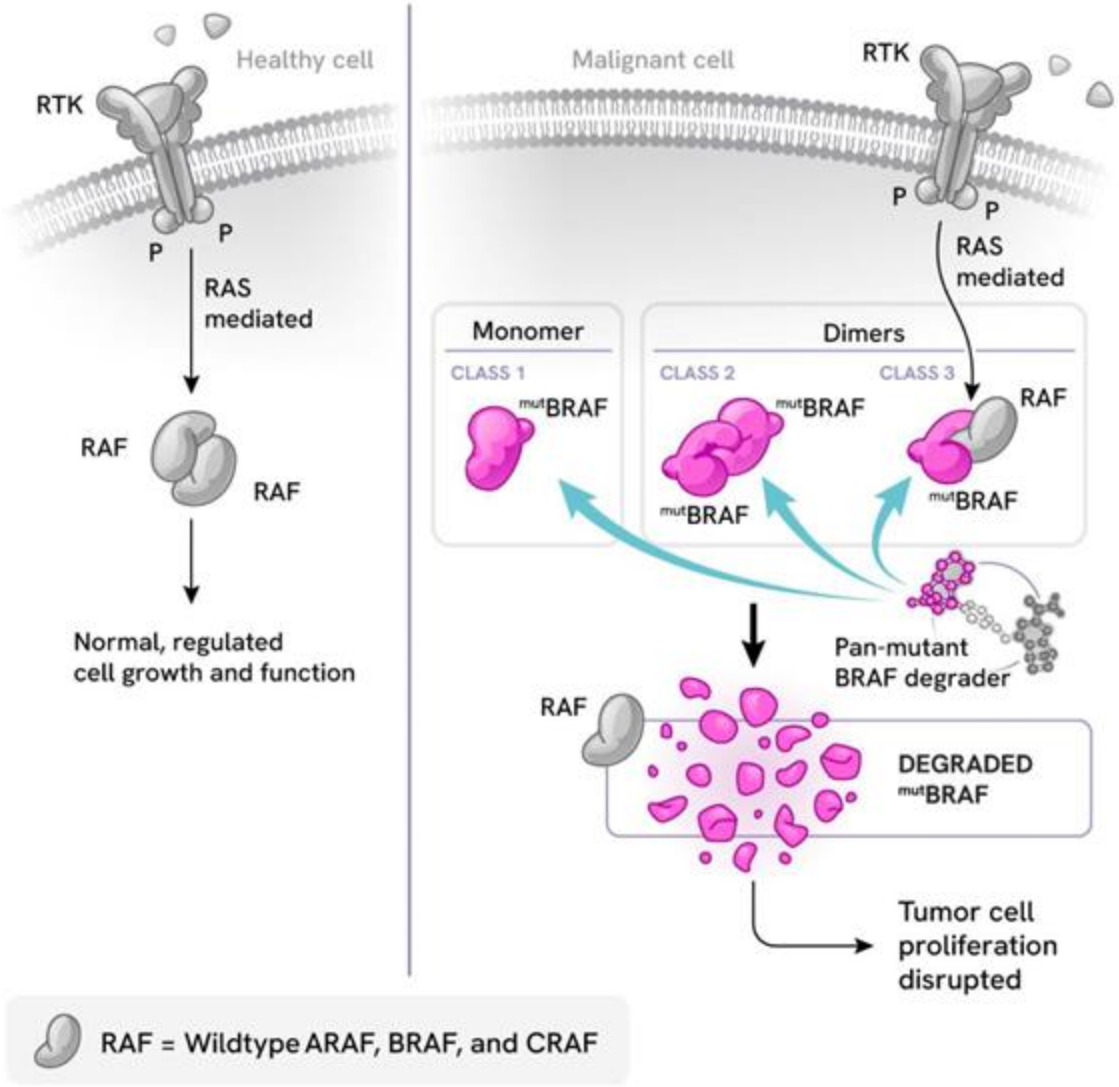
CSF exposure quantified in rat and brain exposure quantified in mouse following a single oral dose; mean ± SEM displayed.

BRAF Mutations Activate the MAPK Pathway and Are Associated with Cancer

A crucial node in the MAPK oncogenic pathway

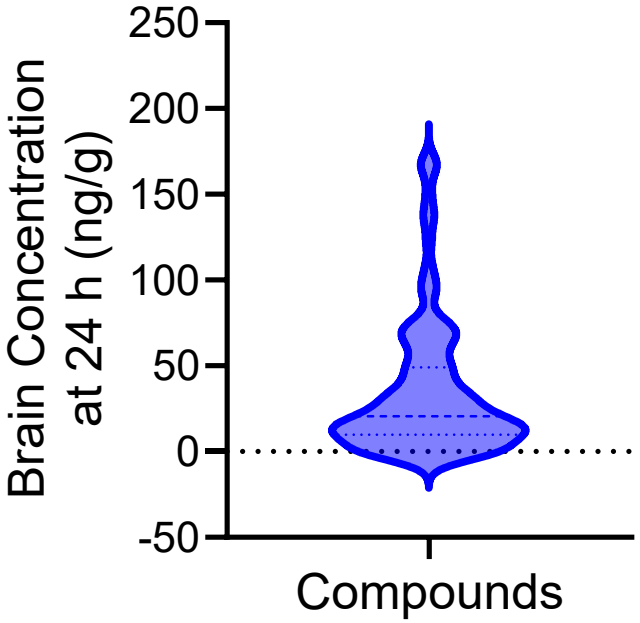
- Mutations in BRAF drive constitutive pathway activation and oncogenic transformation
- BRAF mutations are categorized into three classes:
  Class 1, Class 2, and Class 3
- Current approved BRAFi can only benefit patients with Class 1 BRAF mutations
- ~30-40% of patients on BRAFi present with CNS metastasis; BRAF mutations also drive primary CNS tumors (e.g. gliomas)

Nurix has designed a brain-penetrant, pan-mutant BRAF degrader that addresses these liabilities



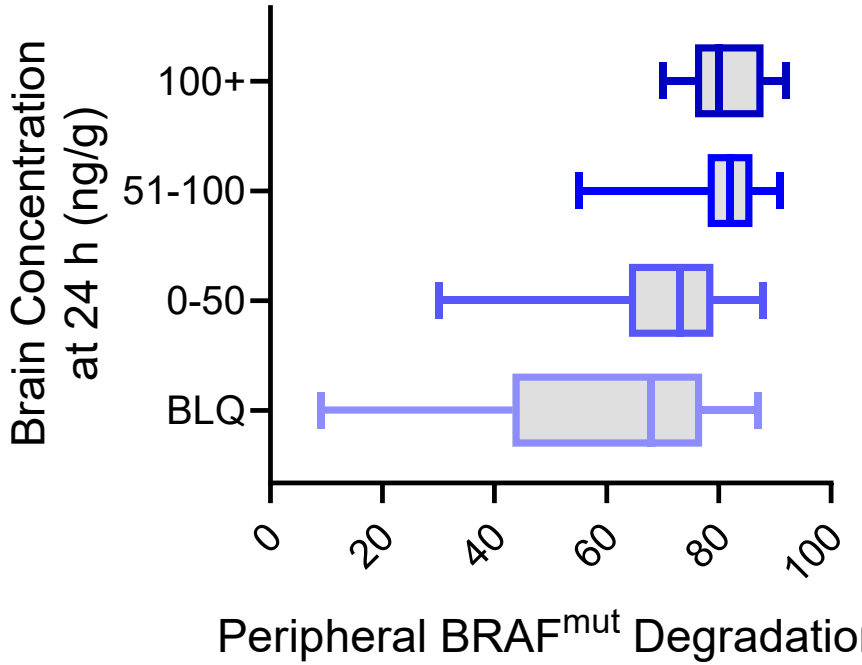
Nurix Has Optimized BRAF Degraders for High CNS Exposure and Deep BRAF Degradation in Tumors

Brain Exposure of BRAF Degraders



The majority of *in vivo* screened compounds have measurable brain exposure

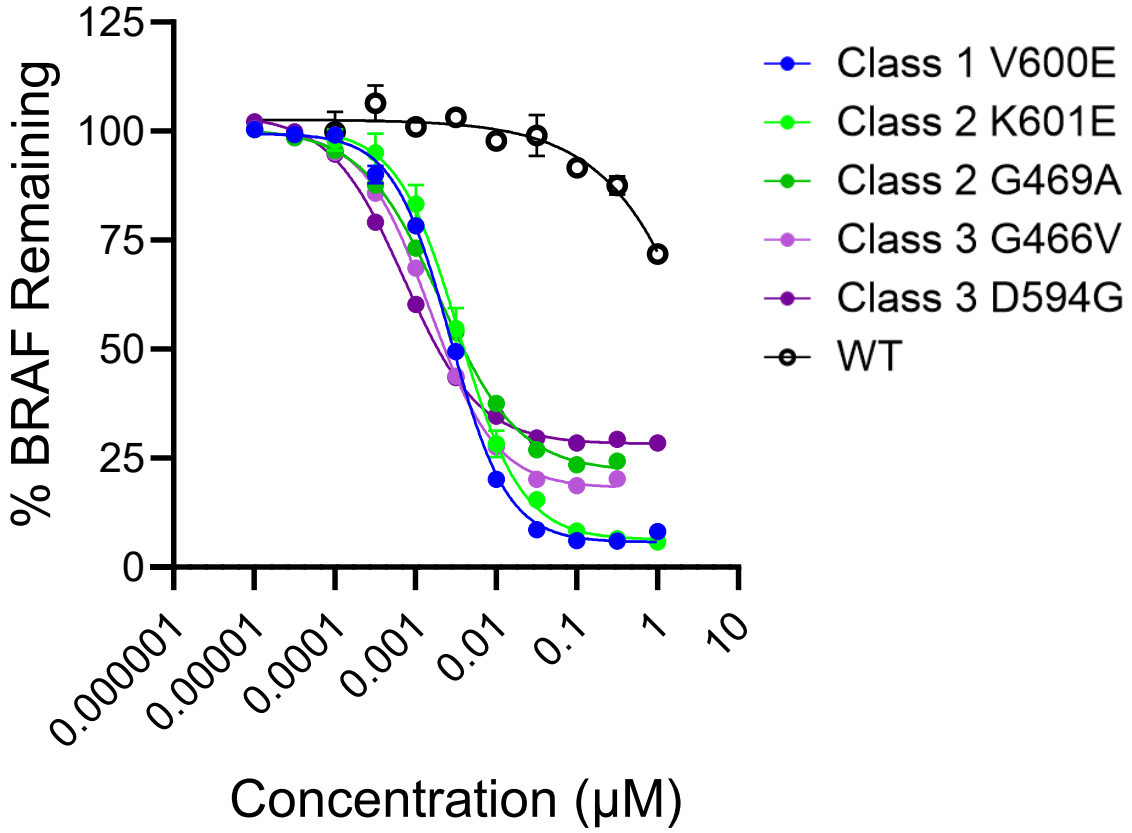
Higher Brain Exposure Correlates with Peripheral Target Coverage



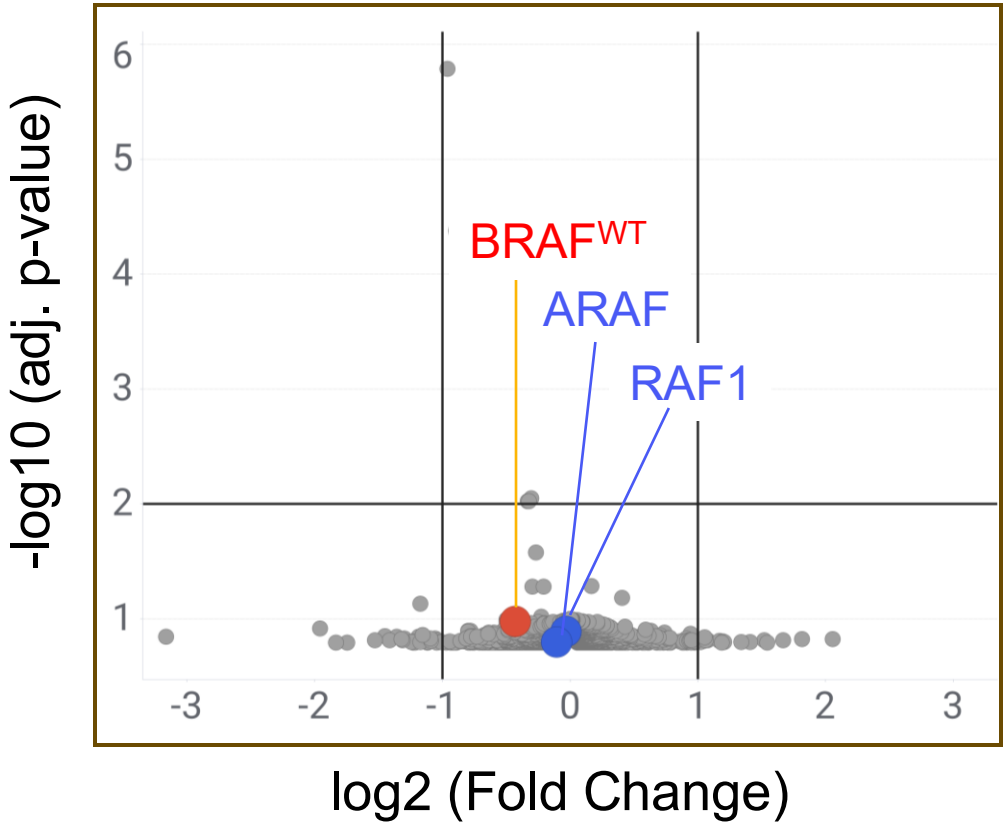
Compounds that induce potent mutant BRAF degradation in subcutaneous tumors also exhibit high brain exposure

NRX-0305 Is a Potent and Selective Pan-Mutant BRAF Degrader

Pan-Mutant BRAF Degradation



Global Proteomics in IMR-90

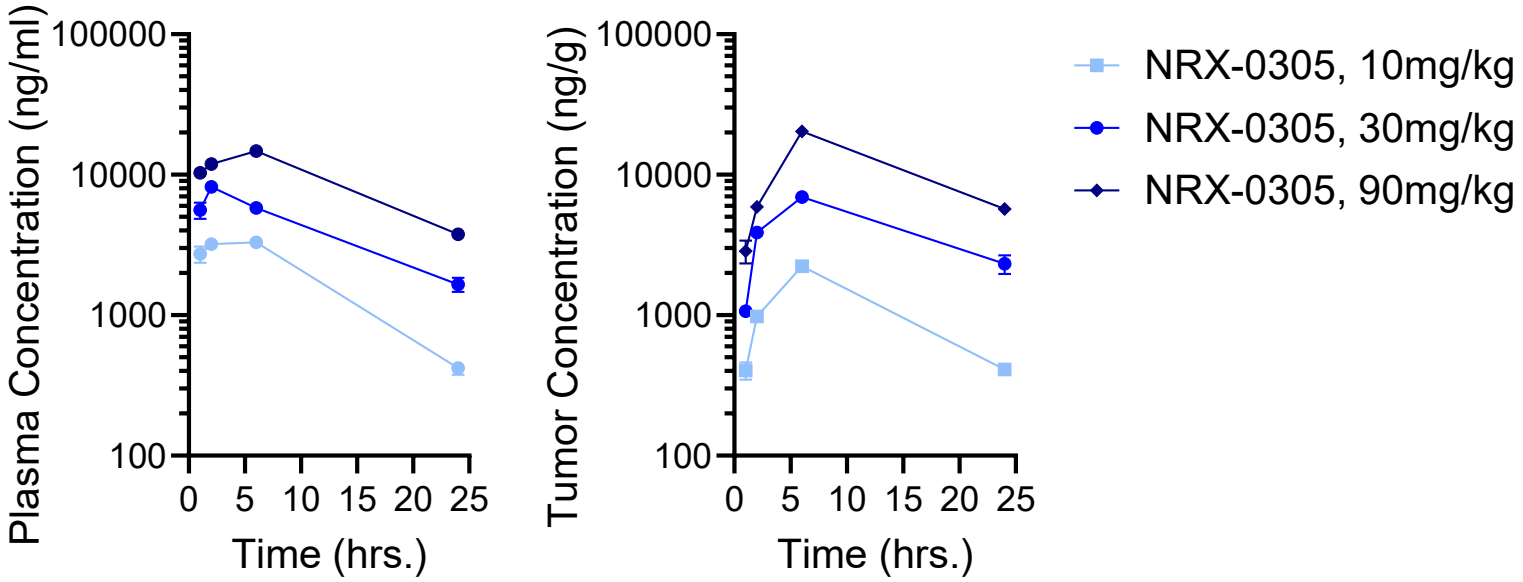


Class 1 V600E A375 and Class 2 K601E WM3130 cell lines contain HiBiT (bioluminescent tag) KI
Class 2/3 G469A, G466V, and D594G are engineered HiBiT overexpression systems in HCT116 BRAF-/-
WT BRAF degradation in human peripheral mononuclear cells, 24 hrs drug treatment

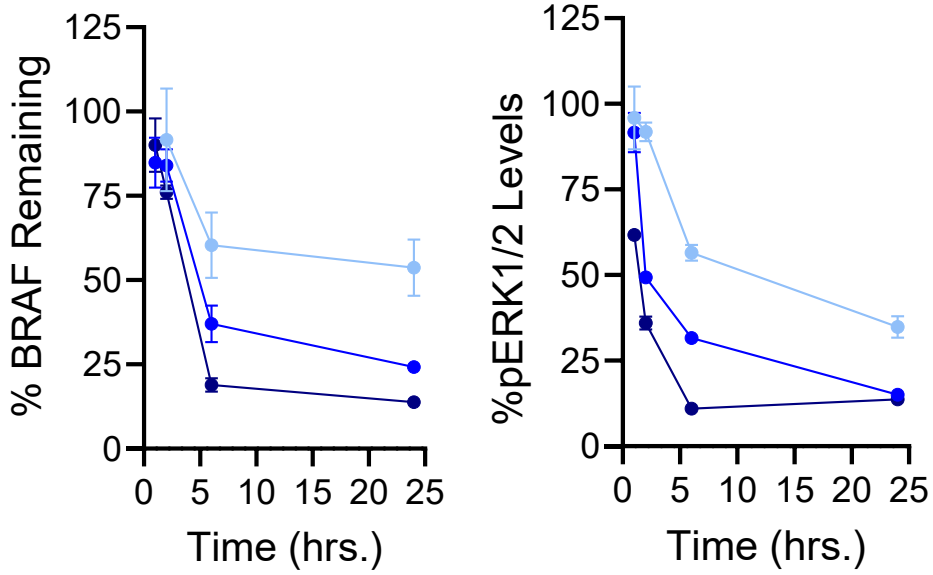
Assessment at 50x BRAF V600E DC50, calculated in A375 cells
24 hrs drug treatment in IMR-90 cells, >6400 unique protein IDs in experiment
Differential expression > 2-fold change / DMSO & adjusted p-value < 0.01

NRX-0305 Exhibits Dose-Proportional Pharmacokinetics and Pharmacodynamics Following a Single Oral Dose *In Vivo*

Plasma and Tumor PK



Tumor PD



Class 1 V600E A375 sub-cutaneous flank mouse CDX model, QDx1
PK/PD, pharmacokinetics/pharmacodynamics; QD, daily dosing; CDX, cell line-derived xenograft.

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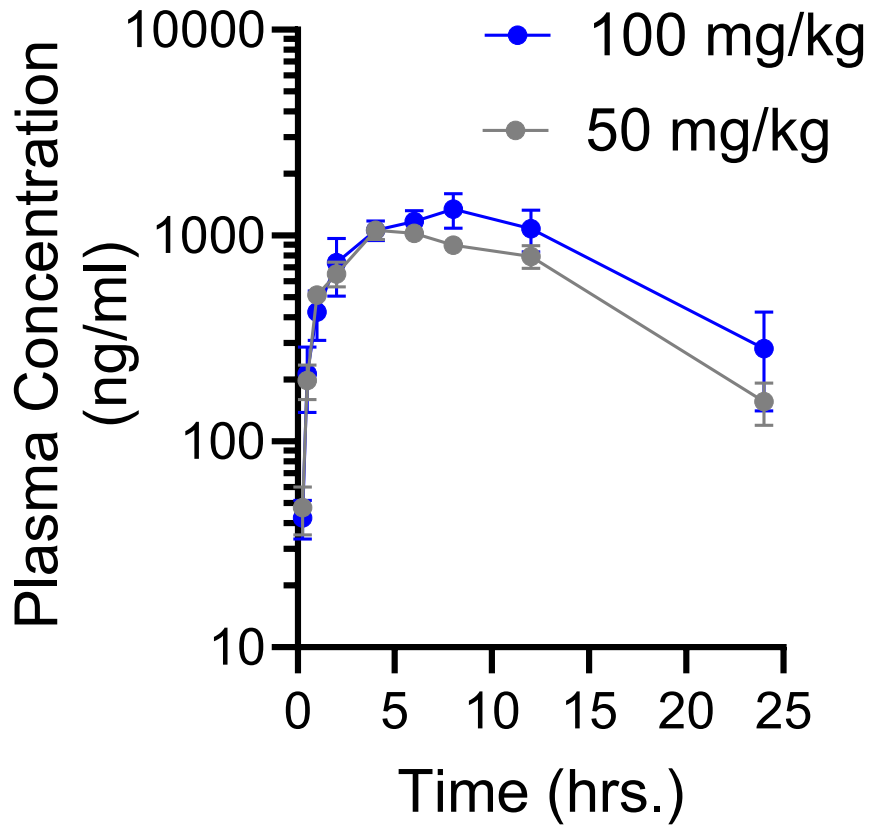
NRX-0305 Is CNS Penetrant with Favorable Cross-Species Bioavailability

Rat Plasma PK and Brain/Plasma Ratios



NRX-0305	B/P at C_{min}
50 mg/kg	0.22
100 mg/kg	0.62

Bioavailability

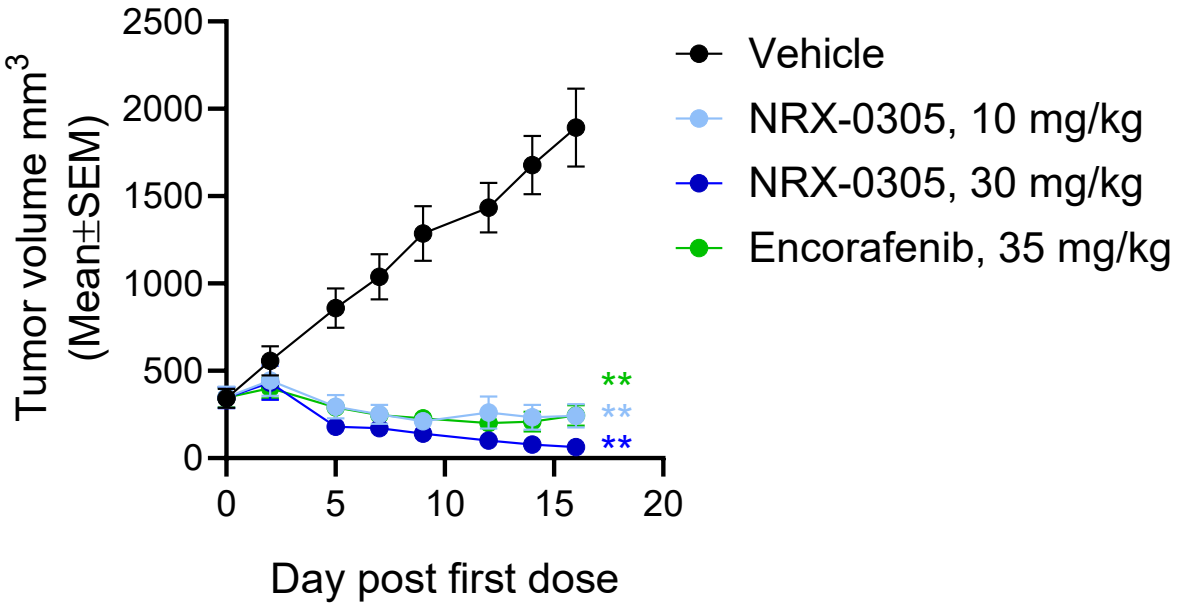
NRX-0305	%F
Mouse	71
Rat	47
Dog	28
Cyno	28

Rat PK with NRX-0305 eutomer, QDx1

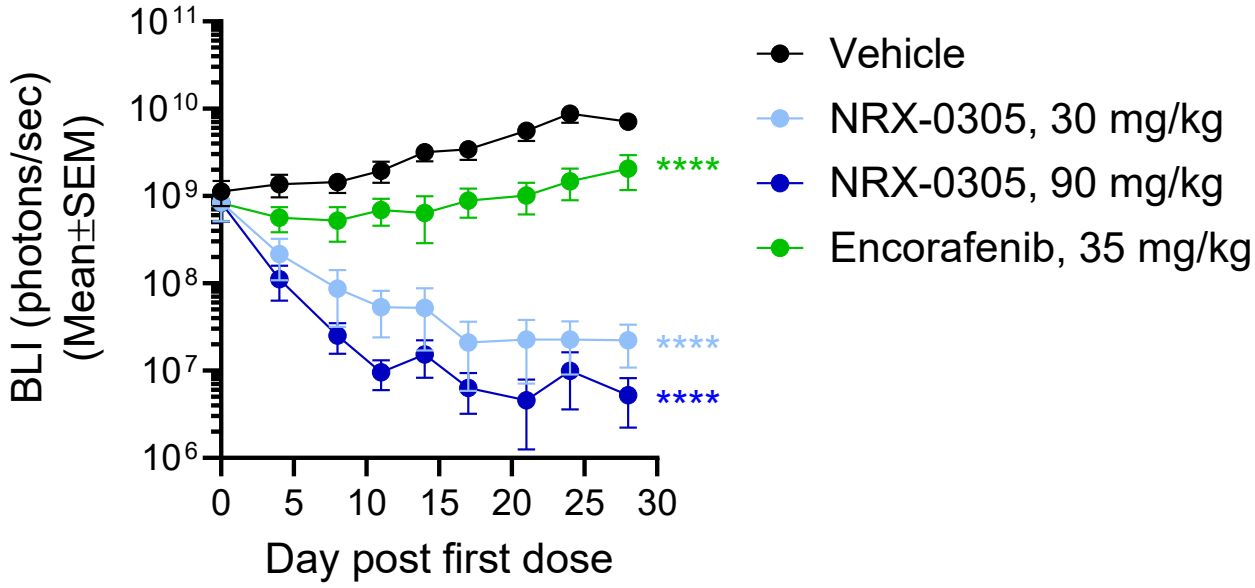
Dog and cyno bioavailability obtained with NRX-0305 eutomer
Dog bioavailability obtained without pentagastrin pre-dosing

NRX-0305 is Efficacious in Subcutaneous and Intracranial Tumor Models

Subcutaneous CDX Model



Intracranial CDX Model

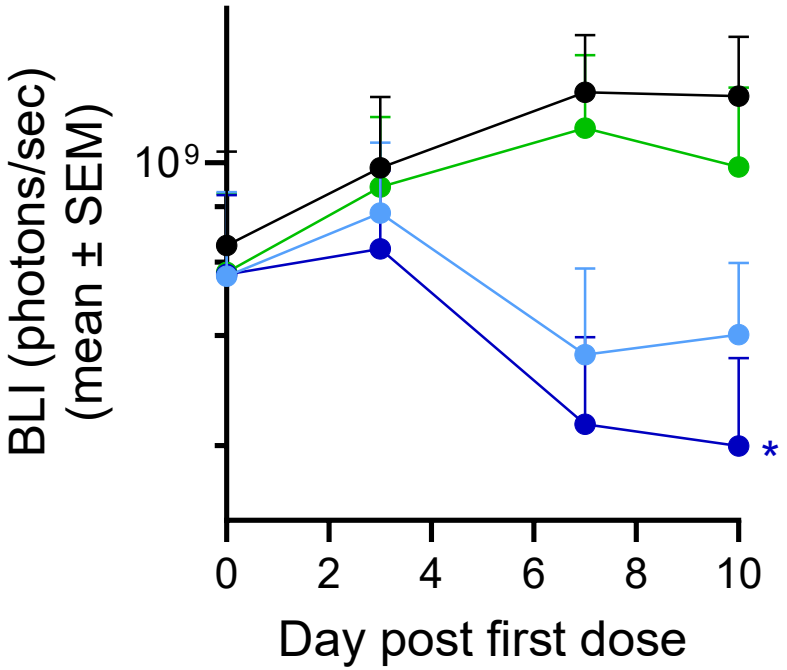


Class 1 V600E A375 sub-cutaneous flank mouse CDX model, efficacy arm, QDx17
Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test

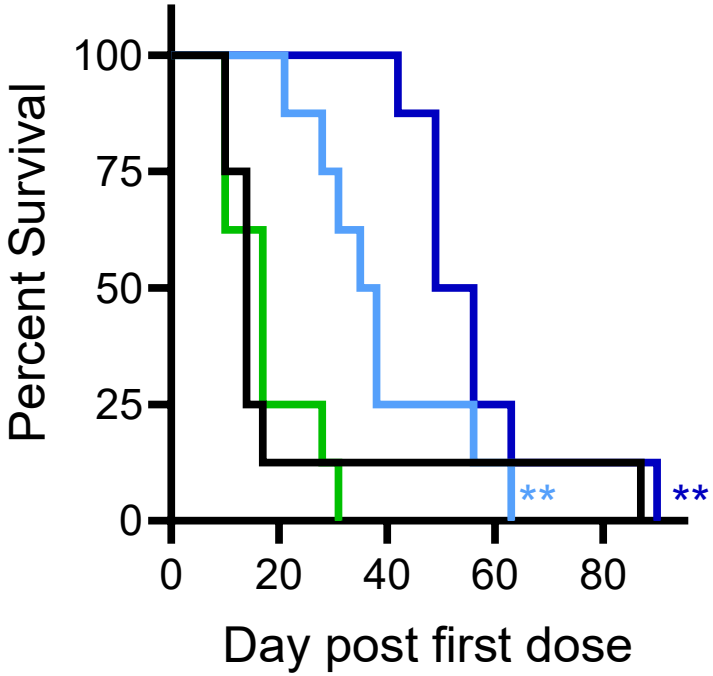
Class 1 V600E A375-luciferase-tagged intracranial mouse CDX model, efficacy arm, QDx28
One-way ANOVA with Dunnett's multiple comparisons test at day 28

NRX-0305 is Efficacious in Intracranial V600E Glioma Model

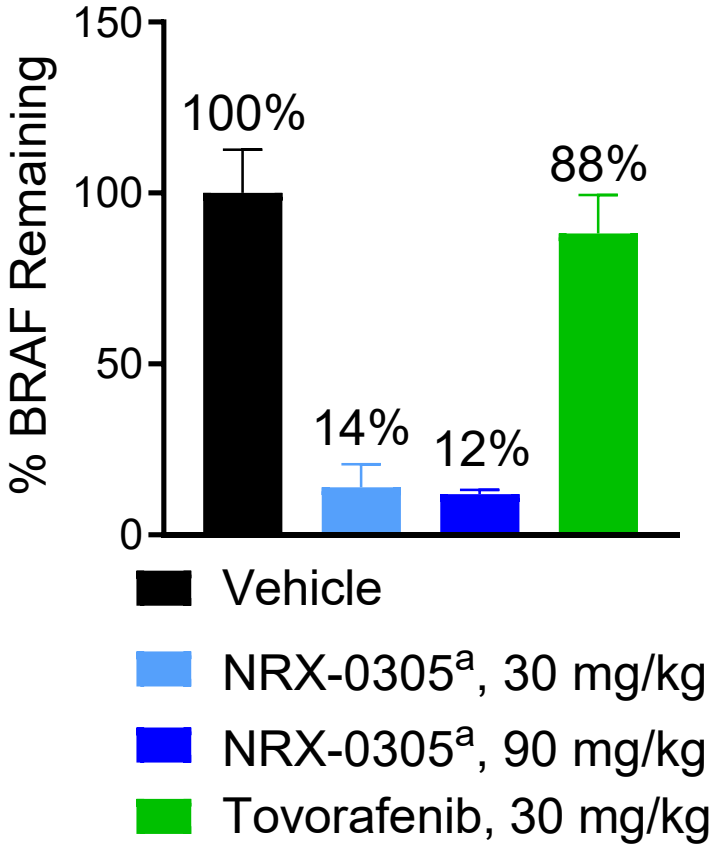
Tumor Growth Inhibition



Survival



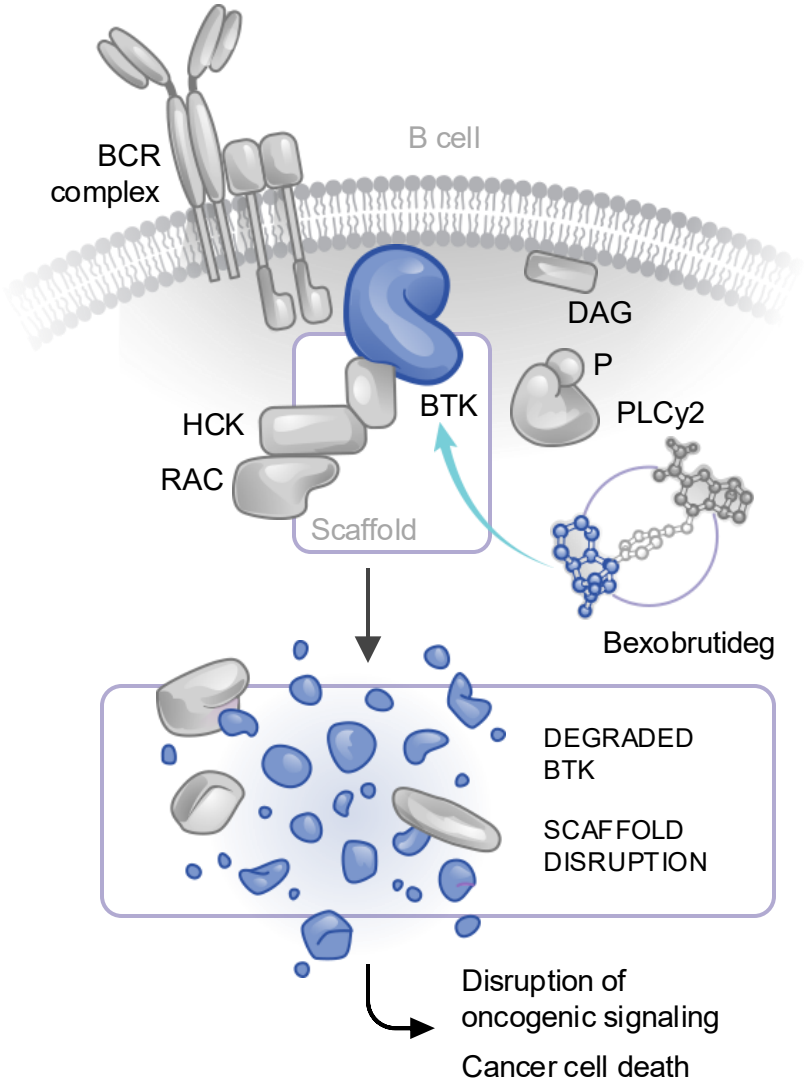
V600E Degradation



Class 1 V600E AM38-luciferase-tagged intracranial mouse CDX model, efficacy arm, QDx10, PD arm, QDx3
Efficacy: One-way ANOVA with Dunnett's multiple comparisons test on day 10
Survival: Grehan-Breslow-Wilcoxon test

a. NRX-0305 Eutomer

BTK Degradation as a Strategy for the Treatment of B Cell Malignancies



- The BCR signaling pathway mediated by BTK is a key driver in oncogenesis and a validated therapeutic target in multiple lymphoid malignancies

- BTK degraders:
  - Can overcome treatment-emergent BTK inhibitor resistance mutations[1,2]
  - Address BTK scaffolding function – the transduction of BCR signal downstream from BTK in the absence of BTK enzymatic activity[3]
  - Demonstrate emerging activity in various B-cell malignancies including CLL and Waldenstrom's Macroglobulinemia[4,5]

1. Noviski et al. iwCLL 2023.
2. Hansen G.M. TPD Basel Sept 19, 2023.
3. Montoya et al. Science 2024;383.
4. Danilov et al. ICML 2025.
5. Lewis et al. ICML 2025.

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CLL and NHL with CNS Involvement Remain an Area of High Unmet Need

- CNS involvement of B cell malignancies spans various conditions including:

Primary CNS Lymphoma (PCNSL)
Comprises ~4% of all primary CNS tumors and 4-6% of all extranodal lymphomas[1]

Secondary CNS Lymphoma (SCNSL)
Affects ~5% of patients with DLBCL[2]

CNS involvement with CLL
Rare complication of CLL with poor prognosis in patients with clinically significant disease[3]

- First-line standard of care typically involves high-dose methotrexate-based chemotherapy regimens with limited option in the relapse / refractory setting
- Investigational drugs (BTKi, CAR-T, immune check point inhibitors) have been used in the relapse/refractory setting with some limitation, including short duration of response and challenging safety profile
- **Point mutations in BTK can confer resistance to BTK inhibitors**

1 Ferreri et al. Nat Rev Dis Primers. 2023 Jun 15;9(1):29. *2 Bobilla et al. Haematologica. 2023 Mar 1;108(3).* *3 Strati P. et al. Haematologica. 2016 Apr; 101(4).*

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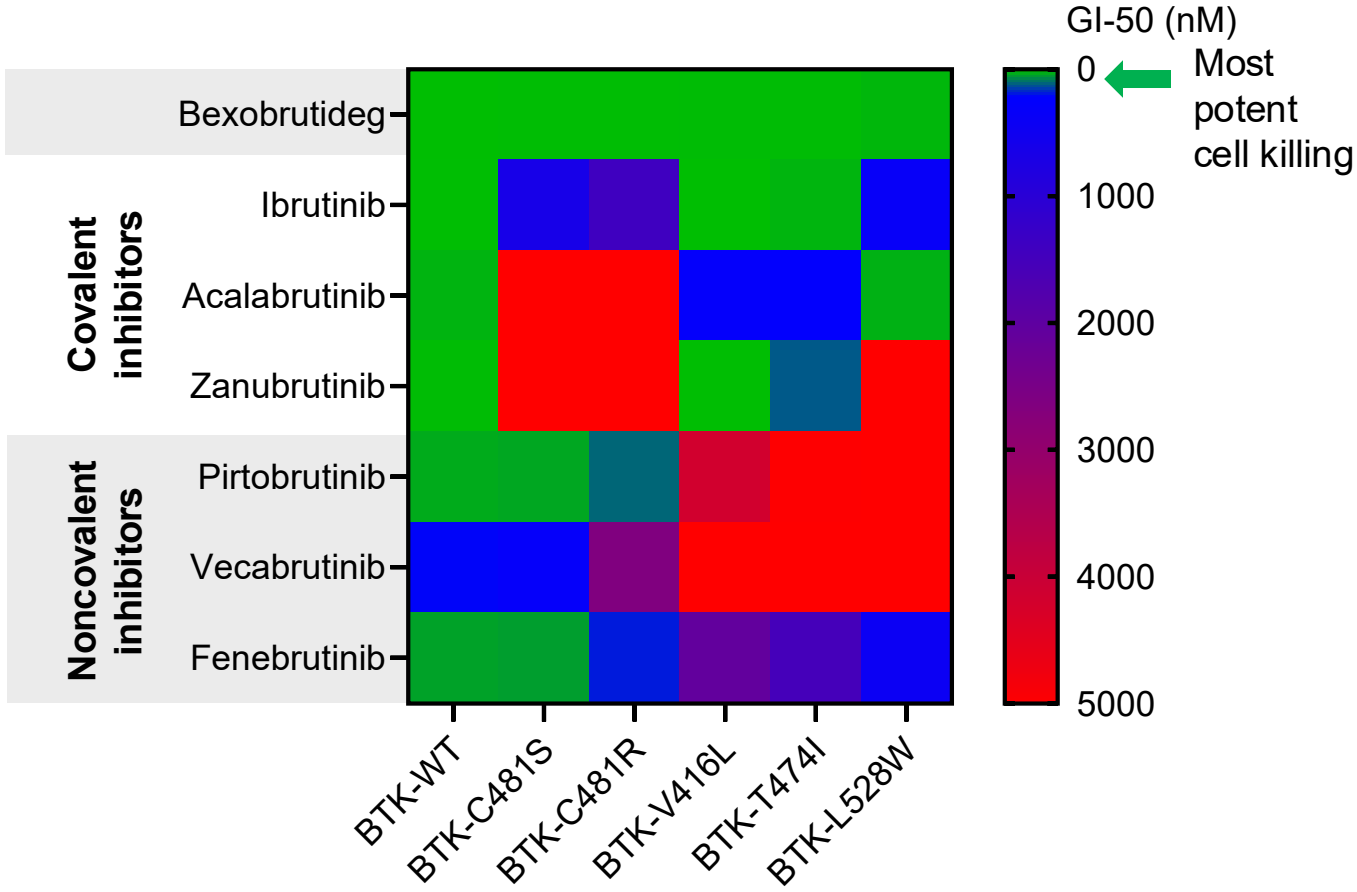
Bexobrutideg Degrades Wild-Type and Mutated BTK with Superior Coverage Compared to All BTK Inhibitors

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

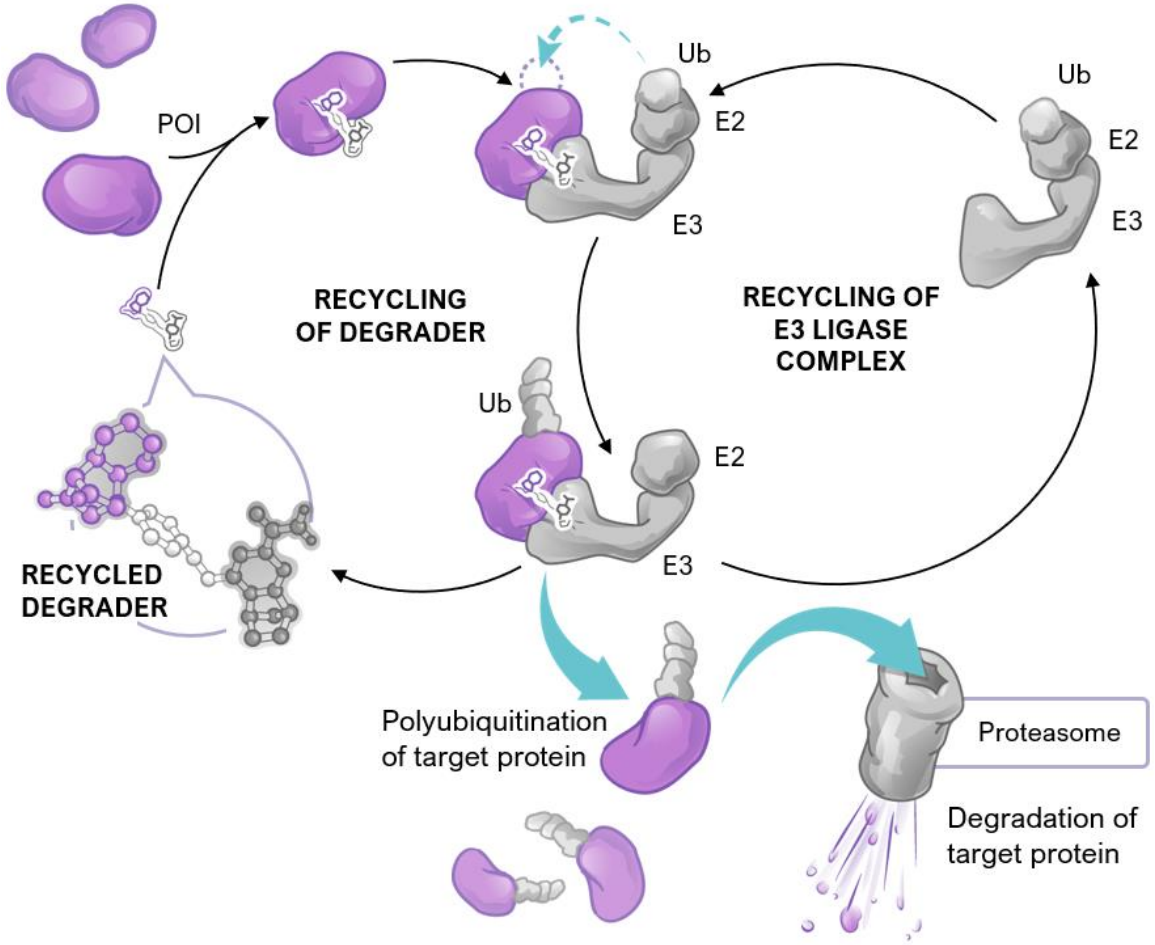
Bexobrutideg shows superior mutational coverage and cell killing compared to BTK inhibitors

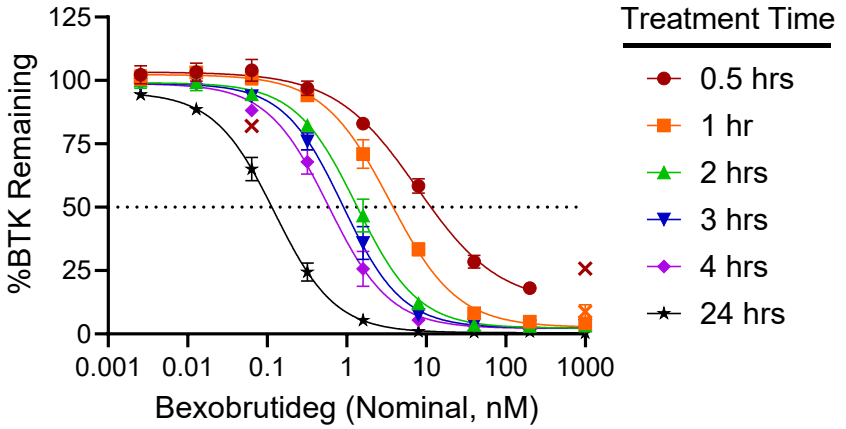


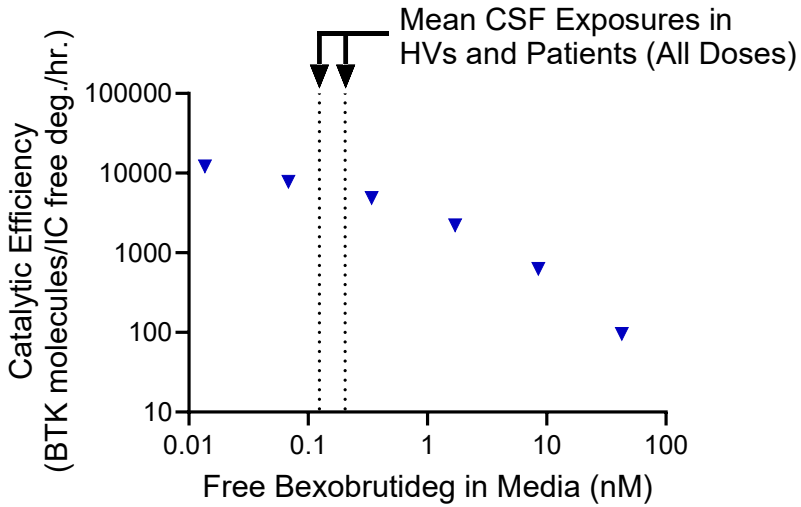
***BTK**, Bruton's tyrosine kinase; **GI-50** growth inhibition 50%; **WT** wildtype*

Degraders Are PK Advantaged Due to Their Catalytic Mechanism of Action

One molecule of bexobrutideg degrades thousands of BTK proteins per hour at clinically-relevant concentrations



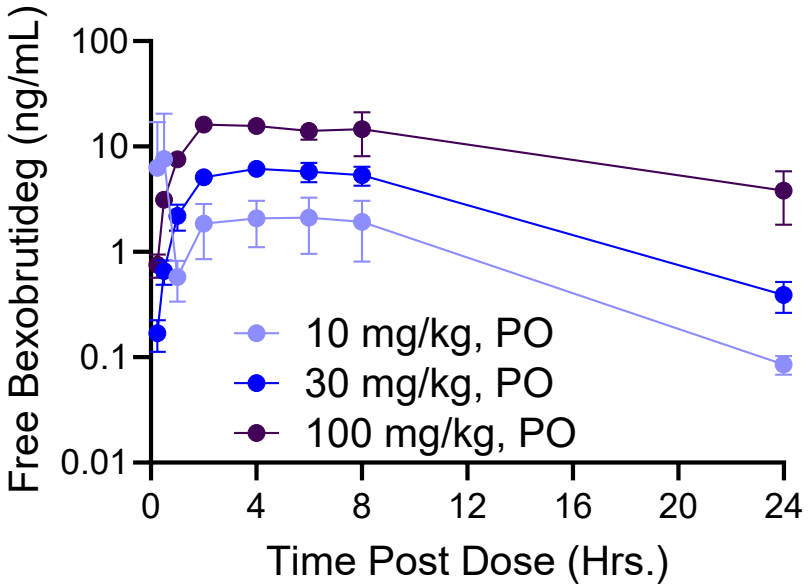




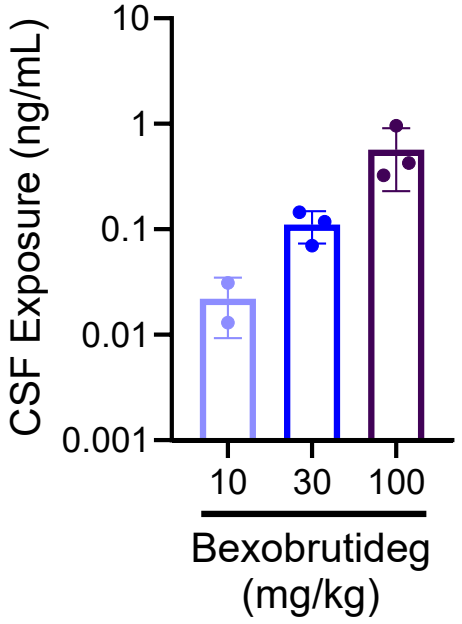
Catalytic efficiency was calculated using a modified version of an approach previously used for other BTK degraders (Lynch et al. 2024. ACS Chem Biol 19(7): 1604-1615.)
Geometric mean of CSF exposure across all dose levels is displayed. Exposure was quantified in healthy volunteers 24 hours after a single dose and in patients at steady state 4 hours after the most recent dose.

Bexobrutideg Degrades BTK in Rat Brain Microglia, Achieving >90% BTK Degradation After a Single Oral Dose

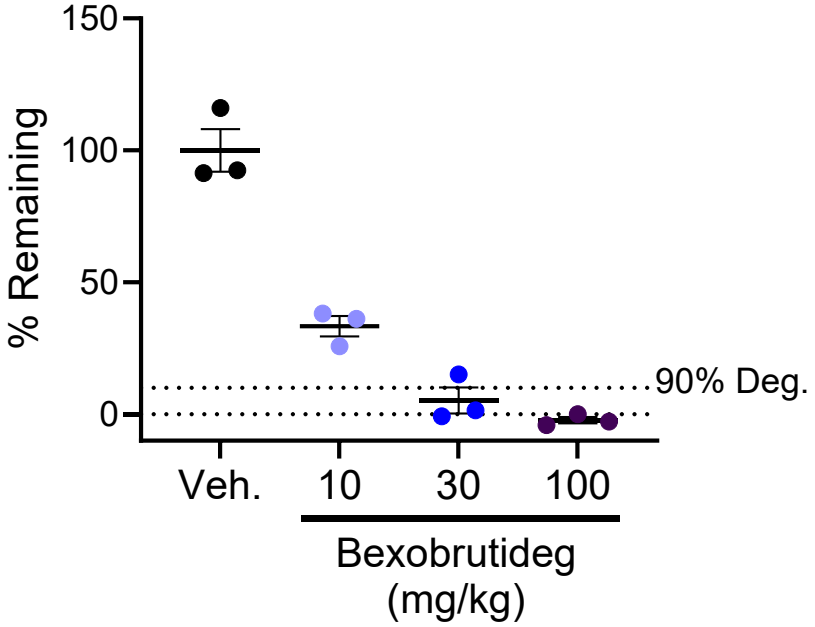
Free Exposure in Plasma



CSF Exposure



BTK Degradation in Microglia

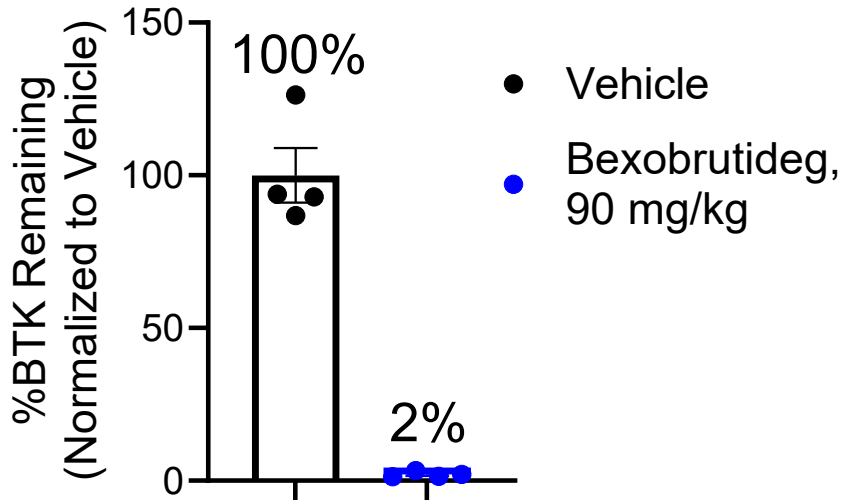


Bexobrutideg demonstrates dose-dependent exposure in CSF and BTK degradation in the brain

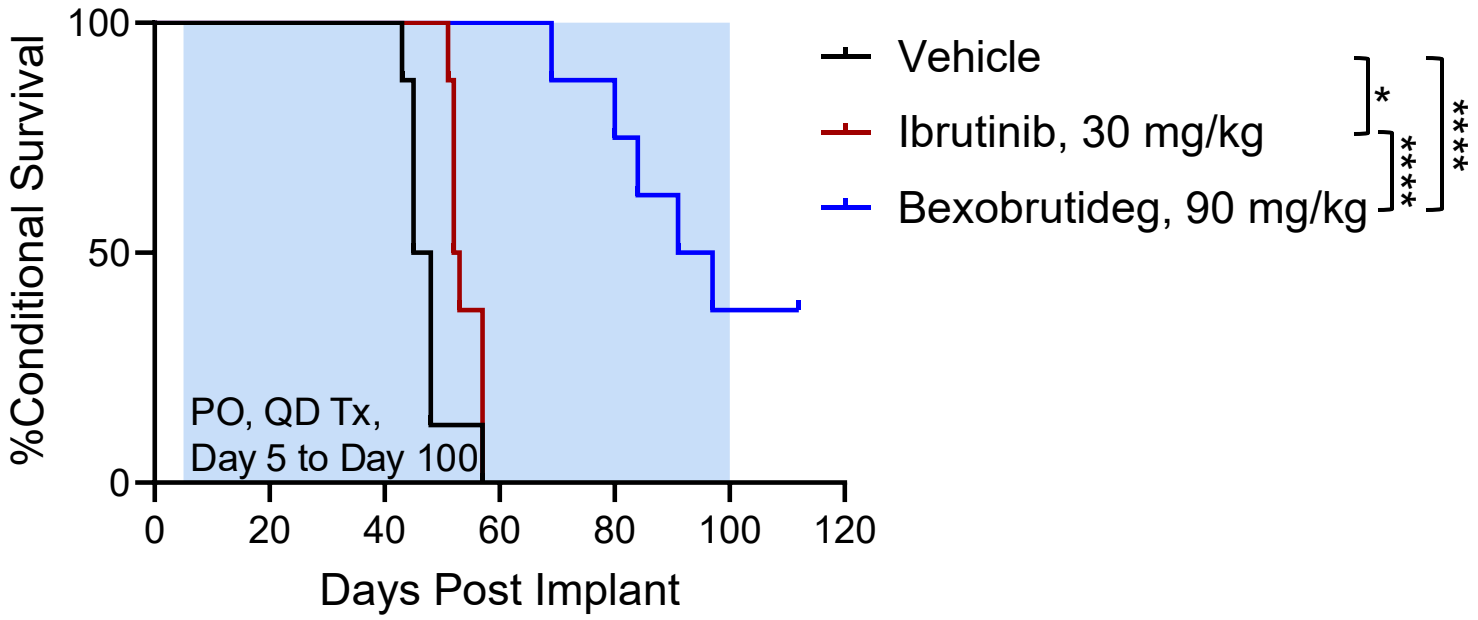
BTK degradation quantified in microglia by flow cytometry. CSF exposure and BTK degradation quantified 24 hours after dosing.

Daily Oral Administration of Bexobrutideg to Mice with Intracranial DLBCL PDX Cells Drives Potent BTK Degradation and Prolongs Survival

BTK Degradation in Tumors



Long-Term Survival



Bexobrutideg significantly prolongs survival compared to ibrutinib in mice with intracranial PDX tumors

SC1 cells are derived from a patient with highly refractory CD79b and EVT6-mutant large B-cell secondary CNS lymphoma, resistant to R-CHOP, high-dose methotrexate/rituximab, etoposide, Ara-C and irradiation. Data generated in collaboration with Dr. James Rubenstein (UCSF)

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Case Study: Patient with CLL and CNS Involvement

Relevant Medical History

- Anxiety: 2015-ongoing
- Depression: 2015-ongoing
- Previous Hep B infection: 2015 (on anti-viral prophylaxis, no evidence of recurrent disease)
- Face numbness: Unknown-ongoing
- Constipation: 21Jun23-ongoing

Prior Systemic Therapies

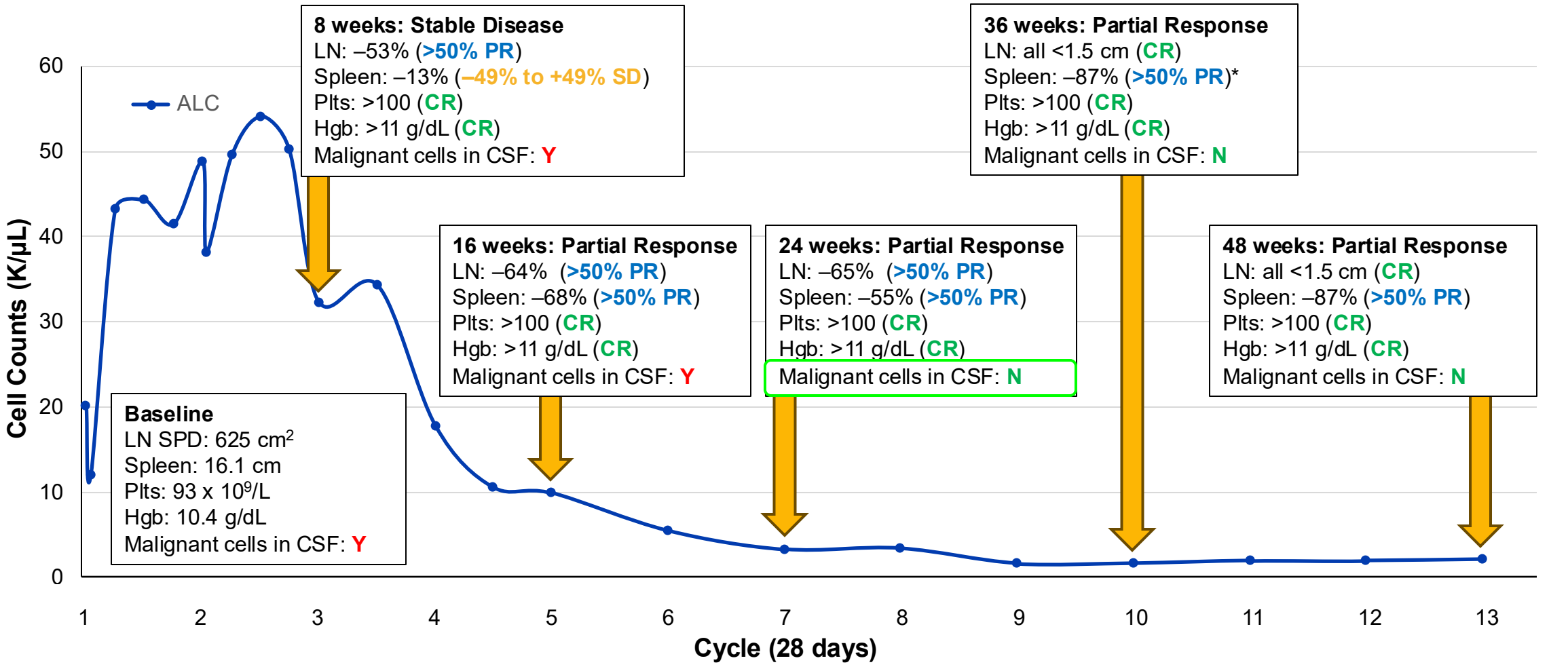
- Idelalisib: 2015-2018
- Venetoclax+Rituximab: 2018-2022
- Acalabrutinib: Oct 2022-June 2023

Prior Radiotherapy

- None

Age, Race, M/F	59, White M
Diagnosis	CLL, High Risk, Stage C
Initial Diagnosis	May 2015
Recent Progressions	03 Oct 2022 (with CNS relapse) 25 Jun 2023
Dose	100 mg -> 300 mg
C1D1	27-Jun-23
Status	On Treatment

Patient with CLL with CNS Involvement Treated with Bexobrutideg Showed Deepening Response over Time Approaching Complete Response



Dose escalated to 600 mg, patient remains on study as of October 14, 2025

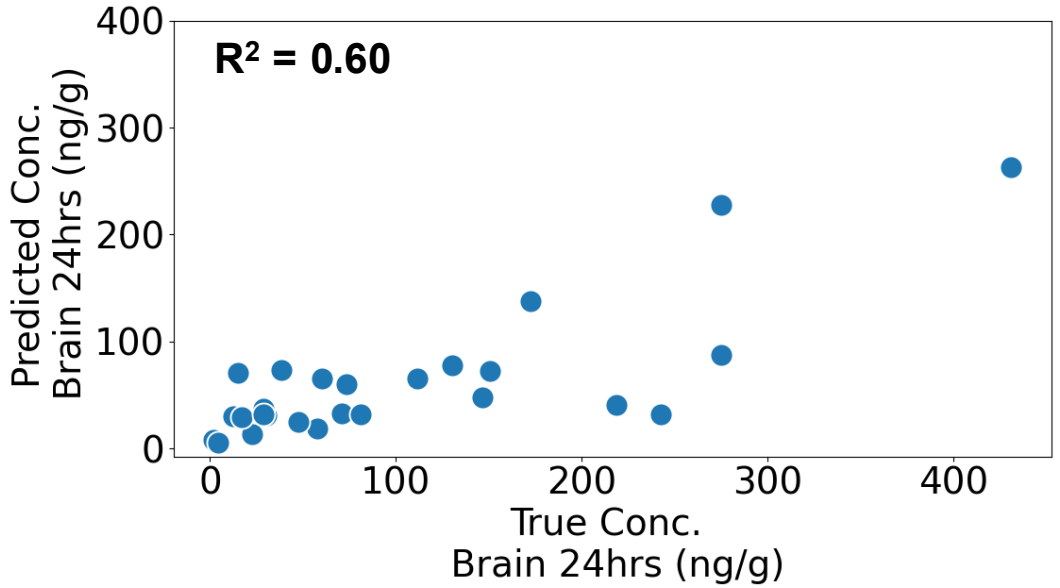
**Normal spleen: 13 cm; 36-48 week: 13.4 cm*
The overall response assessments are from the investigators while the individual parameter response assessment criteria are calculated per iwCLL from the data entered
ALC, Absolute lymphocyte count; CSF, cerebrospinal fluid; Hgb, hemoglobin; LN, lymph nodes; Plts, platelets

NX-5948-301 Ph1a/b clinical study
Data cutoff: 10 June 2024

The Rules for Designing Brain-Penetrant Degraders Are Still Undefined

- Targeted protein degraders have the potential to address CNS malignancies by providing superior **target coverage**, addressing **scaffolding functions**, and targeting **inhibitor-resistant mutants**
- By optimizing for degrader **potency** and leveraging the **catalytic MOA**, degraders can achieve efficacy in the CNS at concentrations lower than required for inhibitors
- Traditional small molecule metrics are inadequate for bifunctional degrader optimization, necessitating efficient screening approaches and potentially machine learning models to aid identification of brain-penetrant degraders

Machine learning models may accelerate discovery of brain-penetrant degraders

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