An Orally Bioavailable, Brain Penetrant, Pan-Mutant BRAF Degrader for the Treatment of Primary and Inhibitor-Resistant Solid Tumors

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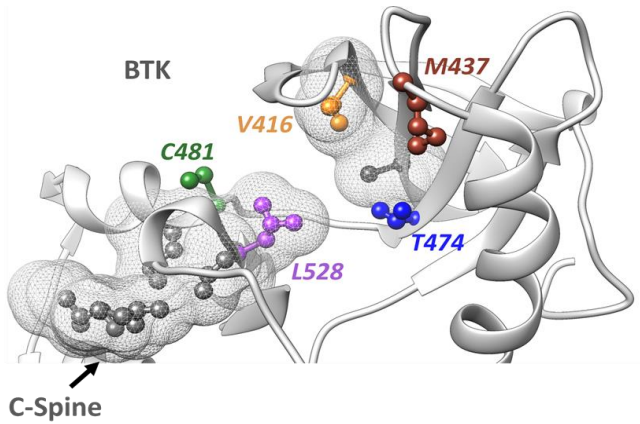
Drug Discovery Pipeline Strategy

Meeting The Needs of Patients With Breakthrough Therapies

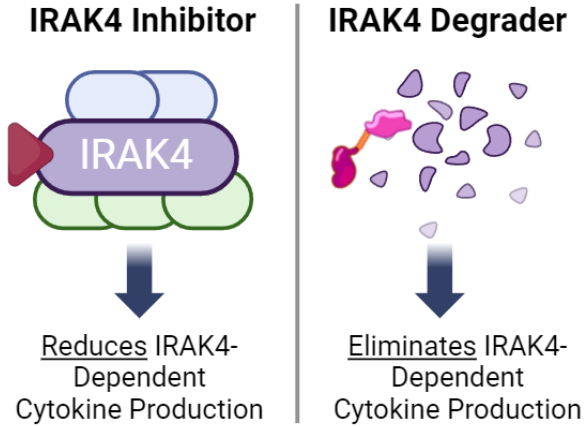
Clinically validated targets where inhibitors fail to address resistance and scaffolding



Kinase targets in cancer

BTK – B-cell malignancies and I&I
BRAF – solid tumors

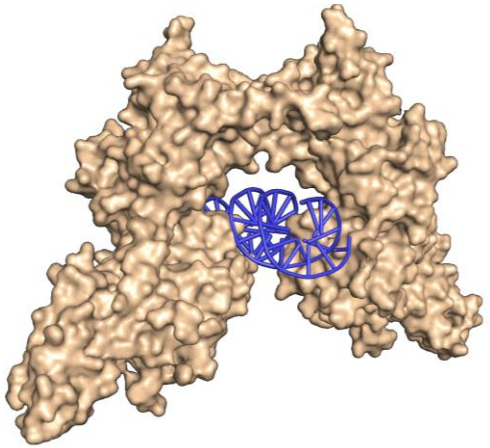
Unmet medical need due to insufficient efficacy or tolerability



Signaling proteins with scaffolding function

IRAK4 – rheumatoid arthritis

"Undruggable" targets



Transcriptions factors; fusion proteins; E3 ligases

STAT6 – T2 inflammatory diseases
DNAJB1-PRKACA – liver cancer
CBL-B – immuno-oncology

Nurix Is Advancing a Pipeline of Proprietary and Partnered Programs in Oncology and Inflammation & Immunology

Program	Target	MOA	Therapeutic area	Discovery – Lead Op	IND enabling	Phase 1a	Phase 1b
NX-5948	BTK	TPD	B-cell malignancies				
NX-2127	BTK-IKZF	TPD	B-cell malignancies				
NX-1607	CBL-B	TPE	Immuno-Oncology				
BRAF degrader	Pan-mutant BRAF	TPD	Solid tumors				
Multiple	Undisclosed	TPD/DAC	Undisclosed				
Multiple	Undisclosed	TPD	Undisclosed		GILEAD	sanofi	
Multiple	Undisclosed	DAC	Oncology		Pfizer		
NX-5948	BTK	TPD	Inflammation / autoimmune				
NX-0479/GS-6791	IRAK4	TPD	RA & inflammatory diseases		GILEAD		
STAT6 degrader	STAT6	TPD	T2 inflammatory diseases		sanofi		
Multiple	Undisclosed	TPD	Inflammation / autoimmune		sanofi		
Undisclosed	Undisclosed	TPD/DAC	Inflammation / autoimmune				

TPD: Targeted Protein Degradation; **TPE**: Targeted Protein Elevation; **DAC**: Degrader Antibody Conjugate; **RA:** Rheumatoid arthritis; **T2:** Type 2

BRAF Mutations Activate the MAPK Pathway and Are Associated with Cancer

Class 1 BRAF mut+

63% of all patients with BRAF alterations

Class 2/3 BRAF mut+

34% of all patients with BRAF alterations

	Class 1 BRAF mut+			Class 2/3 BRAF mut+	
	BRAF mutation rate in cancer type[1]	2024 US incidence[2]		BRAF mutation rate in cancer type[1]	2024 US incidence[2]
Melanoma	30.8%	31,000		8.1%	8,200
CRC	6.9%	10,500		1.1%	2,600
NSCLC	1.3%	2,500		2.6%	5,200
Thyroid	32.5%	14,000		1.1%	3,300
Prostate					

CNS BRAF mut+

CNS metastasis occurs in ~30-40%[3] of BRAF driven cancers

17,000

BRAF and RAS mutations drive **primary CNS tumors** (eg gliomas)

1,500

2021 US incidence[4]

1 Owsley 2021 Exp Biol Med 2 NCI-SEER 2024, adjusted with Owsley %BRAF mutation rate in cancer type % 3 Mgmt of brain metastasis in melanoma - UpToDate
4 EvaluatePharma Epi for incidence by tumor type (2021, US), publication and GENIE/TCGA datasets for mutation prevalence by tumor types

Figure made in BioRender

Pan-Mutant BRAF Degrader: A Novel Approach for Broadly Targeting BRAF Mutations and Overcoming BRAFi Resistance

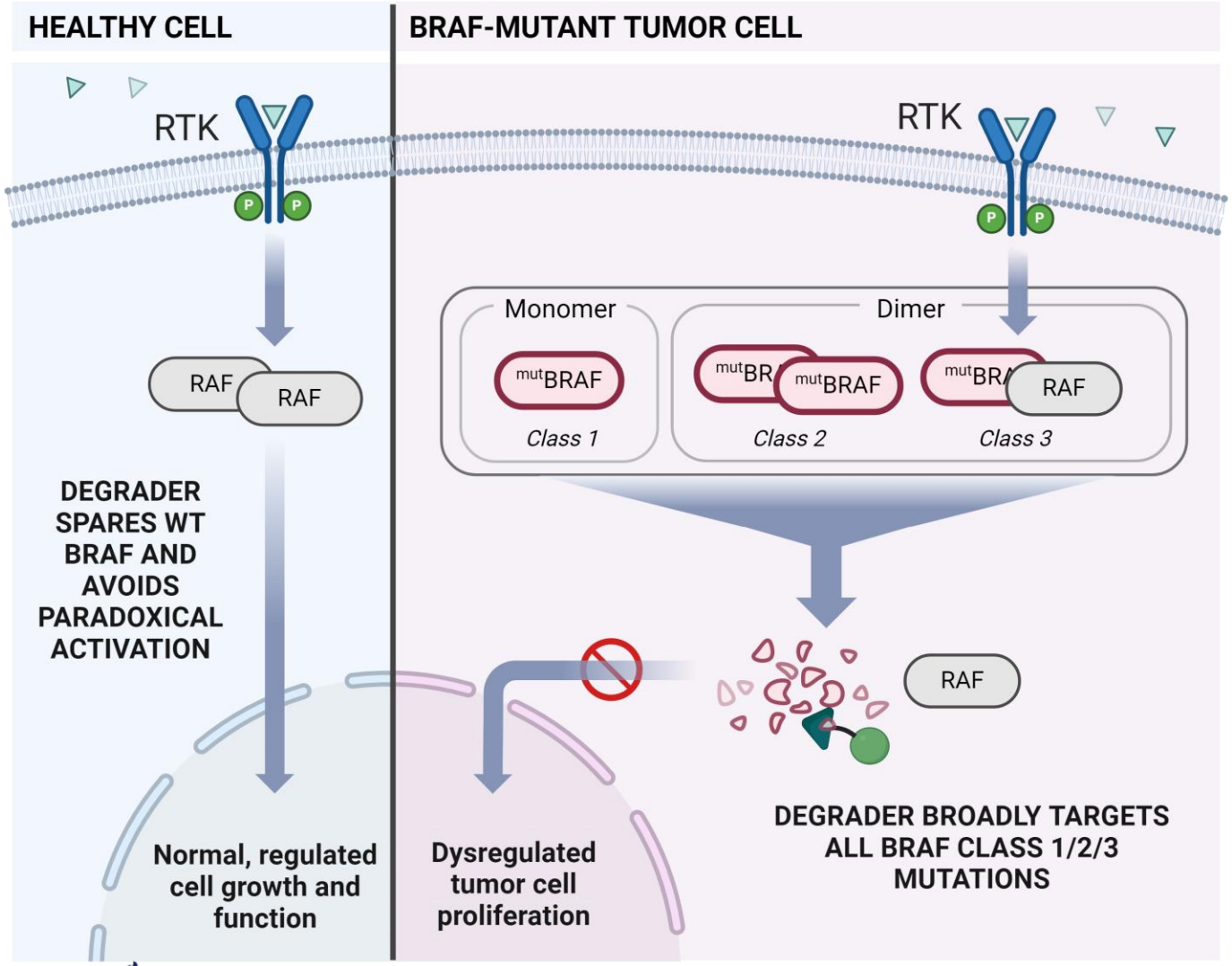
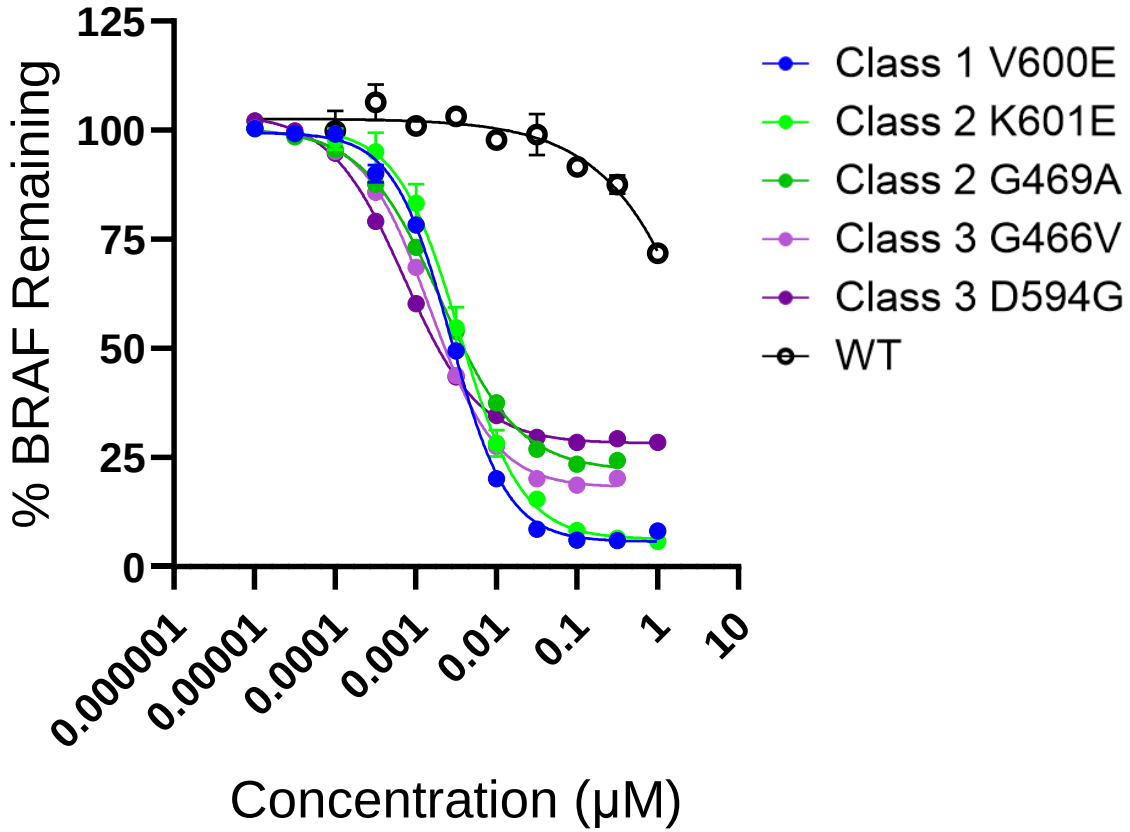


Figure made in BioRender

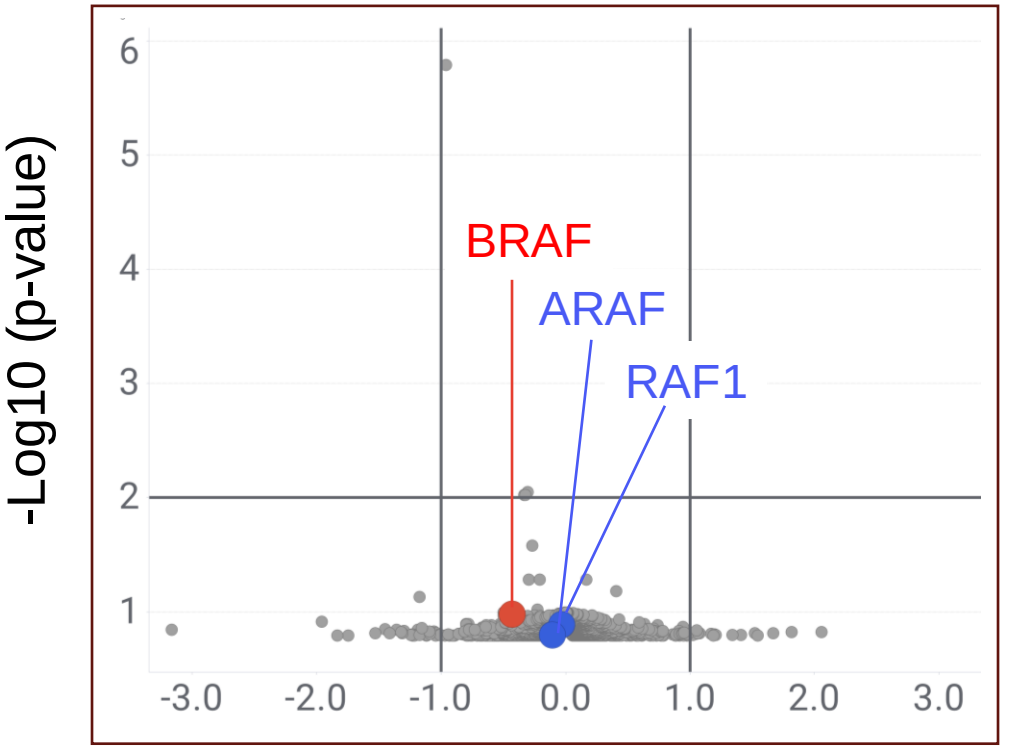
- Targets mutant BRAF while sparing wildtype BRAF, which is critical for normal cellular function
- Prevents dimer formation and avoids paradoxical activation
- Degrader provides sustained MAPK pathway suppression through catalytic MoA
- May delay and/or circumvent BRAFi-induced MAPK pathway resistance

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

Pan-Mutant BRAF Degradation



IMR-90 Global Proteomics, 50x DC50*

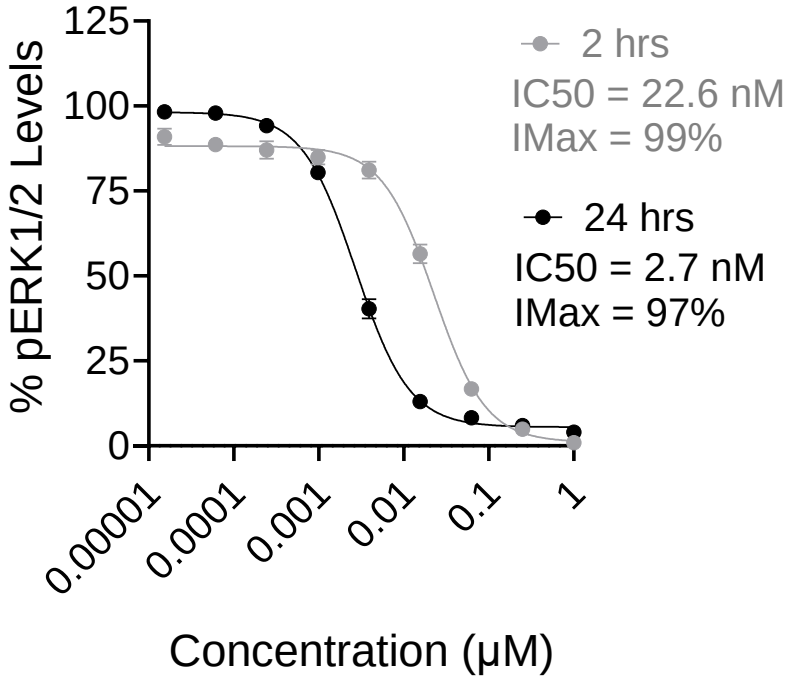


Class 1 V600E A375 and Class 2 K601E WM3130 cell lines contain HiBiT (bioluminescent tag) KI
Class 2/3 G469A, G466V, and D594G are engineered HiBiT overexpression systems in HCT116 BRAF-/-
WT BRAF degradation in human peripheral mononuclear cells, 24 hrs drug treatment

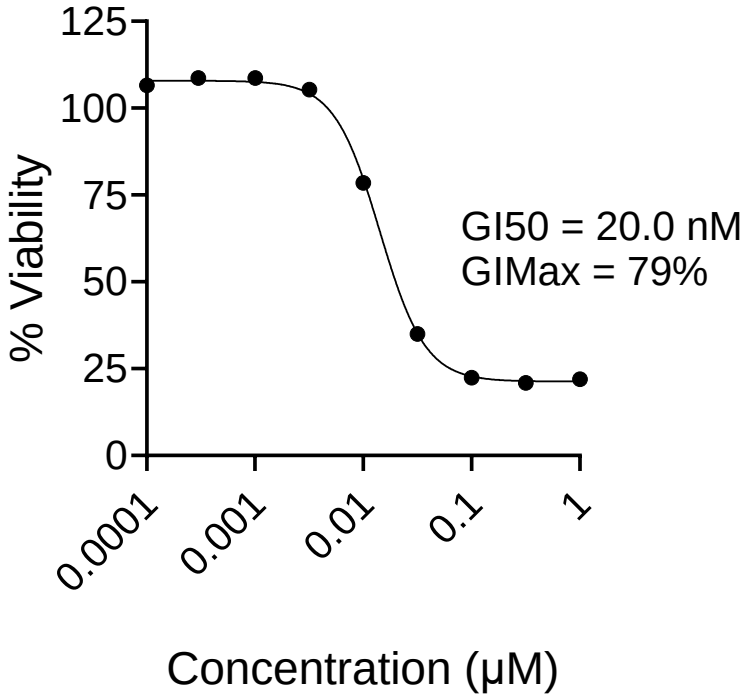
*24 hrs drug treatment, 50% fold change, 1% FDR, *potency measured in A375 cells*

BRAF V600E Degradation by NRX-0305 Inhibits pERK, Induces Anti-Proliferative Activity and Circumvents Paradoxical Activation

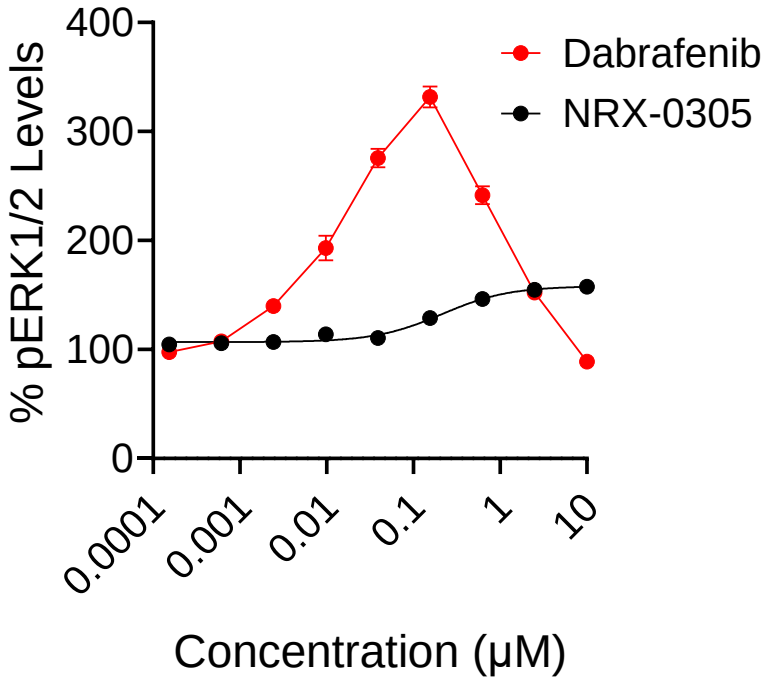
pERK1/2 Inhibition



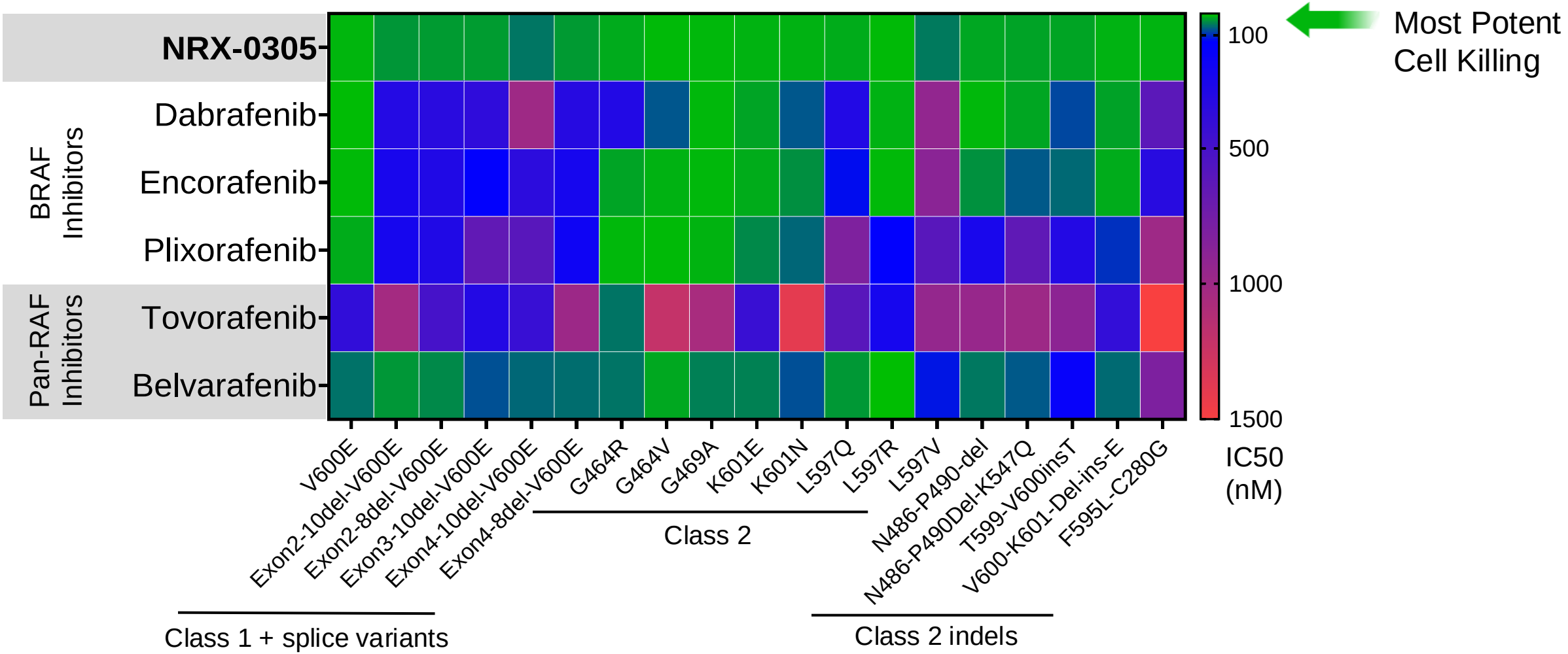
Viability



Paradoxical Activation

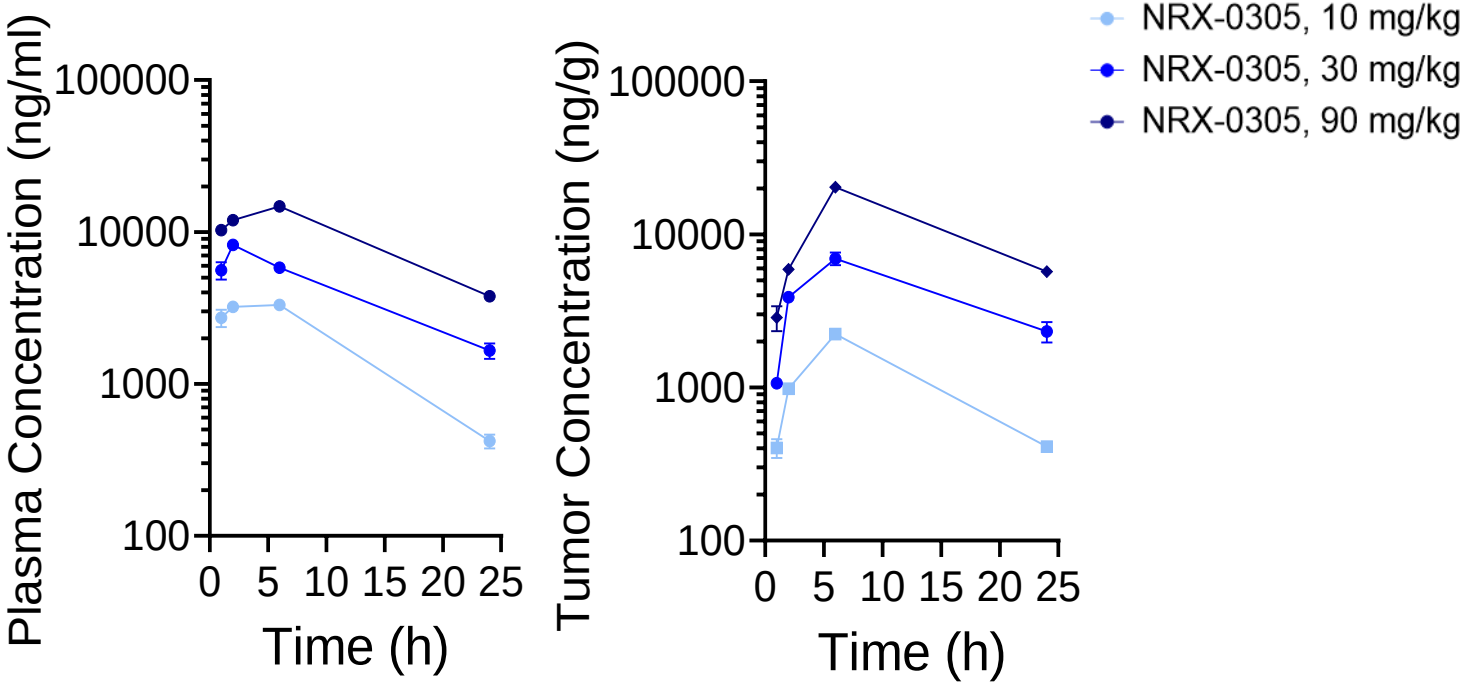


NRX-0305 Shows Improved Coverage of Clinically Relevant BRAF Mutations Compared to Other BRAF and RAF Agents

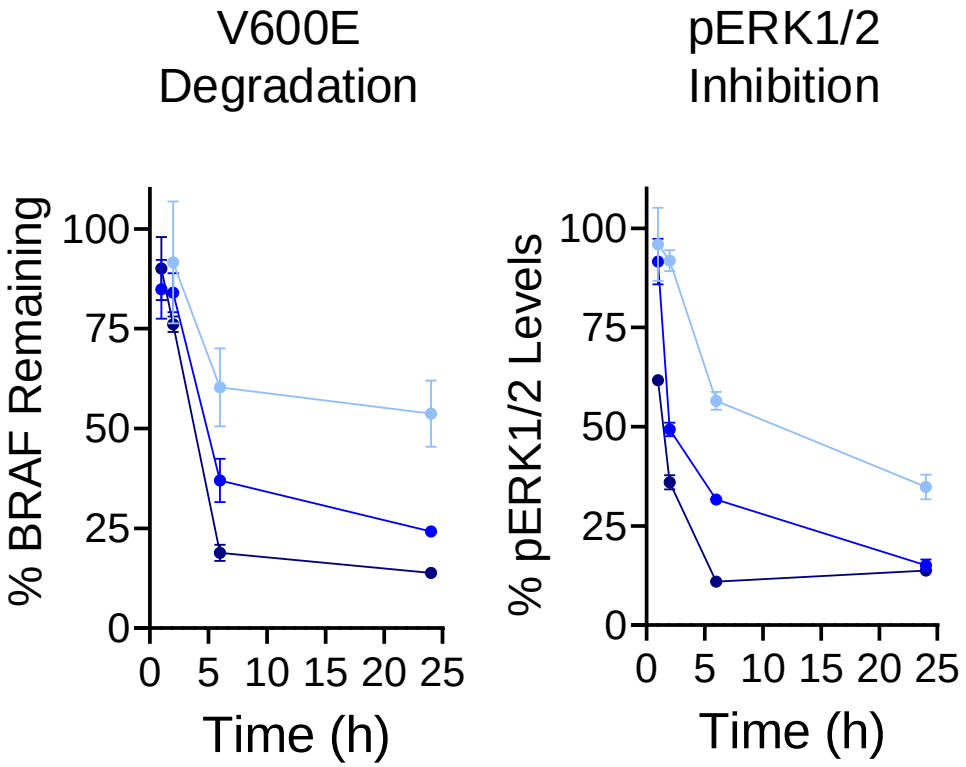


NRX-0305 Exhibits Dose-Proportional Pharmacokinetics and Pharmacodynamics Following a Single Oral Dose *In Vivo*

Plasma and Tumor PK



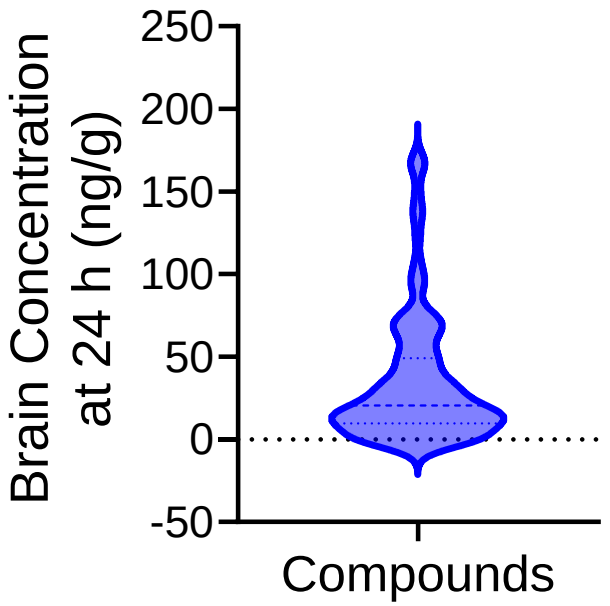
Tumor PD



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

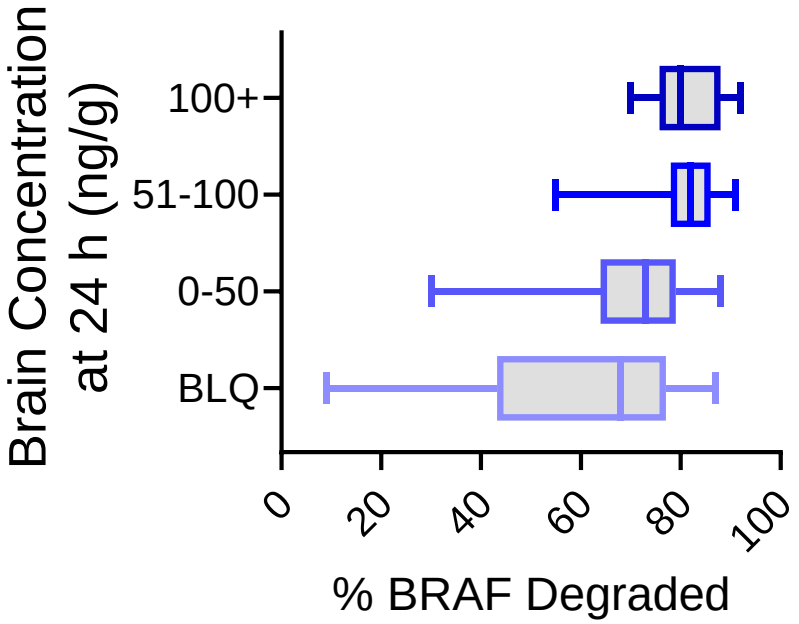
Brain Exposure Is a Key Component of Nurix *In Vivo* Screening, Allowing Identification of CNS Penetrant Degraders

Brain Exposure of BRAF Compounds



84% of *in vivo* screened compounds have measurable brain exposure

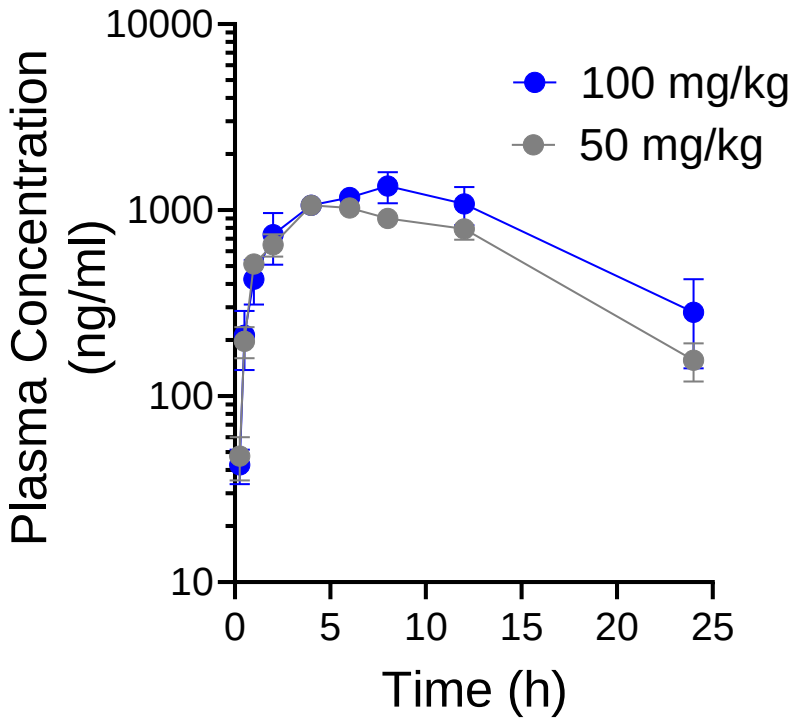
Mutant BRAF Tumor Degradation Correlates with Brain Exposure



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

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

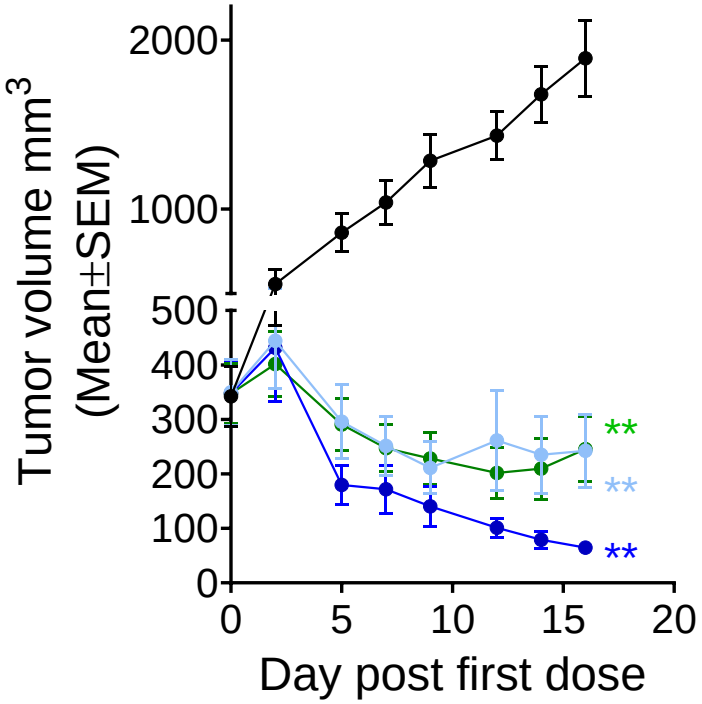
NRX-0305	%F
Mouse	71
Rat	47
Cyno	28

Rat PK with NRX-0305 eutomer, QDx1

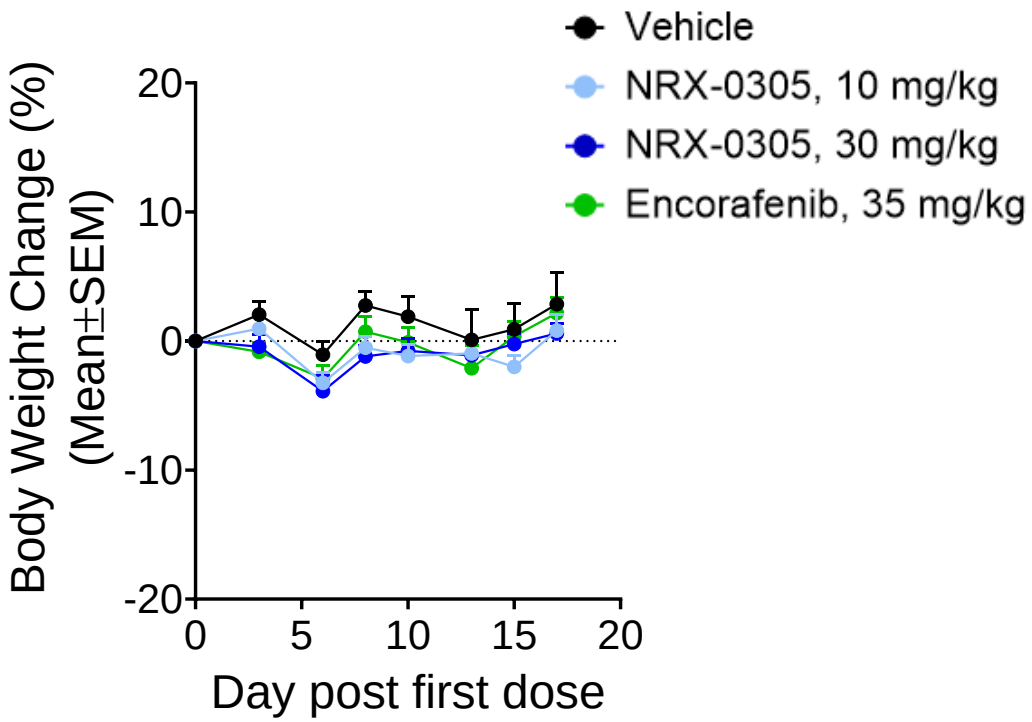
Cyno bioavailability obtained with NRX-0305 eutomer

NRX-0305 Demonstrates Efficacy in a Class 1 V600E Melanoma CDX Model

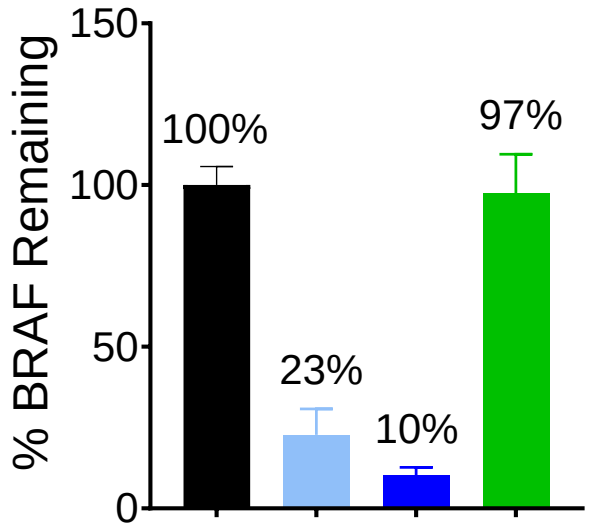
Efficacy



Body Weight



V600E Degradation

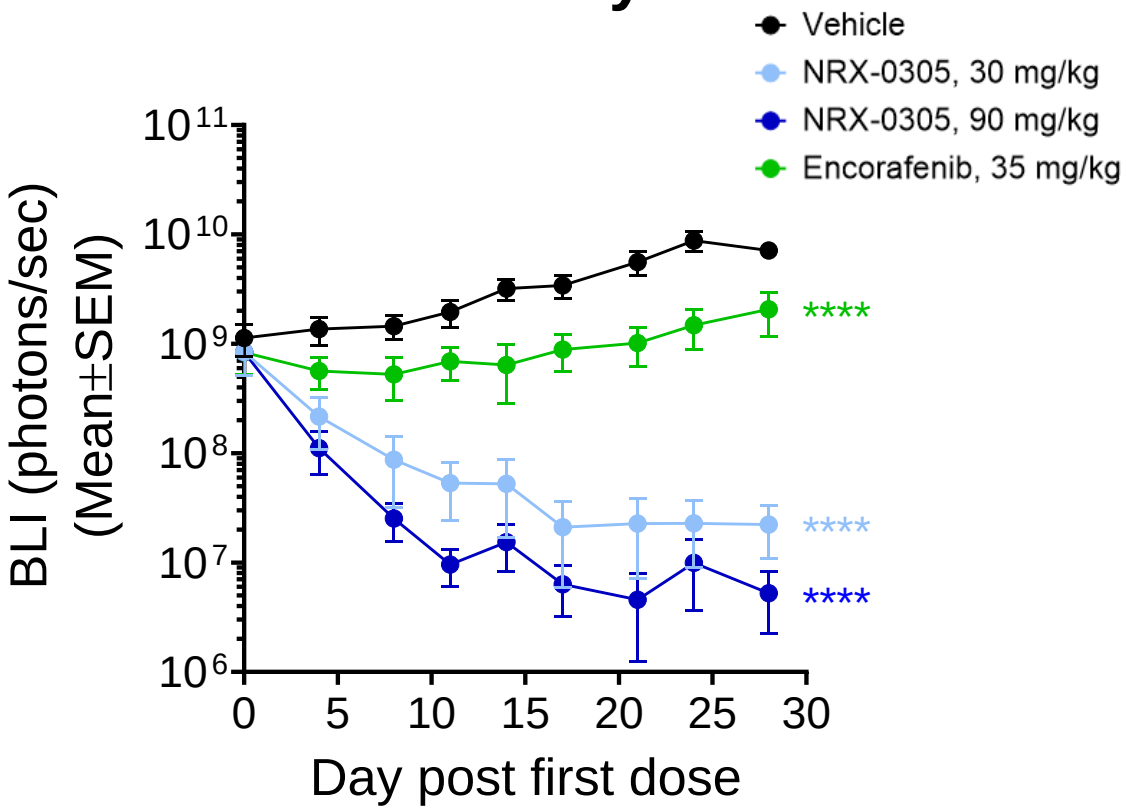


Class 1 V600E A375 sub-cutaneous flank mouse CDX model, efficacy arm, QDx17
Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test

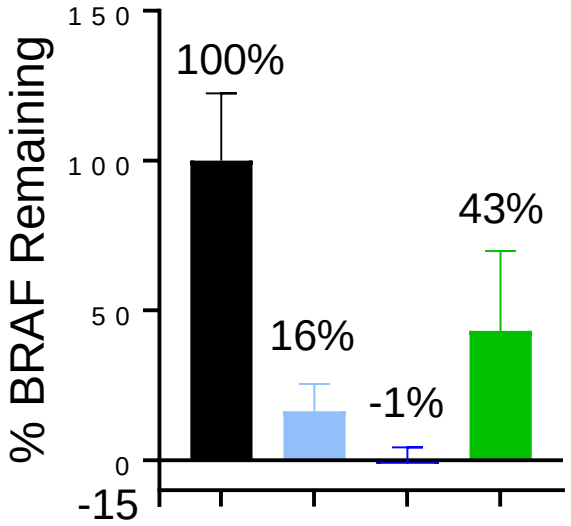
PD arm, QDx3

NRX-0305 Demonstrates Efficacy in a Class 1 V600E Melanoma Intracranial CDX Model

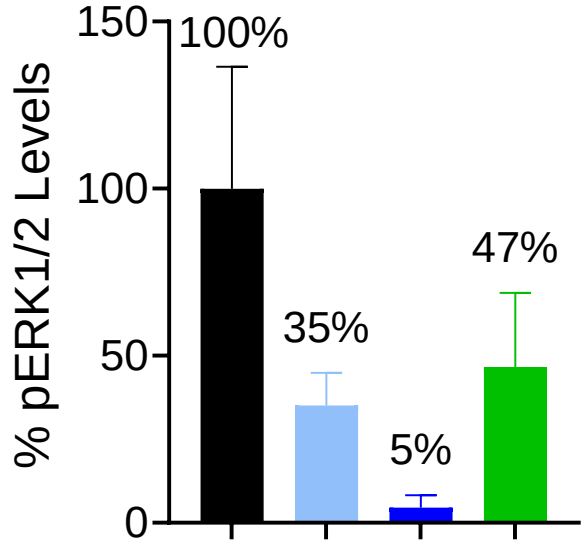
Efficacy



V600E Degradation



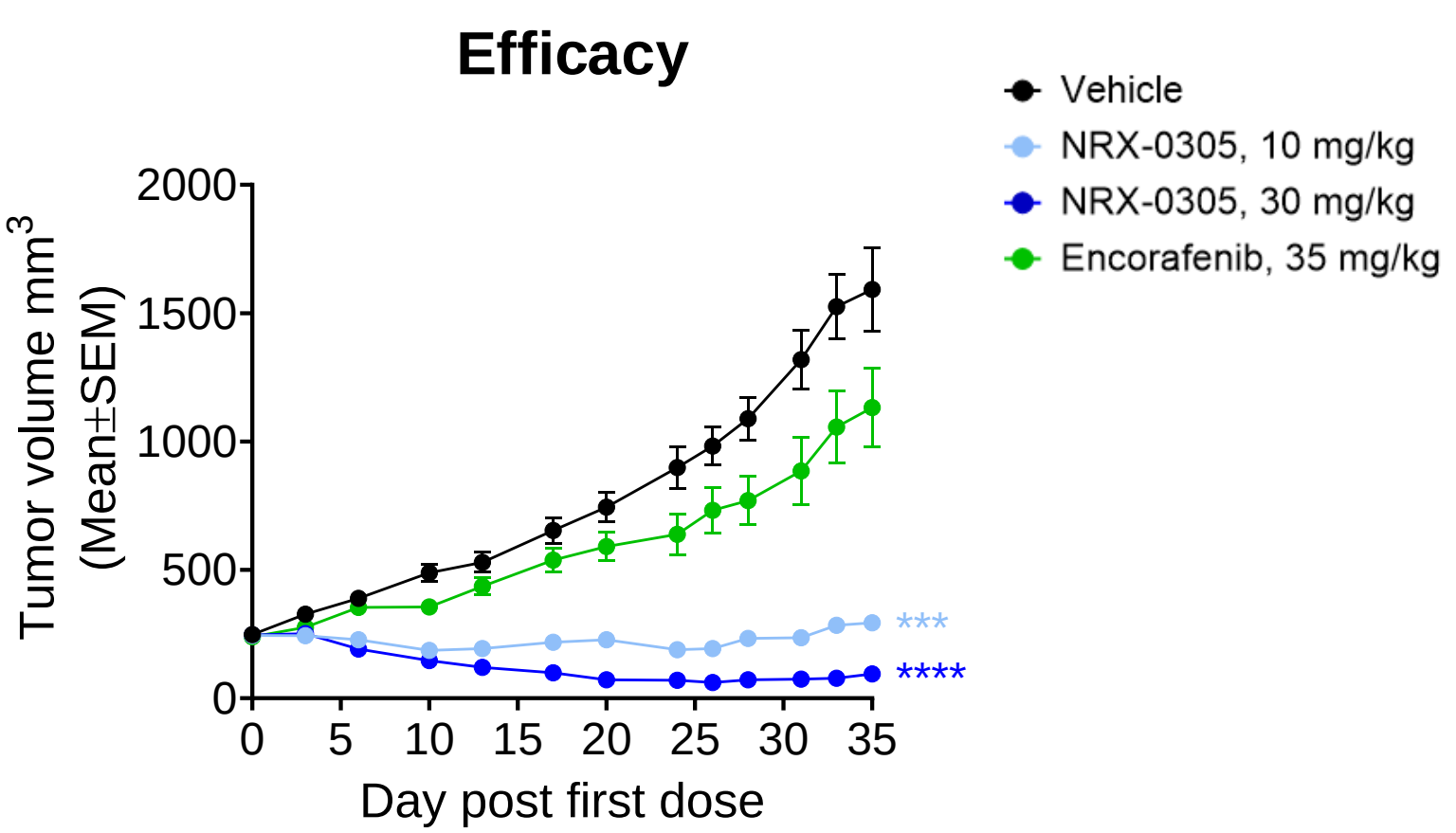
pERK1/2 Inhibition

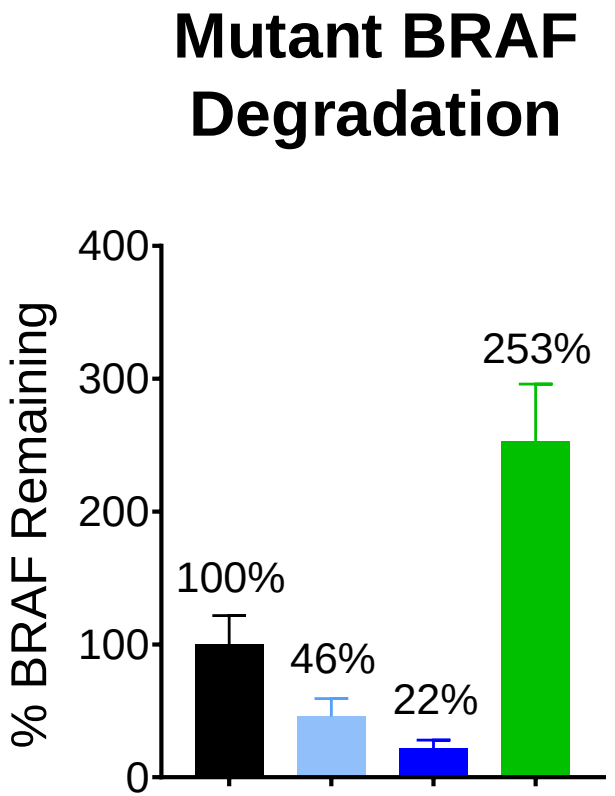


Class 1 V600E A375-luciferase-tagged intracranial mouse CDX model, efficacy arm, QDx28
One-way ANOVA with Dunnett's multiple comparisons test at day 28

PD arm, QDx4

NRX-0305 Demonstrates Efficacy in a Class 2 K601E Melanoma CDX Model

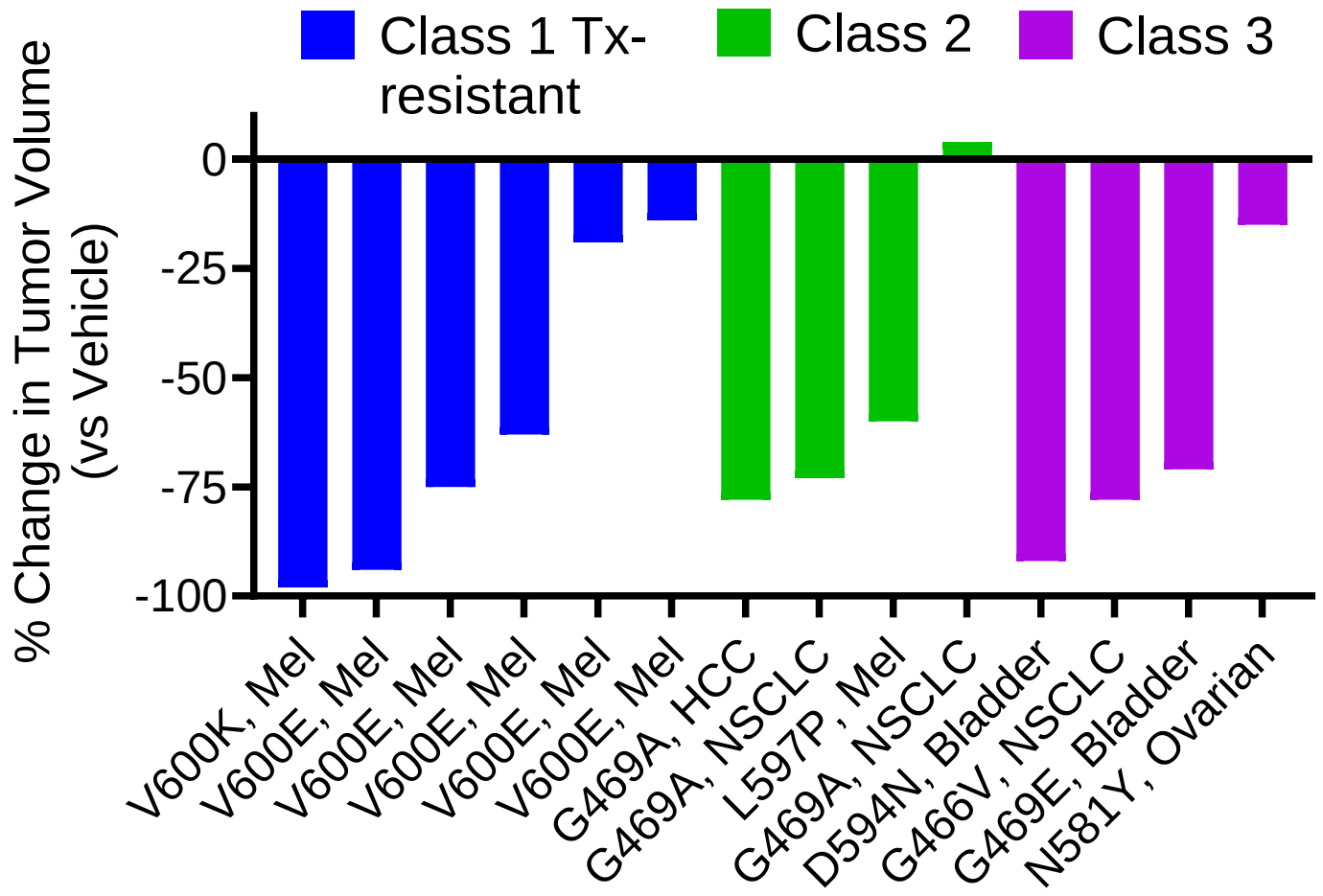




Class 2 K601E WM3130 sub-cutaneous flank mouse CDX model, efficacy arm, QDx35
Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test

PD arm, QDx6

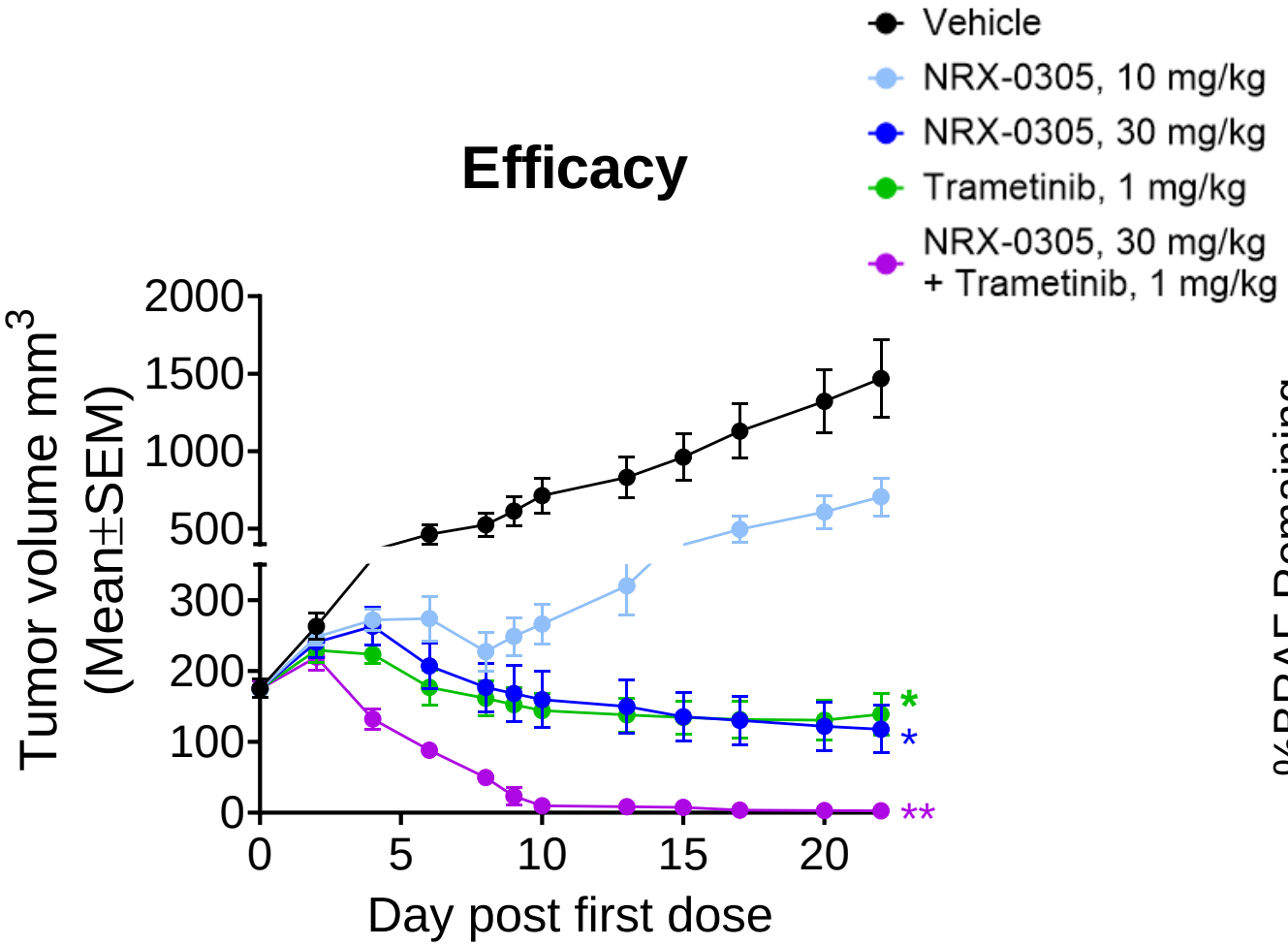
NRX-0305 Inhibits Tumor Growth in Numerous Class 1 Treatment-Resistant and Class 2/3 PDX Models

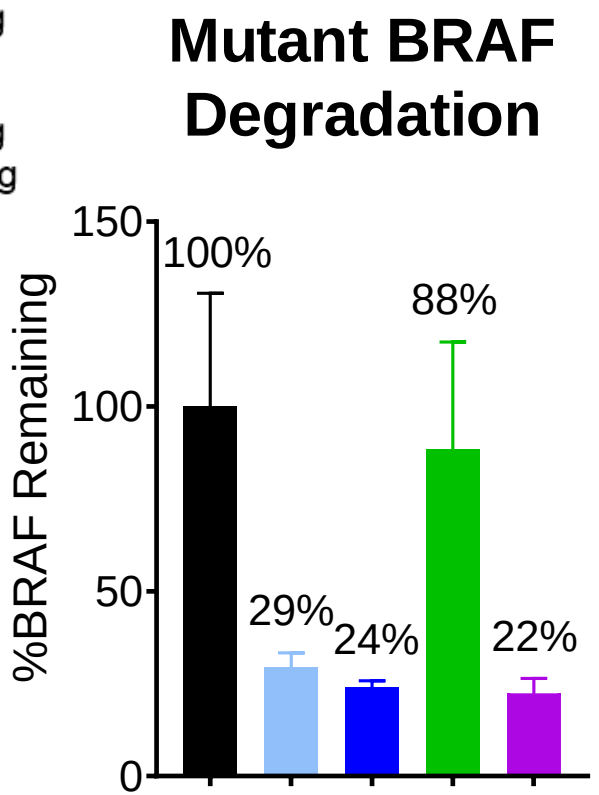


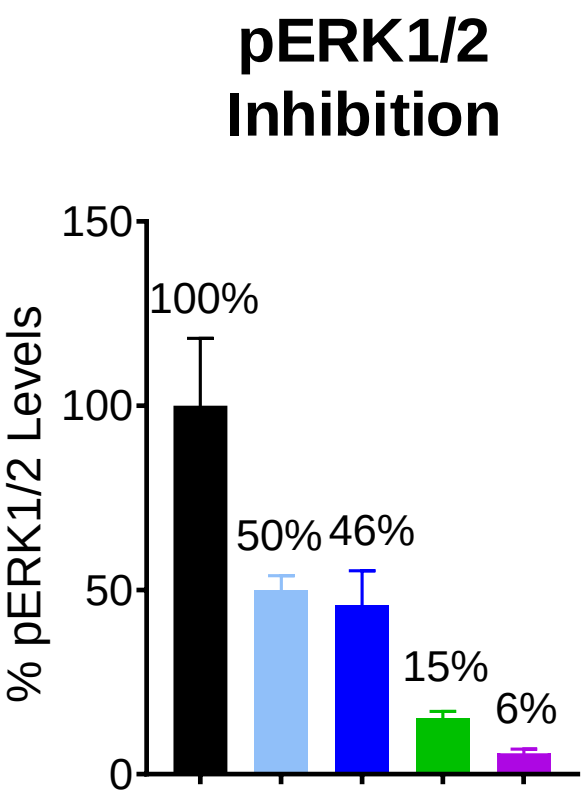
- NRX-0305 demonstrates anti-tumor activity in multiple PDX models in a 14-day exploratory screen

PDX model screening, QDx14 or QDx7 (D594N, Bladder) at 90 mg/kg
Mel, melanoma; HCC, hepatocarcinoma cancer; NSCLC, non-small cell lung cancer

NRX-0305 Is Efficacious in a Class 3 D594N Bladder Cancer PDX Model and Synergizes with MEK Inhibition



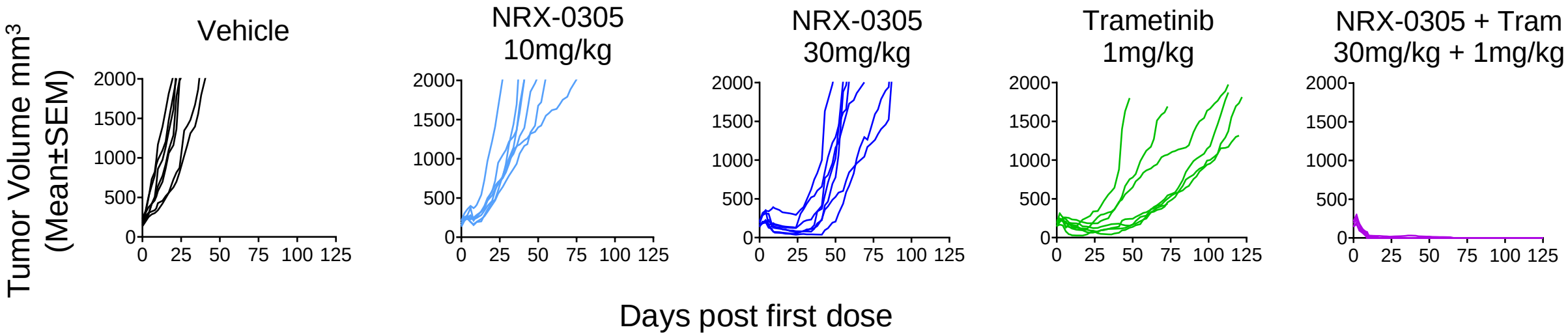




Class 3 D594N sub-cutaneous flank mouse PDX, efficacy arm, QDx22
Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test

PD arm, QDx3

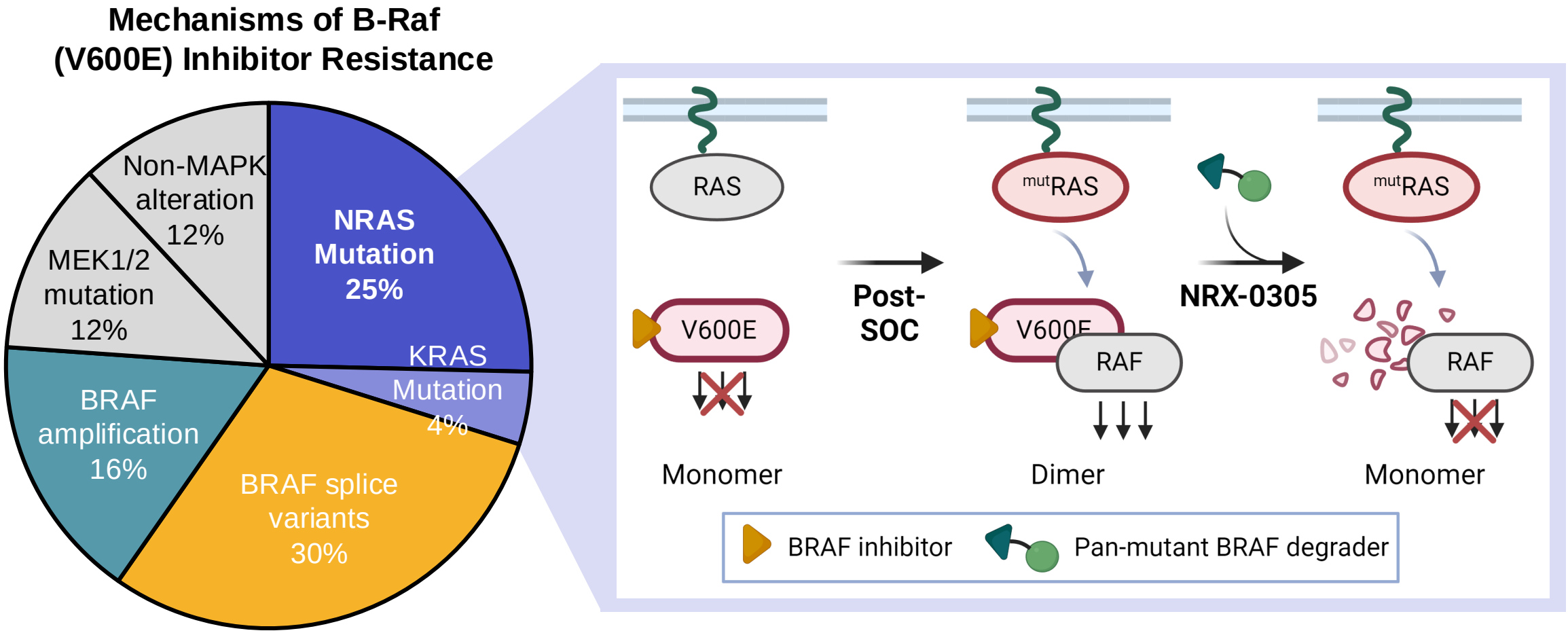
NRX-0305 Synergizes with MEK Inhibition Leading to Complete Tumor Regression in a Class 3 D594N Bladder Cancer PDX Model



- NRX-0305 in combination with MEK inhibitor, Trametinib, results in complete tumor regressions

Class 3 D594N sub-cutaneous flank mouse PDX, efficacy arm, QDx22

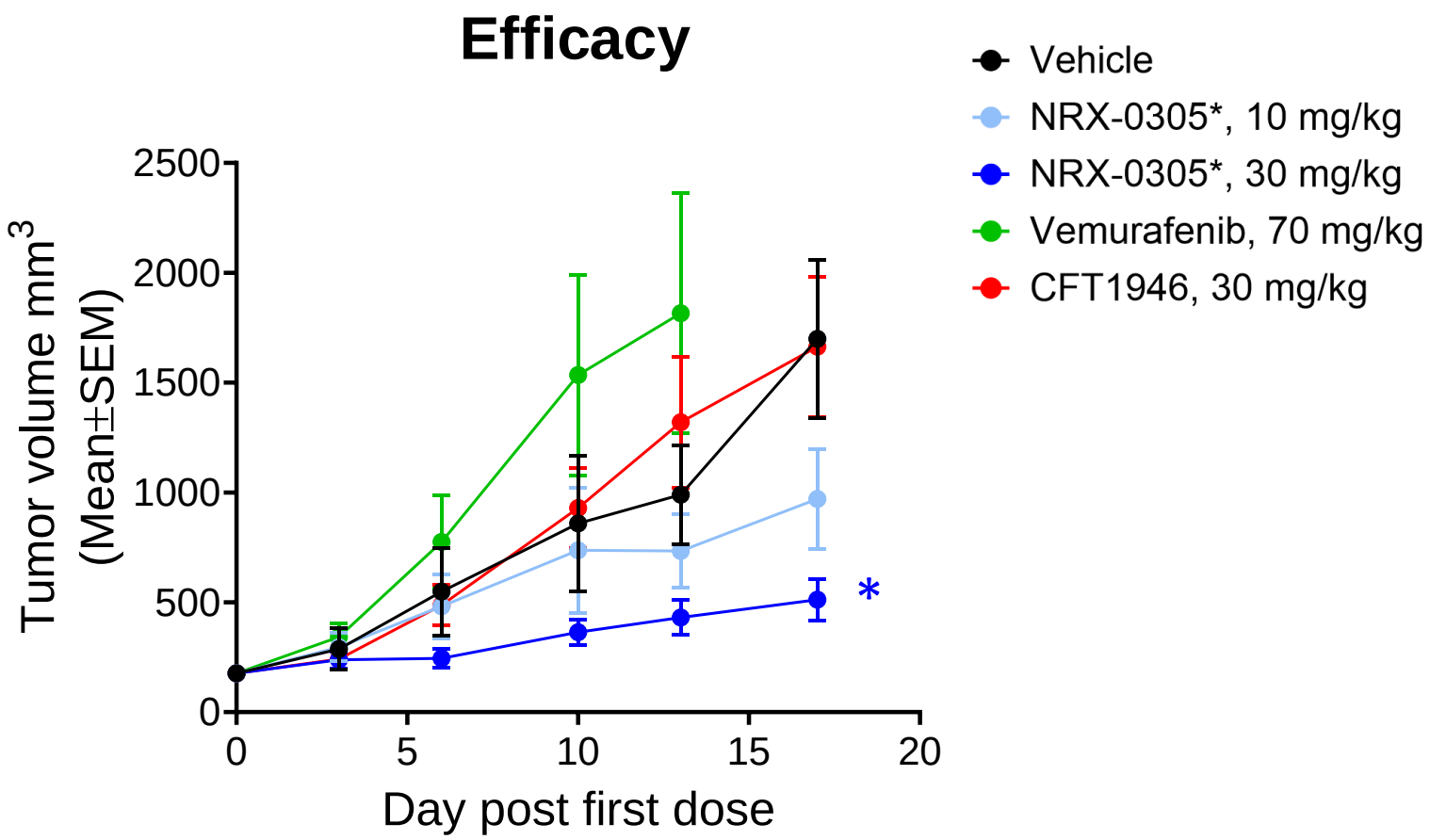
Catalytic MoA and Ability To Degrade Dimeric BRAF Mutants Provide an Opportunity To Clinically Benefit Patients who Have Progressed on BRAFi

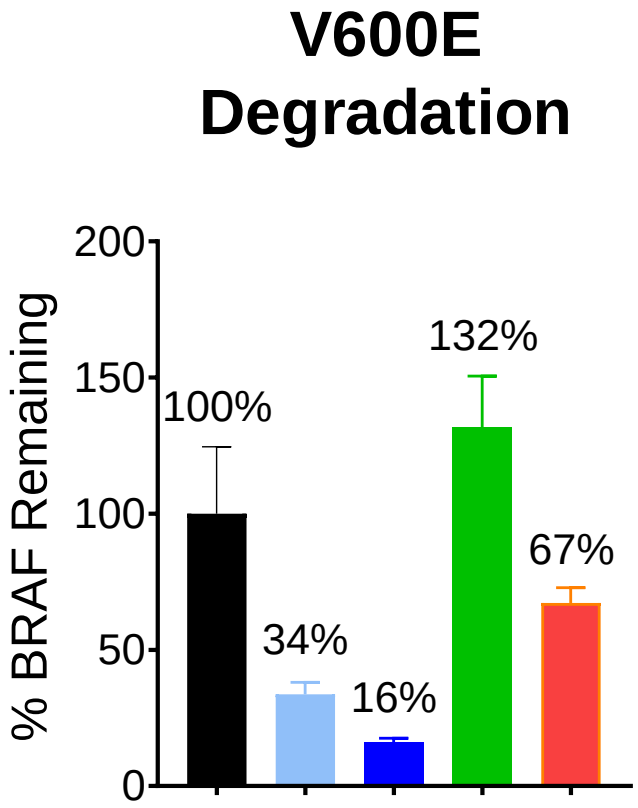


- NRX-0305 is also predicted to have activity against BRAF splice variants and BRAF amplifications, thereby covering >50% of the BRAFi-resistant population

Figure made in BioRender; adapted from Johnson 2015 Eur J Cancer, 51: 723-730.

NRX-0305 Demonstrates Efficacy in a Class 1 (V600E, NRAS Q61R) Pembrolizumab+BRAFi-Resistant Melanoma PDX Model





*Class 1 V600E, NRAS Q61R sub-cutaneous flank mouse PDX, efficacy arm, QDx17; *, NRX-0305 Eutomer*
One-way ANOVA with Dunnett's multiple comparisons test at day 17

PD arm, QDx3

Summary

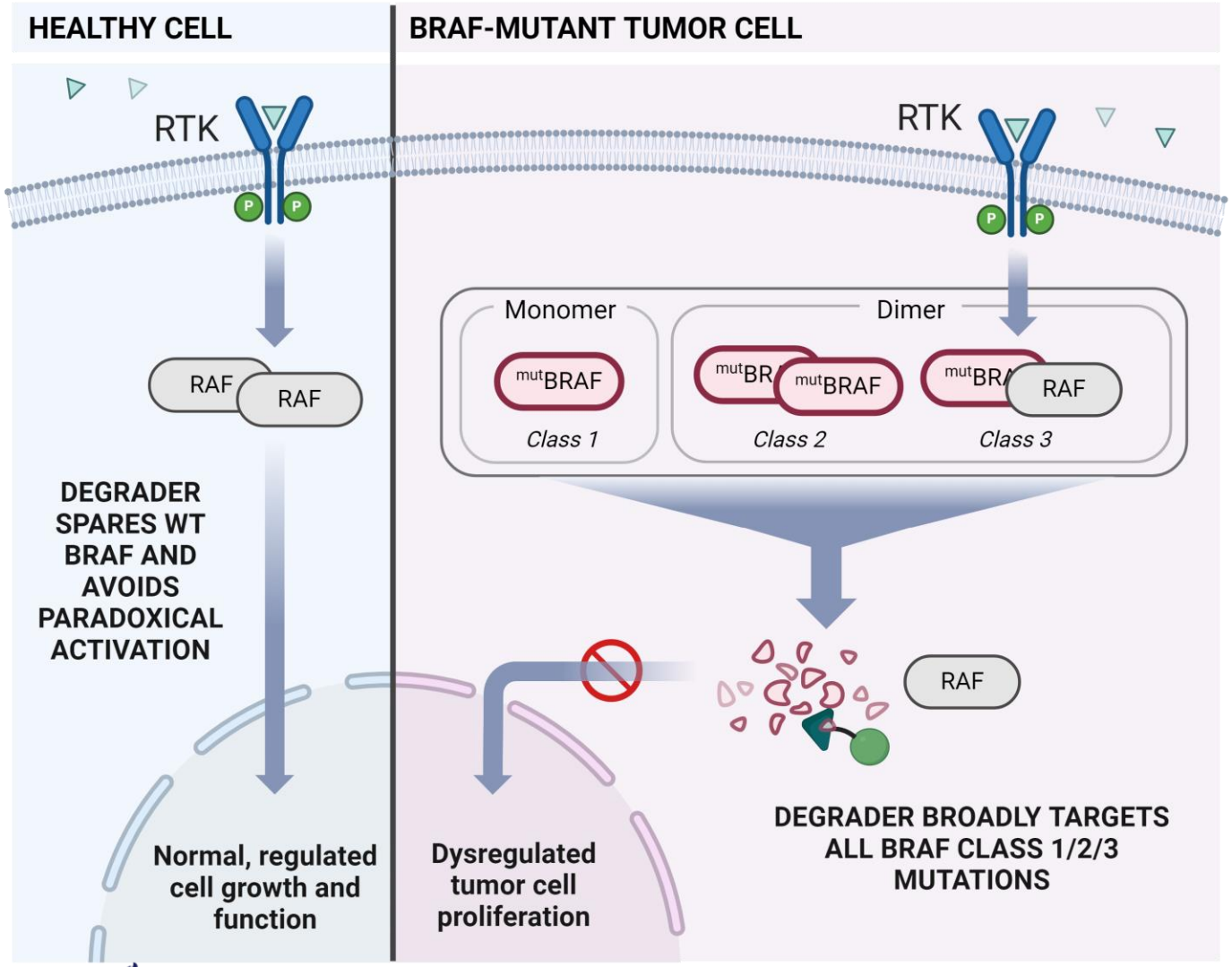


Figure made in BioRender

- NRX-0305 is an orally available and CNS penetrant pan-mutant BRAF degrader
- Potent and selective towards Class 1/2/3 BRAF mutants while sparing wildtype BRAF
- Prevents dimer formation and avoids paradoxical activation
- Demonstrates broad anti-tumor efficacy in BRAF Class 1/2/3 and Class 1 treatment-resistant CDX and PDX models
- Synergizes with MEKi to drive complete regressions in Class 3 BRAF mutant cancers

Acknowledgments

Thank you to the Nurix Research Team for making this work possible