NRX-0305: A Pan-Mutant Brain-Penetrant BRAF Degrader with Broad Preclinical Activity and Synergy with MEKi in Class 1/2/3 BRAF-Mutant Cancers

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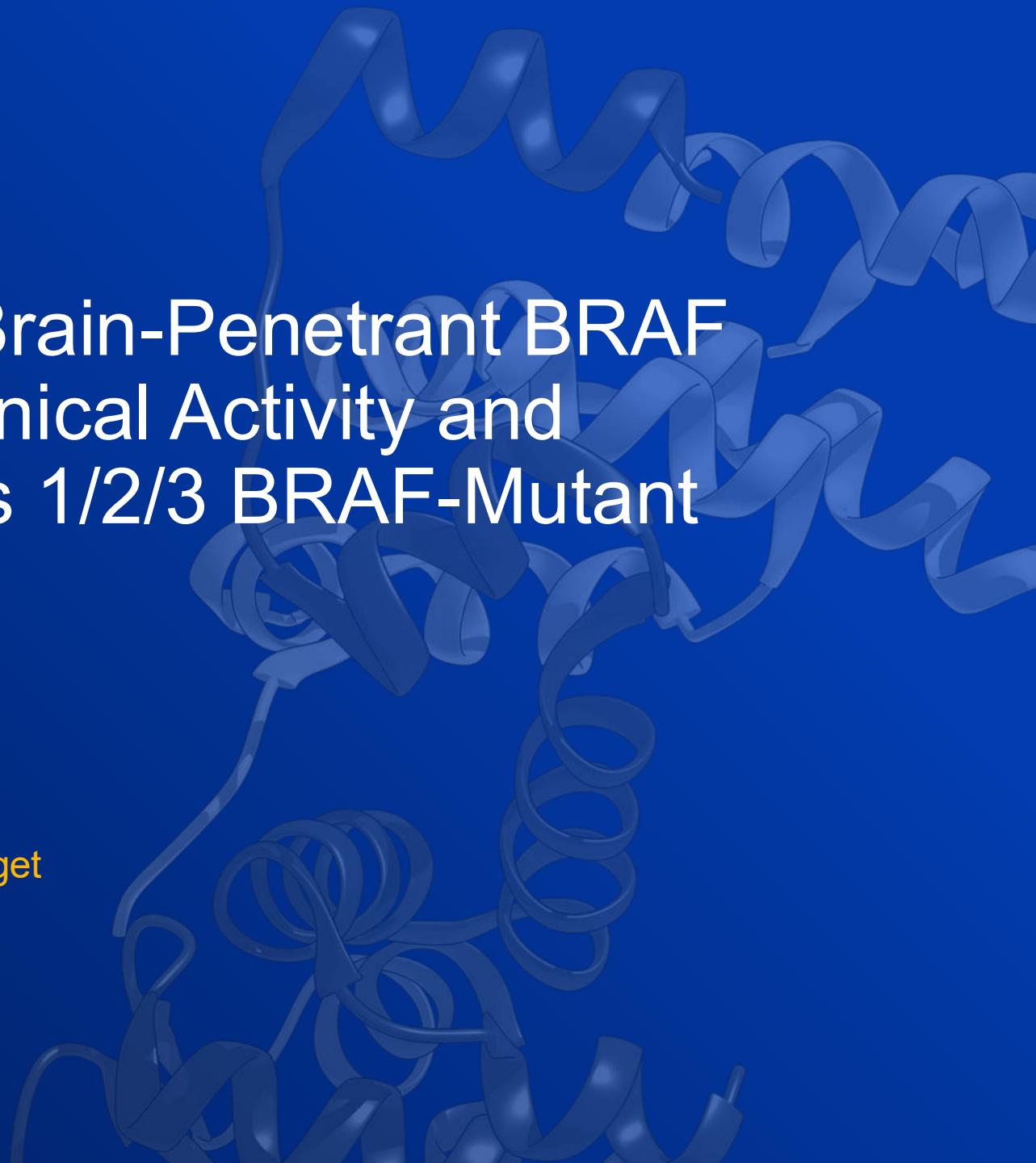
Small Molecules for Cancer Targets, Discovery on Target
Boston, MA
September 23, 2025



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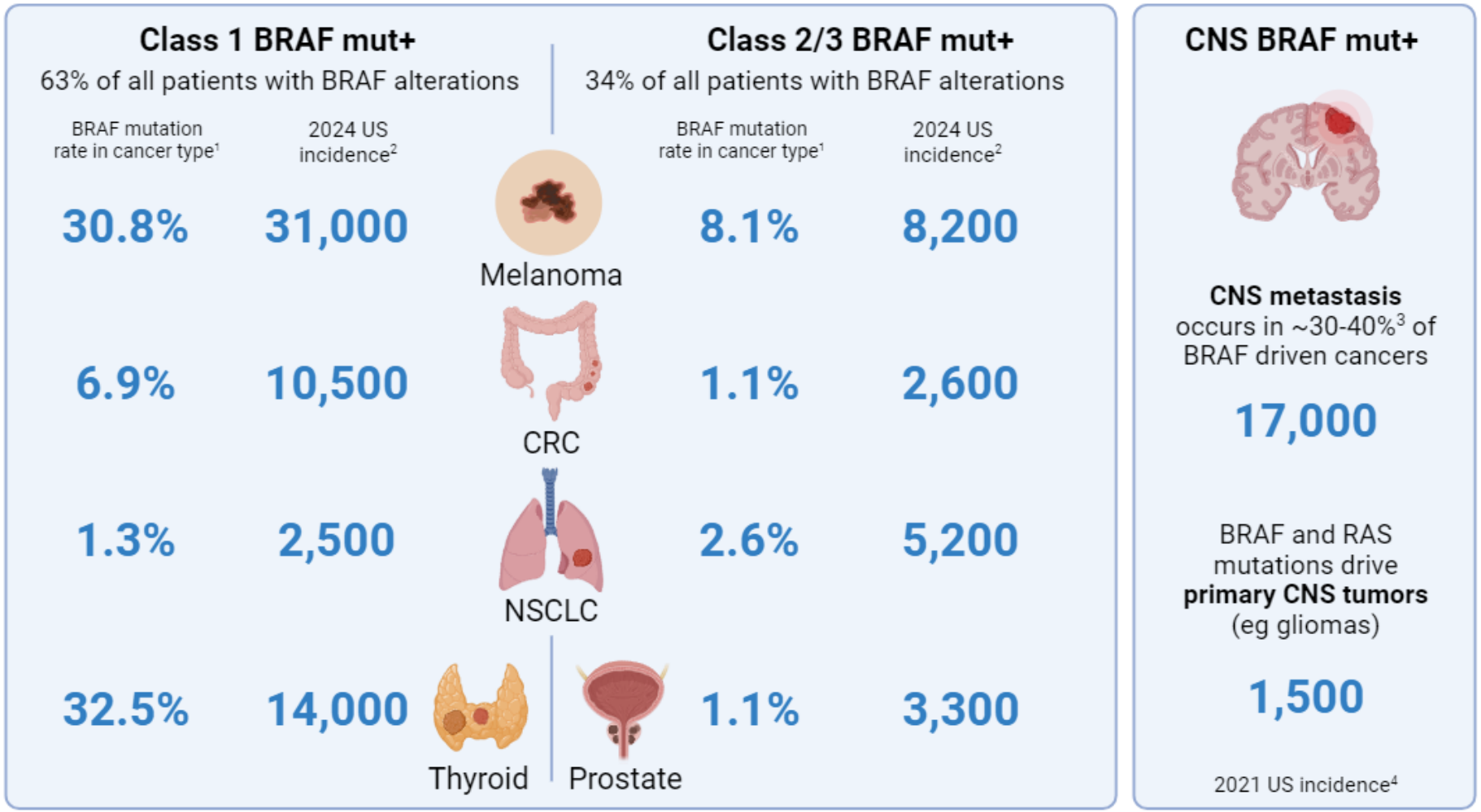
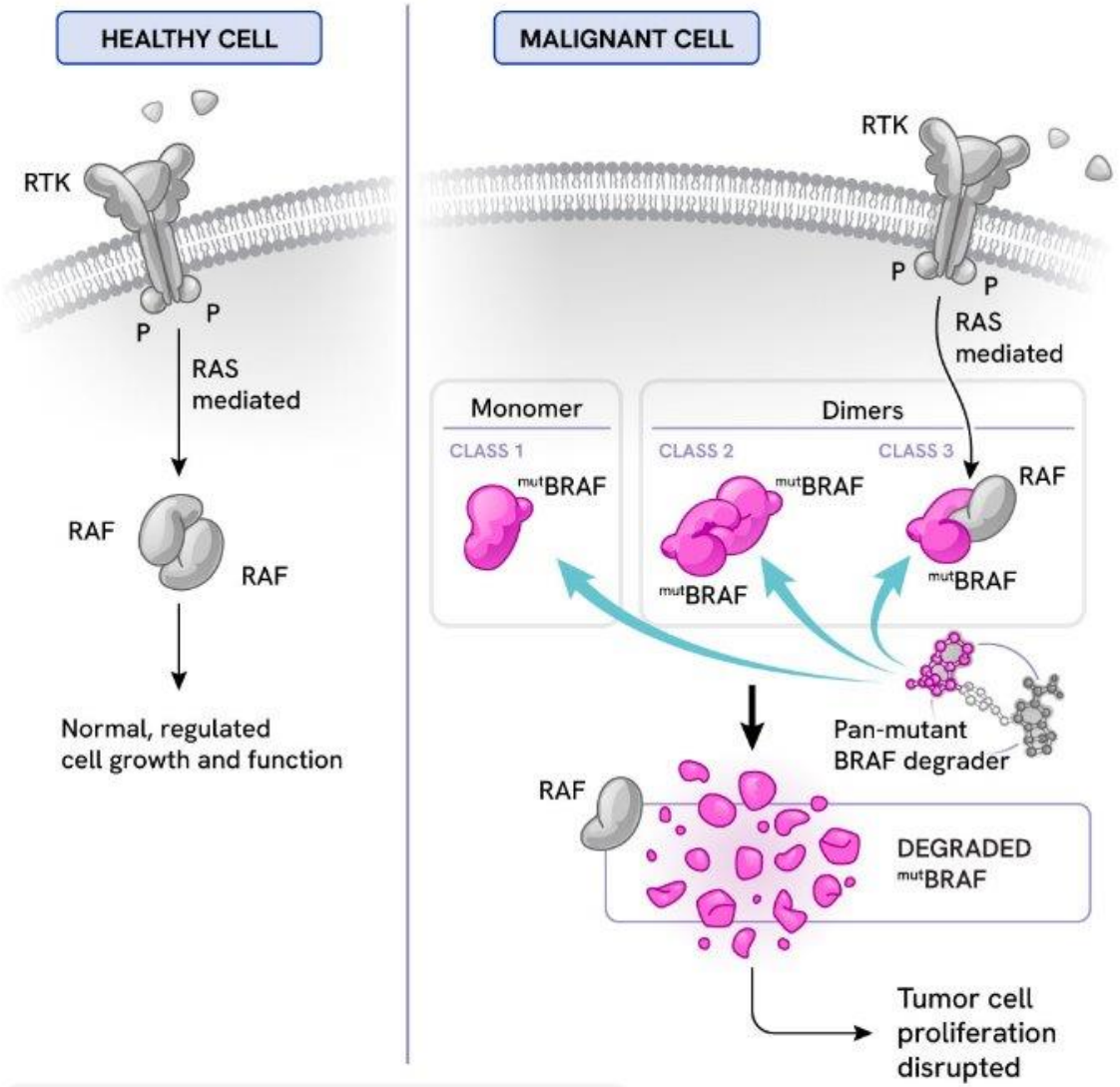
BRAF Mutations Activate the MAPK Pathway and Are Associated with Cancer



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

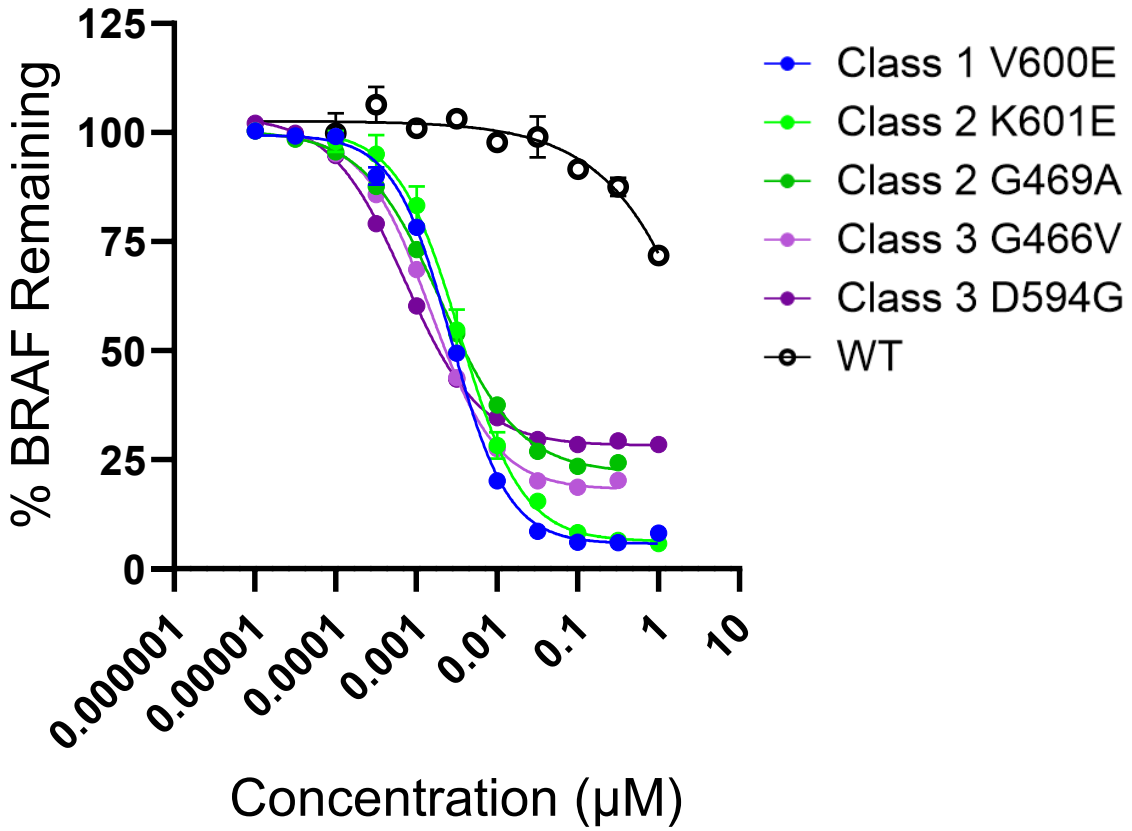
Pan-Mutant BRAF Degrader: A Novel Approach for Broadly Targeting BRAF Mutations and Overcoming BRAFi Resistance



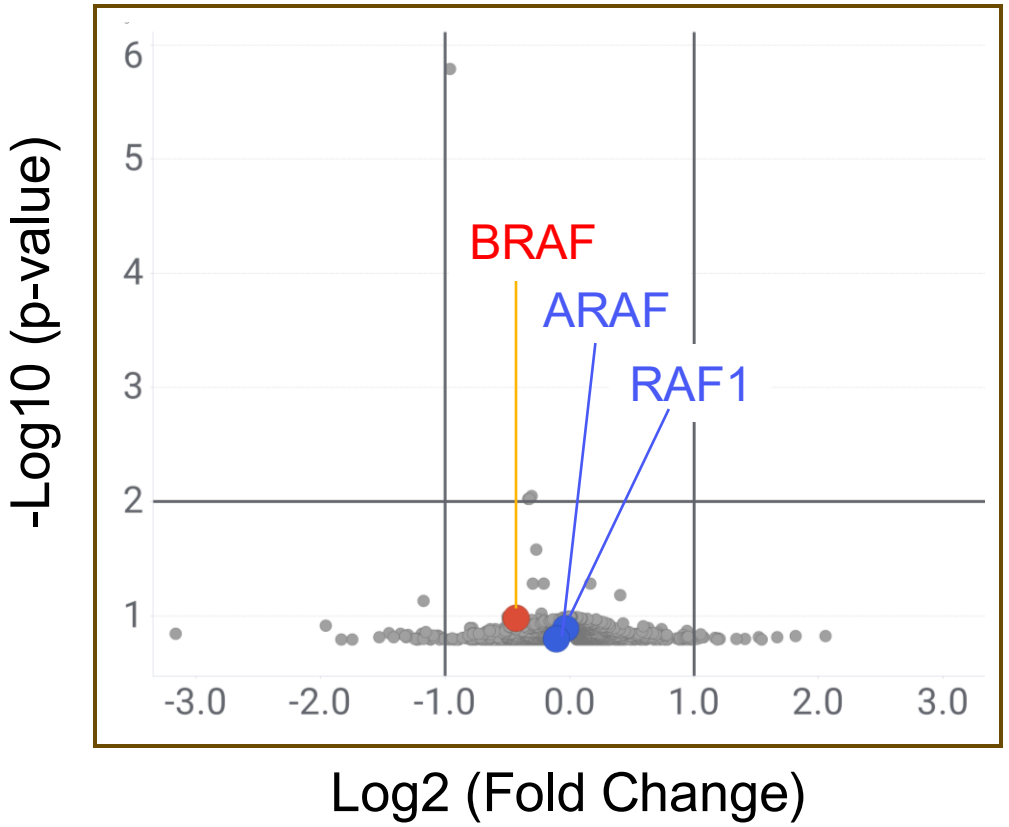
- Targets mutant BRAF while sparing wildtype BRAF, which is critical for normal cellular function
- Prevents dimer formation and avoids paradoxical activation
- Degrader provides sustained MAPK pathway suppression through catalytic MoA
- May delay and/or circumvent BRAFi-induced MAPK pathway resistance

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

Pan-Mutant BRAF Degradation



IMR-90 Global Proteomics, 50x DC_{50}*

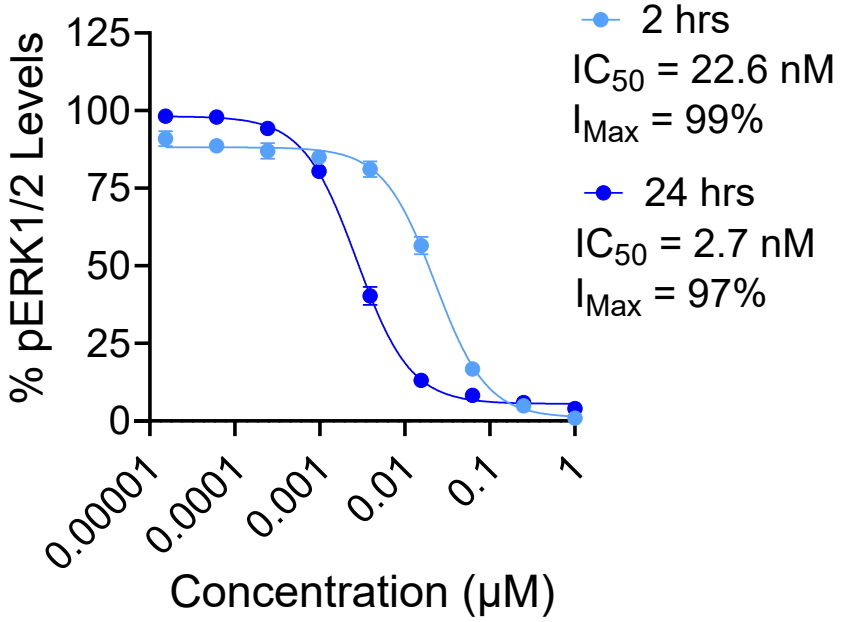


Class 1 V600E A375 and Class 2 K601E WM3130 cell lines contain HiBiT (bioluminescent tag) KI
Class 2/3 G469A, G466V, and D594G are engineered HiBiT overexpression systems in HCT116 BRAF-/-
WT BRAF degradation in human peripheral mononuclear cells, 24 hrs drug treatment

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

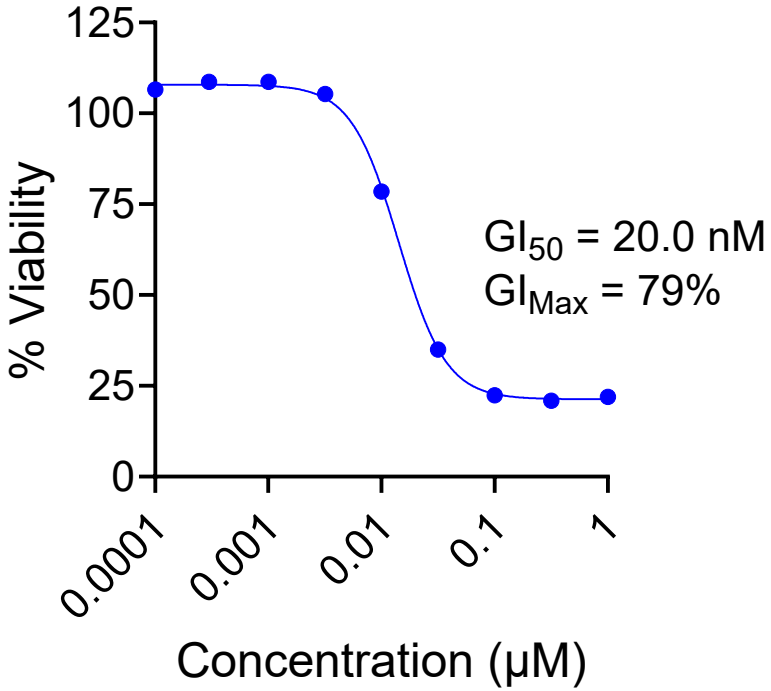
BRAF V600E Degradation by NRX-0305 Inhibits pERK, Induces Anti-Proliferative Activity and Circumvents Paradoxical Activation

pERK1/2 Inhibition



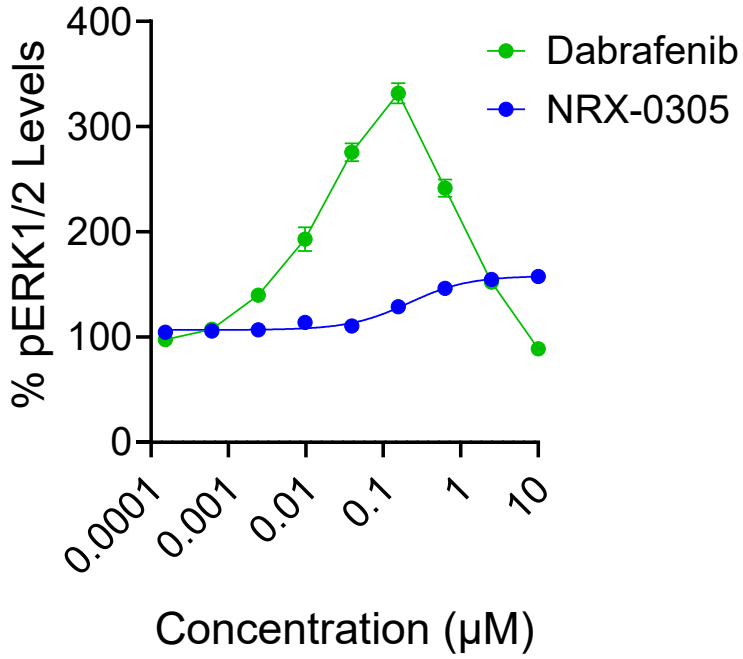
Class 1 V600E A375 cell line

Viability



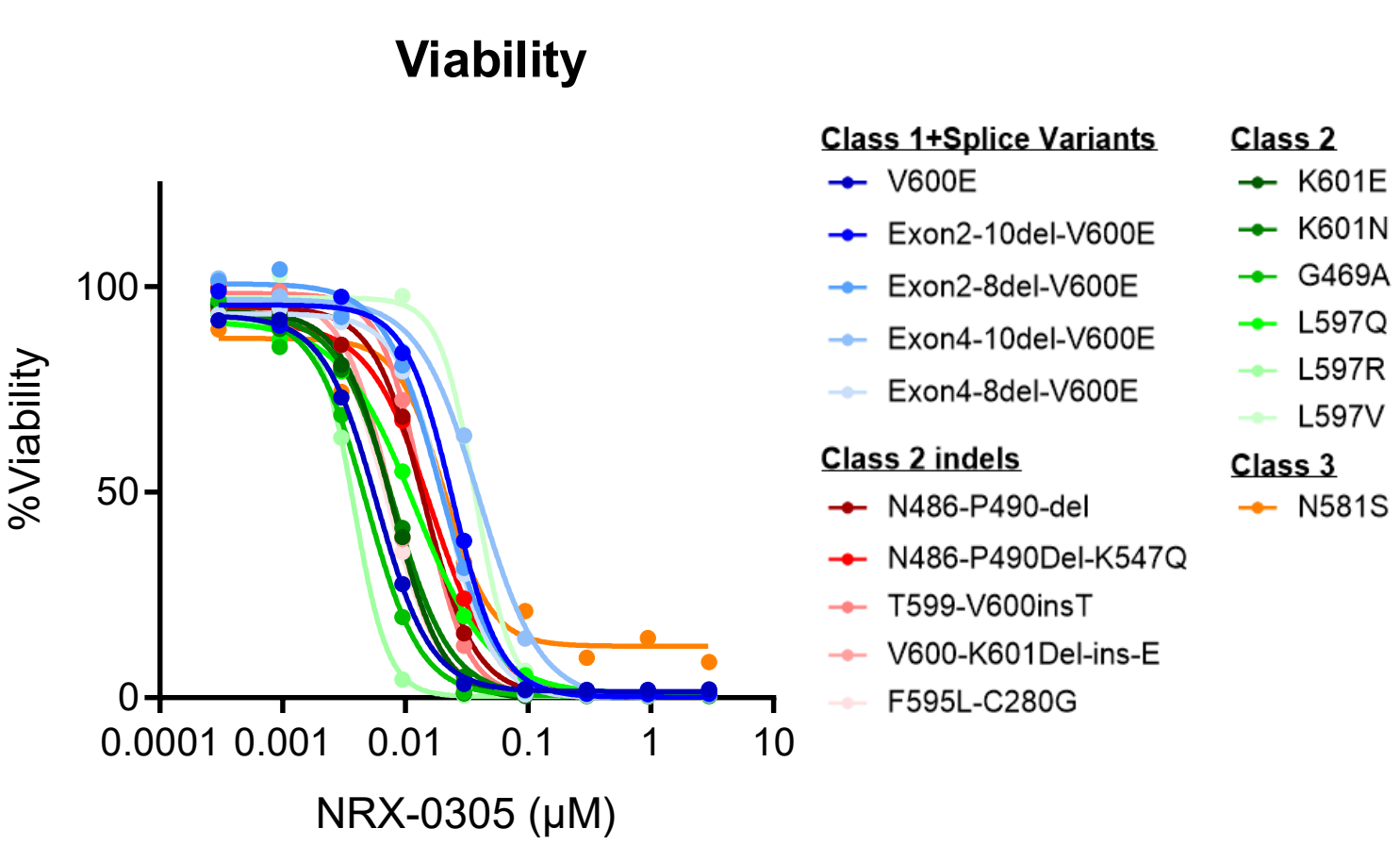
Class 1 V600E A375 cell line, 5-day cell viability

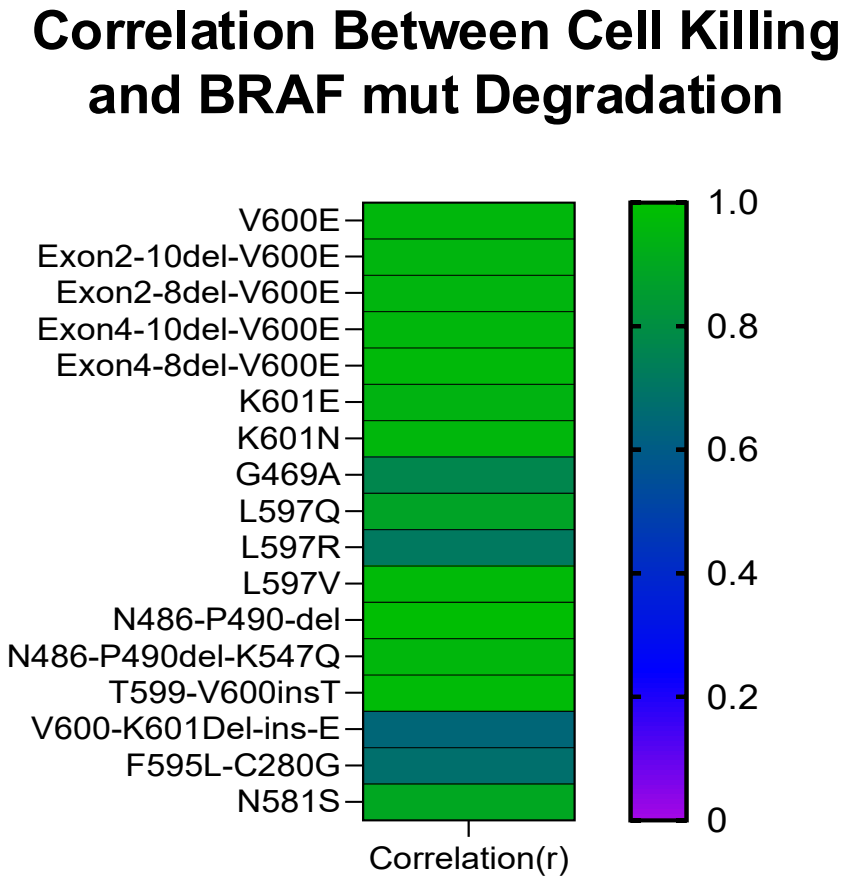
Paradoxical Activation



HCT116 cell line

NRX-0305 Shows Anti-Proliferative Effects Across a Broad Panel of Class 1/2/3 BRAF Mutations, Which Correlates with Mutant BRAF Degradation

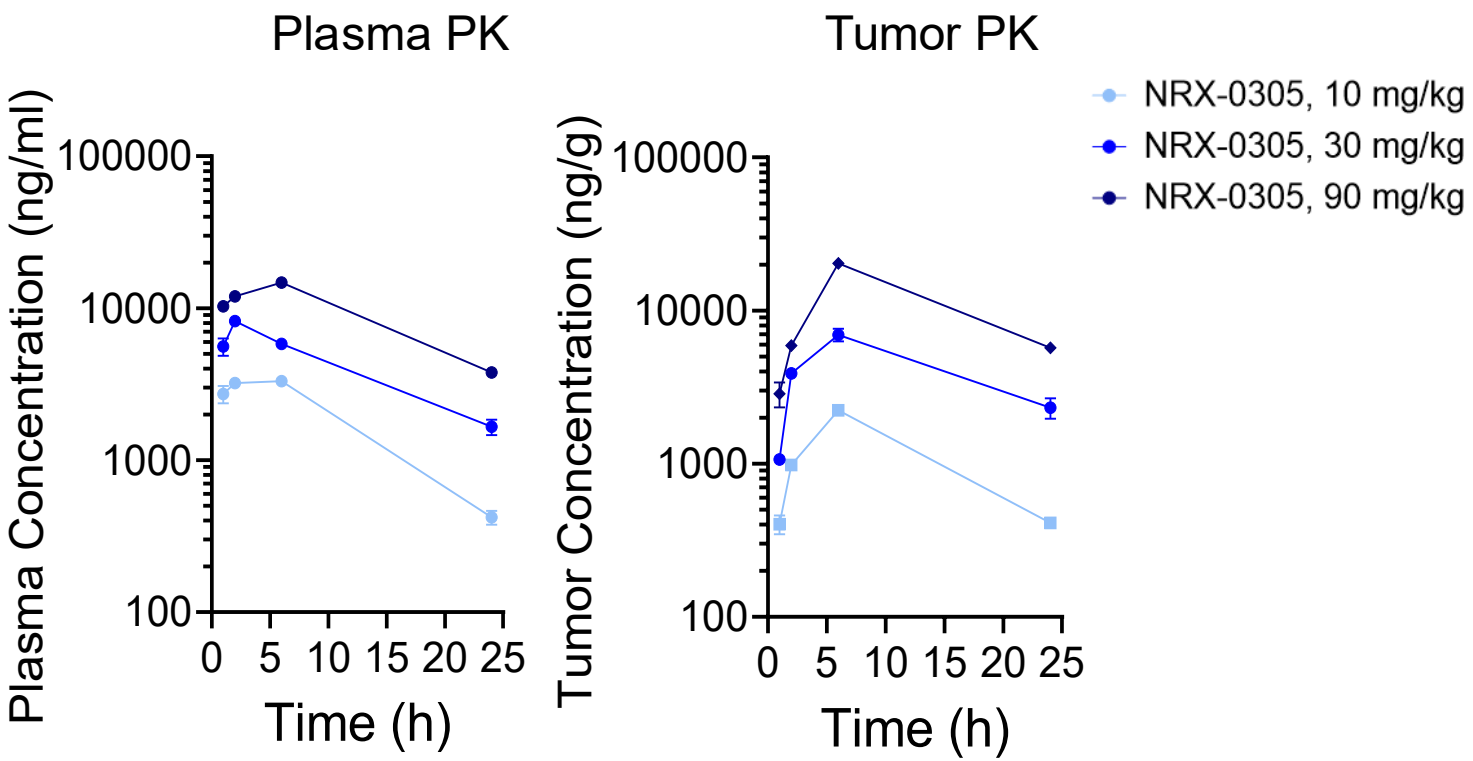




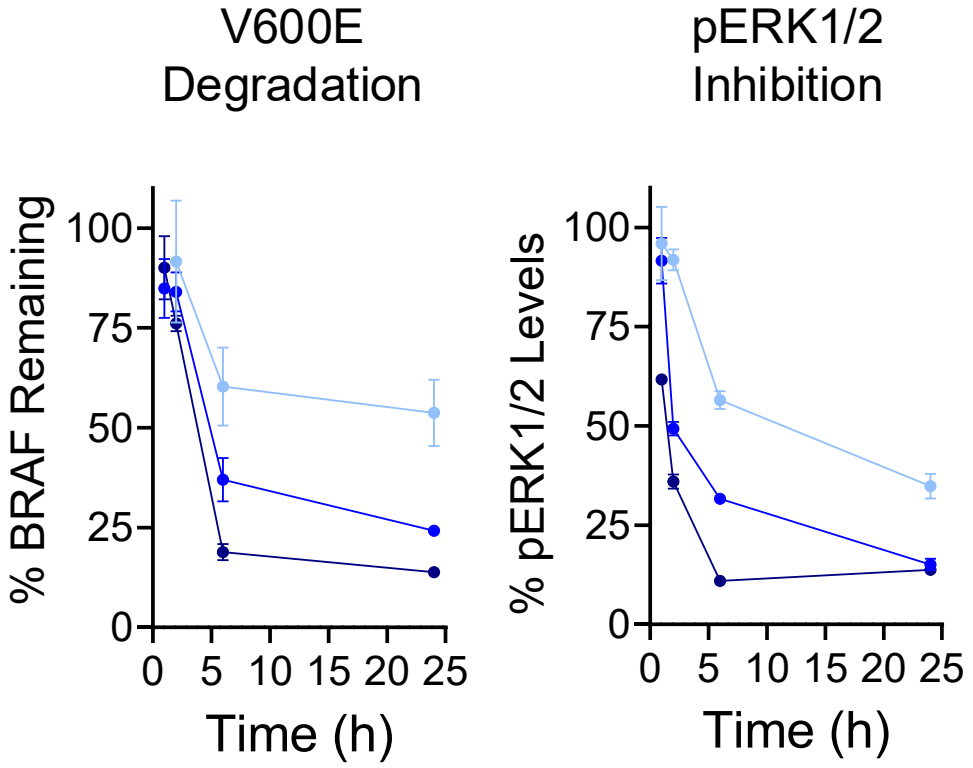
BRAF mutants expressed in mouse Ba/F3 system, without mIL3, 5-day cell viability and 24 hrs drug treatment for degradation. Indel/del/ins, insertion/deletions.

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

Plasma and Tumor PK



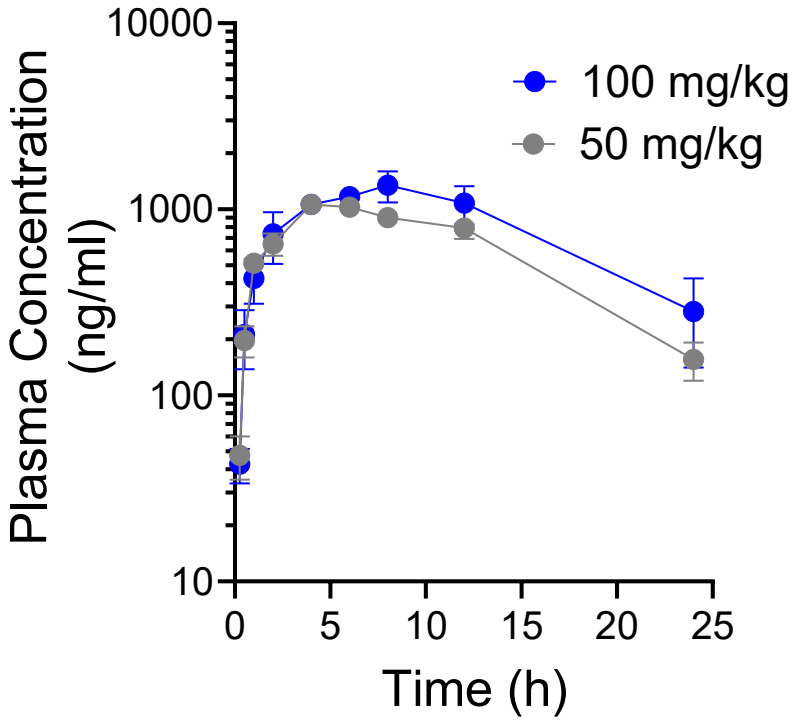
Tumor PD



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

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

Rat PK with NRX-0305 eutomer, QDx1

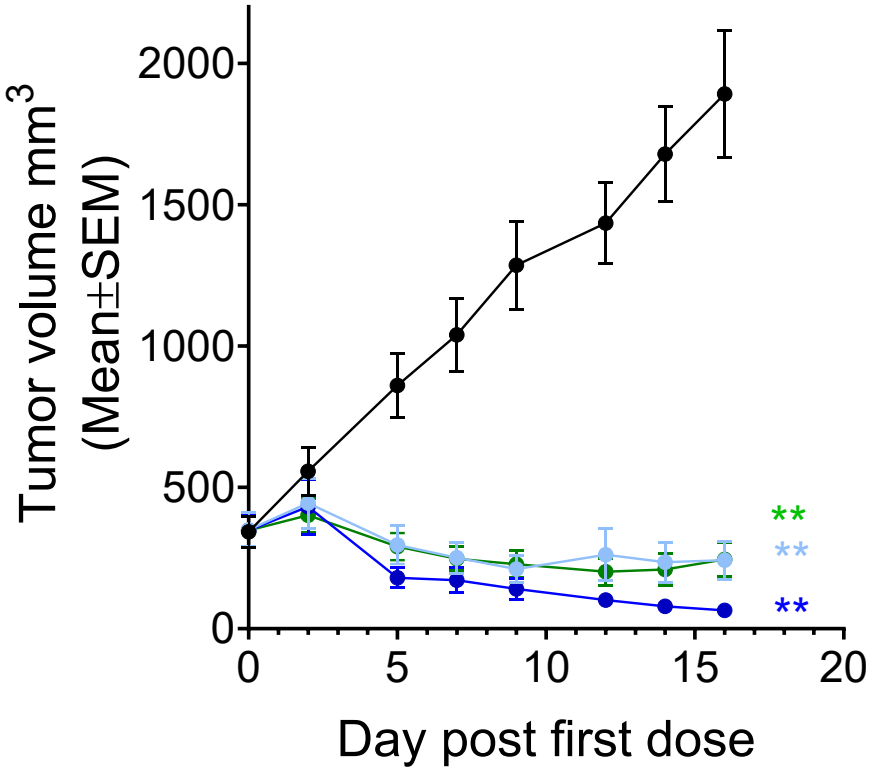
Bioavailability

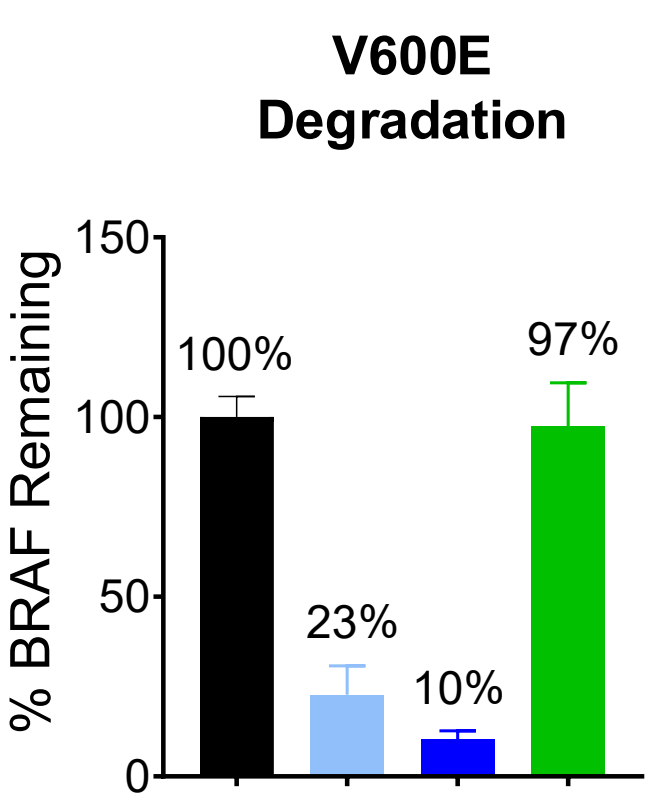
NRX-0305	%F
Mouse	71
Rat	47
Dog	28
Cyno	28

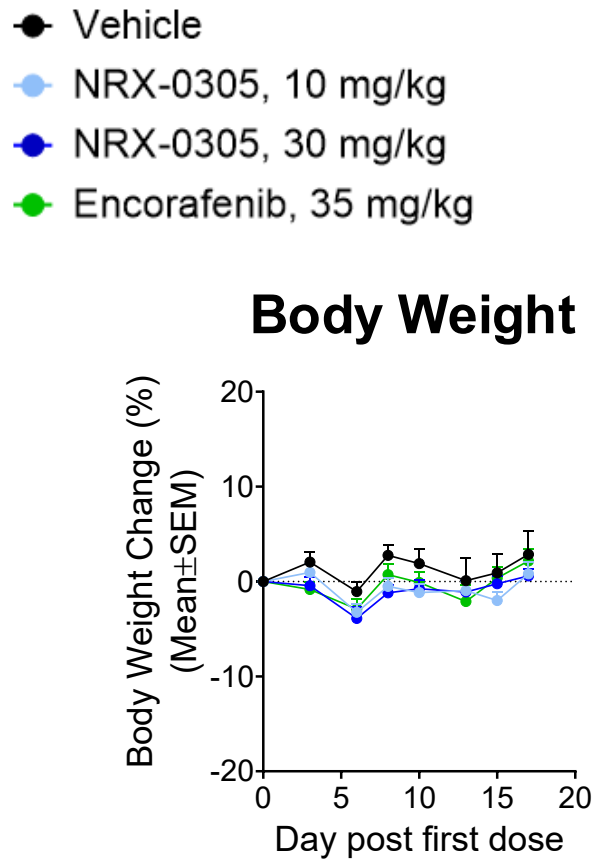
Dog and cyno bioavailability obtained with NRX-0305 eutomer
Dog bioavailability obtained without pentagastrin pre-dosing

NRX-0305 is Efficacious in Class 1 Melanoma

NRX-0305 in (V600E) Subcutaneous 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

PD arm, QDx3

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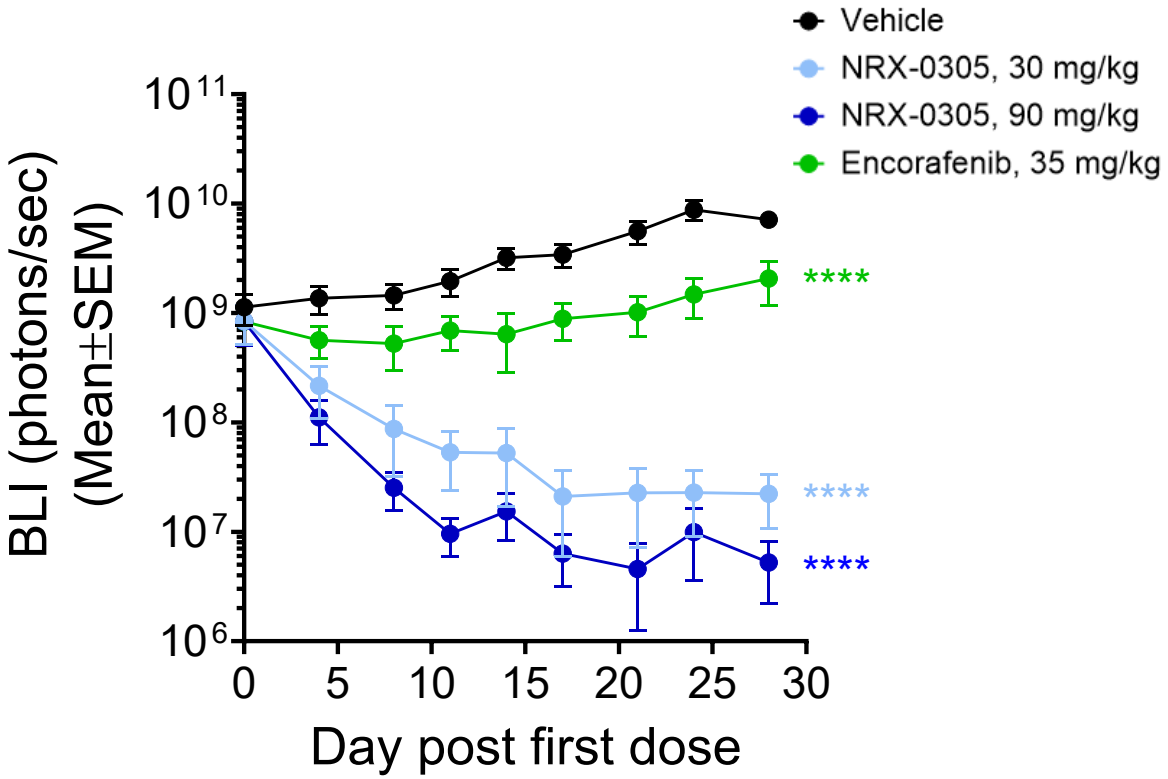
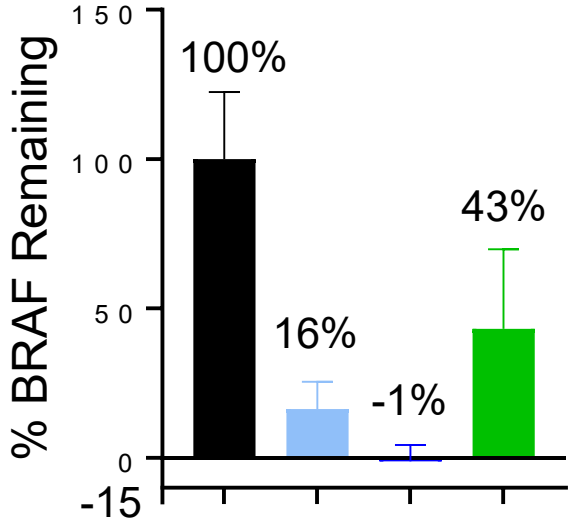
NRX-0305 is Efficacious in Class 1 Intracranial Melanoma

NRX-0305 in (V600E) Intracranial CDX Model

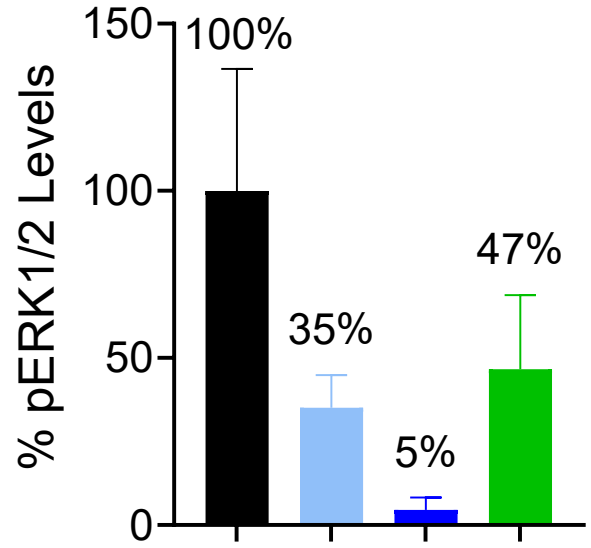
Efficacy



V600E Degradation



pERK1/2 Inhibition



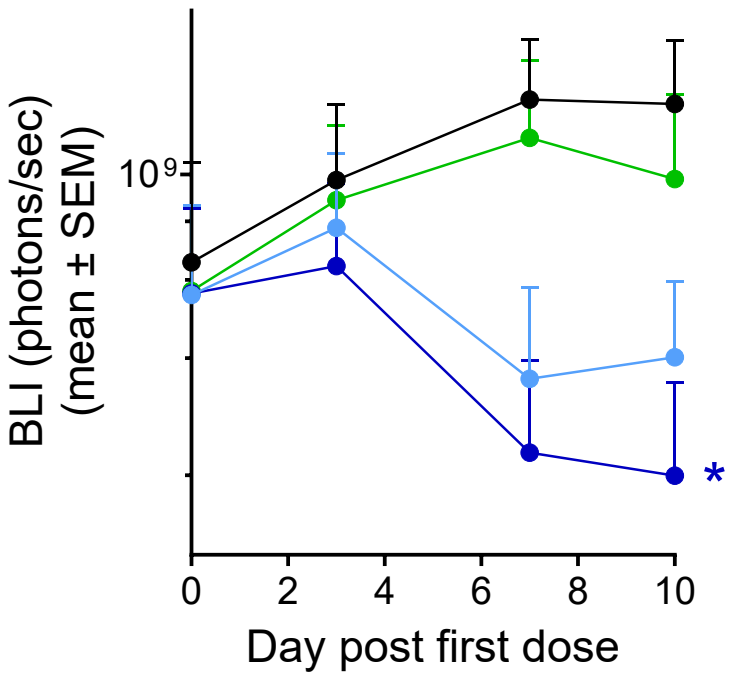
Class 1 V600E A375-luciferase-tagged intracranial mouse CDX model, efficacy arm, QDx28
One-way ANOVA with Dunnett's multiple comparisons test at day 28

PD arm, QDx4

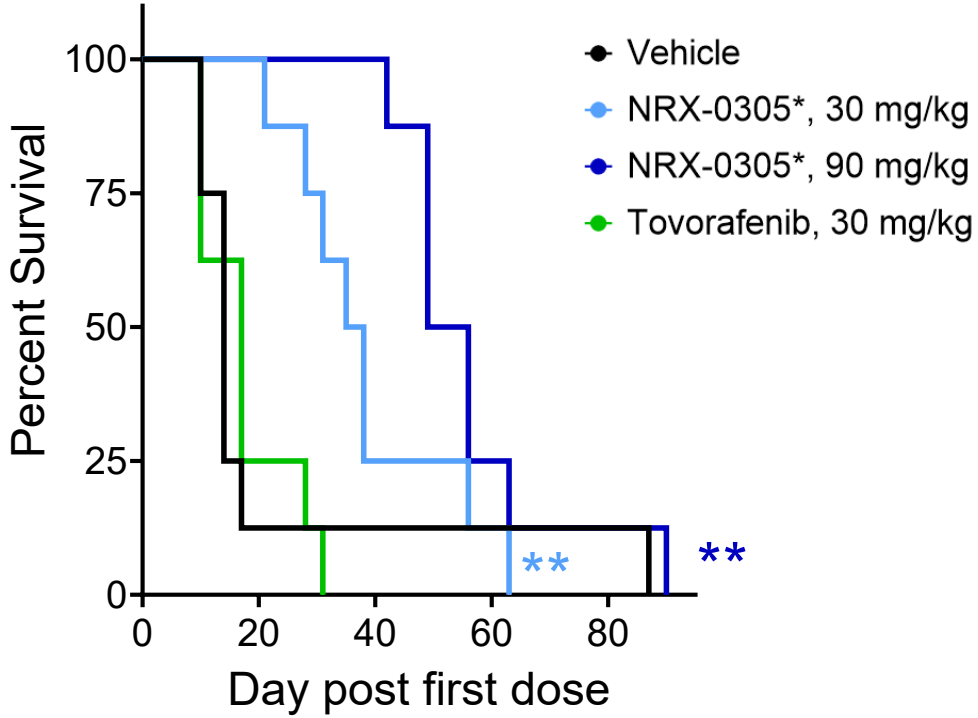
NRX-0305 is Efficacious in Class 1 Intracranial Glioma

NRX-0305 in (V600E) Intracranial CDX Model

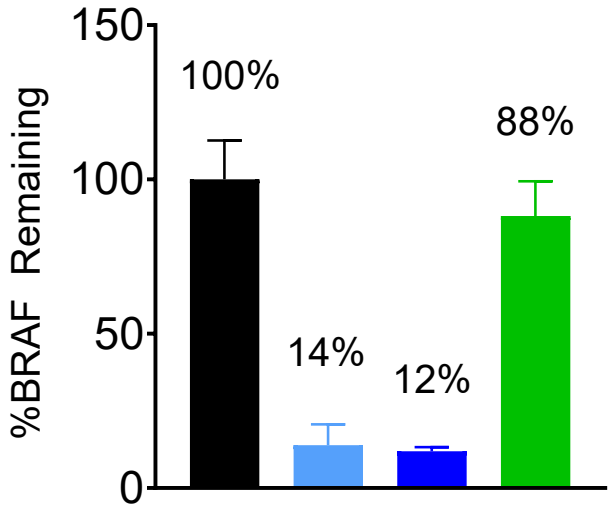
Efficacy



Survival



V600E Degradation

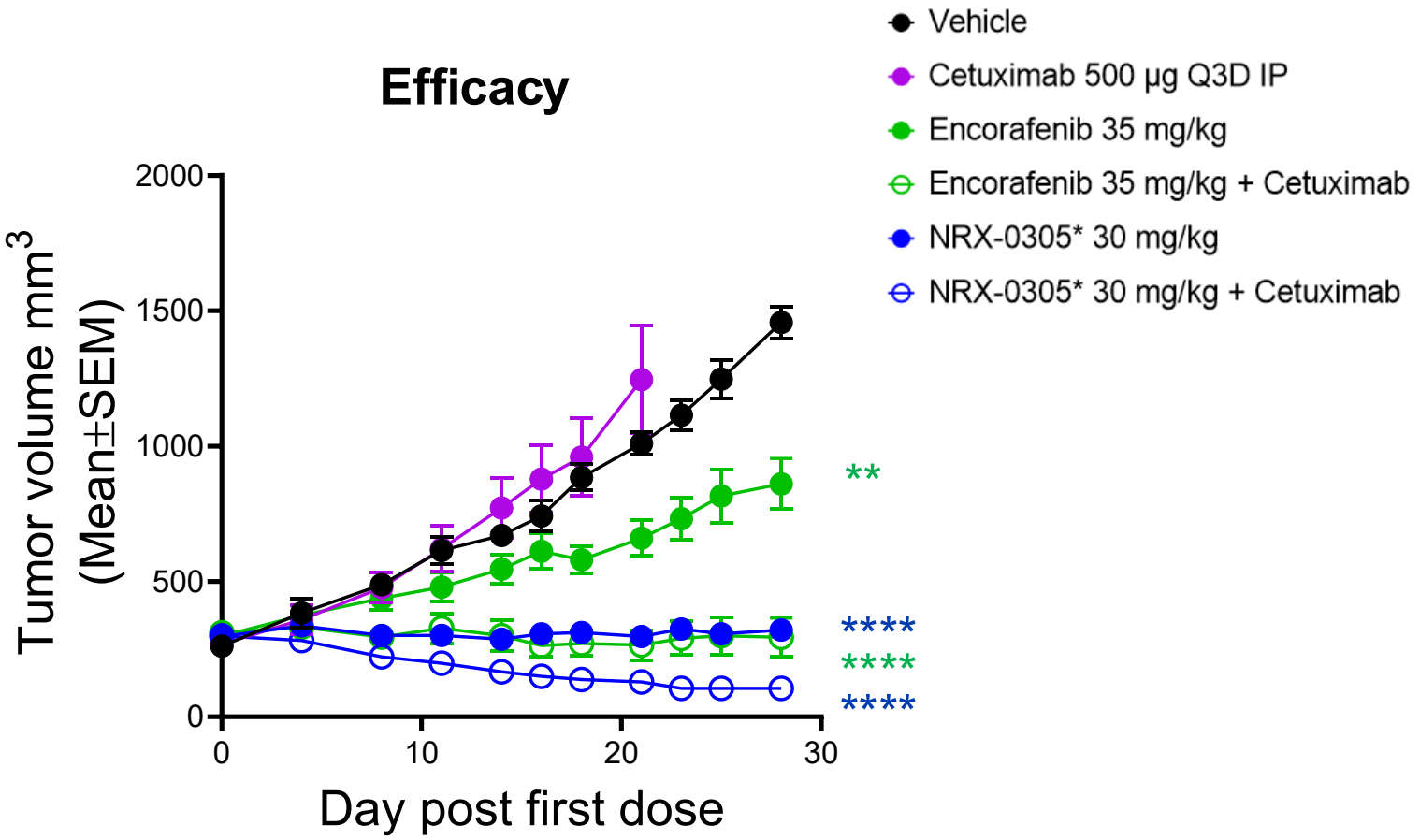


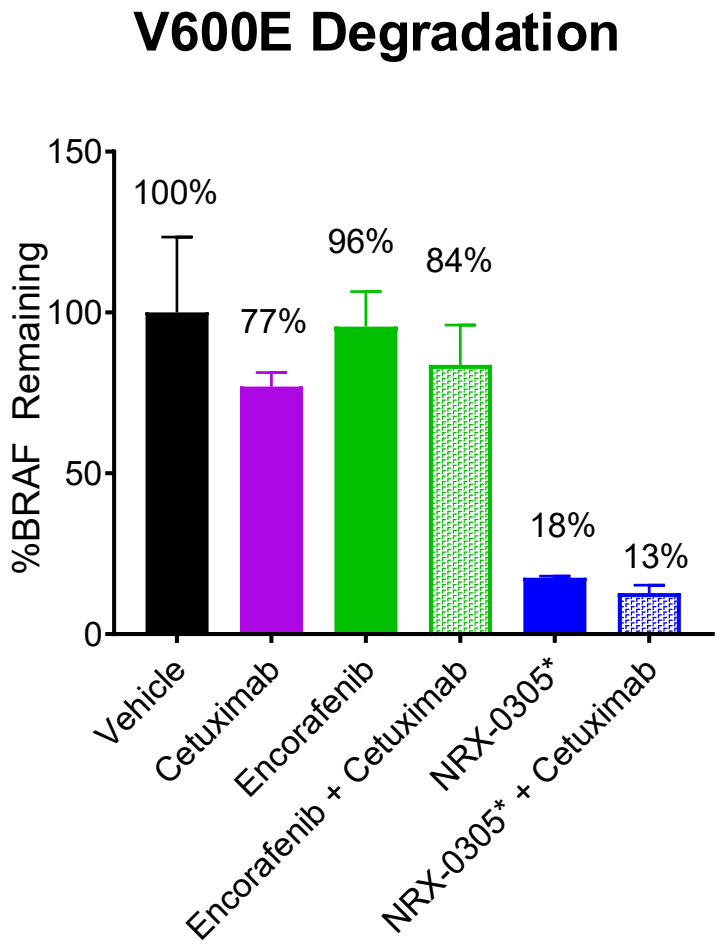
*Class 1 V600E AM38-luciferase-tagged intracranial mouse CDX model, efficacy arm, QDx10, *, NRX-0305 Eutomer*
Efficacy: One-way ANOVA with Dunnett's multiple comparisons test on day 10
Survival: Grehan-Breslow-Wilcoxon test

PD arm, QDx3

NRX-0305 is Efficacious in Class 1 CRC Alone and in Combination with Cetuximab

NRX-0305 in (V600E) Subcutaneous CDX Model





*Class 1 V600E HT-29 sub-cutaneous flank mouse CDX model, efficacy arm, QDx28. *, NRX-0305 Eutomer*
Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test

PD arm, QDx3

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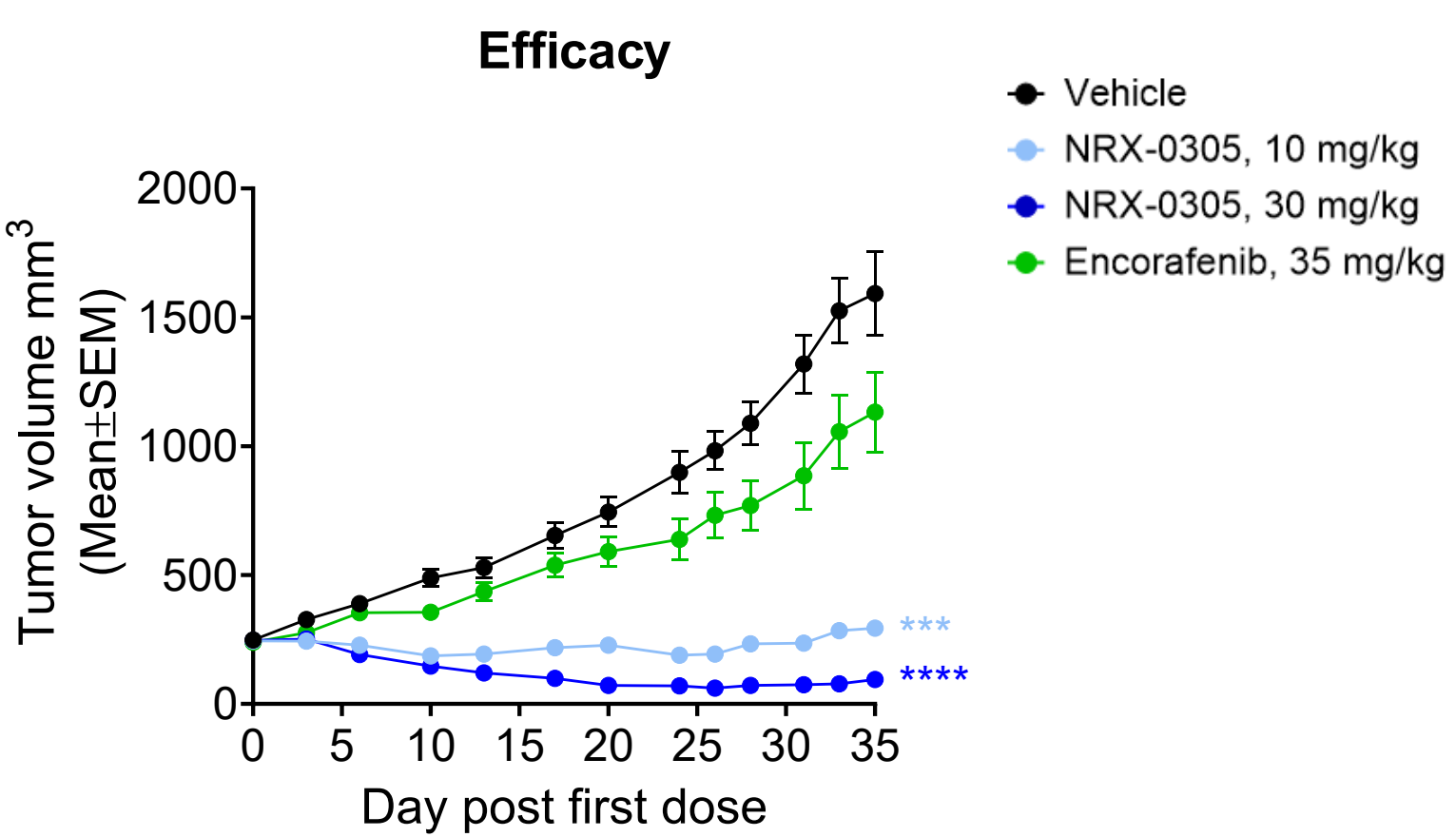
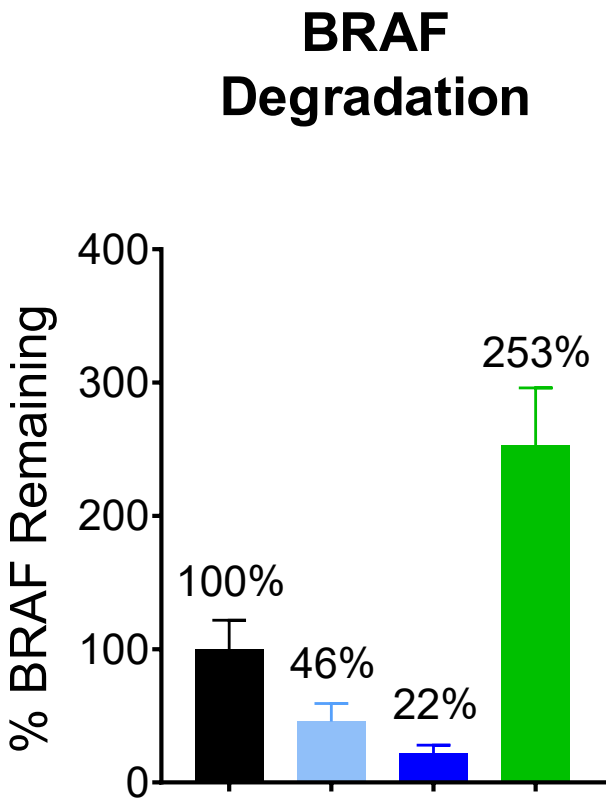
NRX-0305 is Efficacious in Class 2 Melanoma

NRX-0305 in (K601E) Subcutaneous CDX Model





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

PD arm, QDx6

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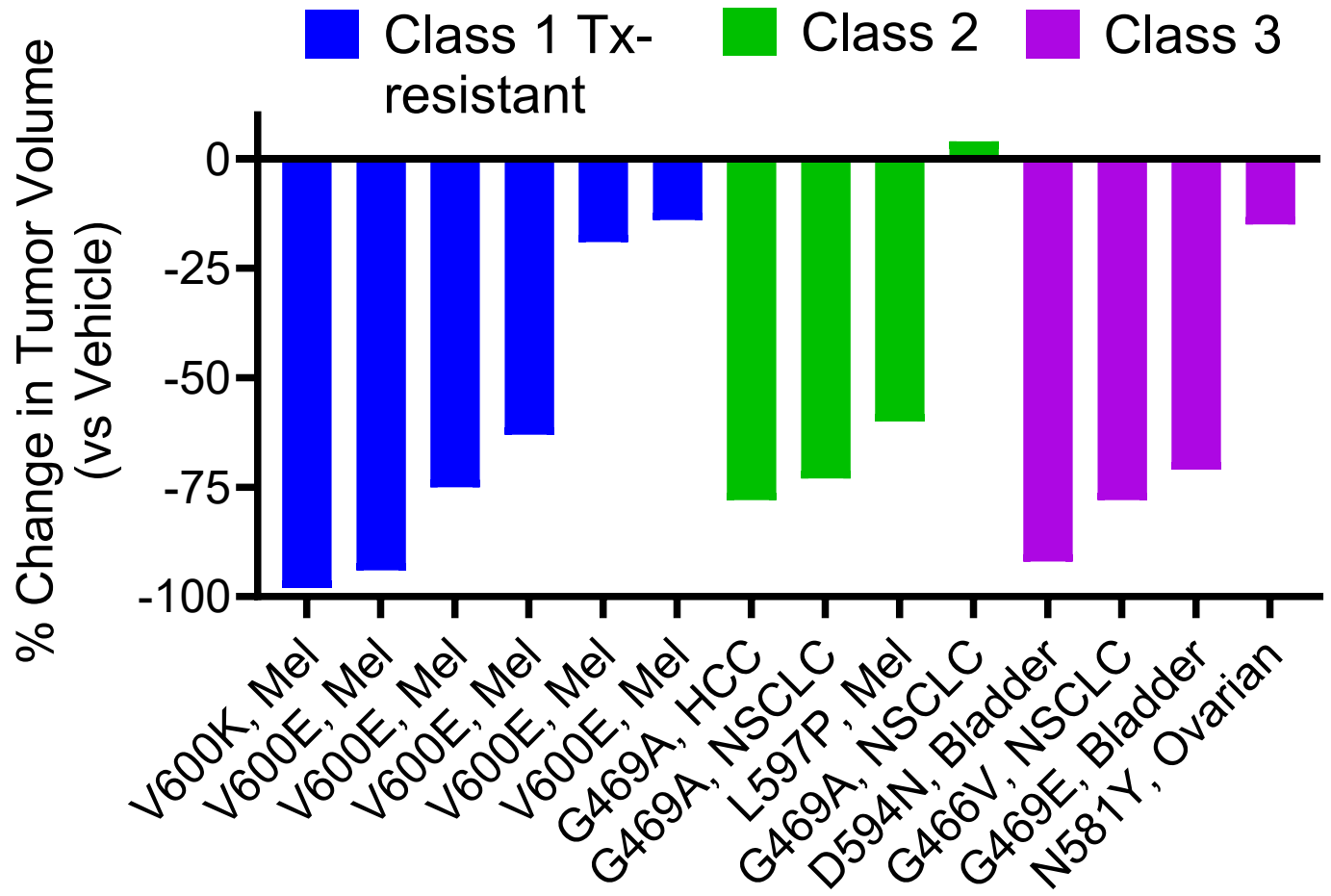
NRX-0305 Inhibits Tumor Growth in Numerous Class 1 Treatment-Resistant and Class 2/3 PDX Models

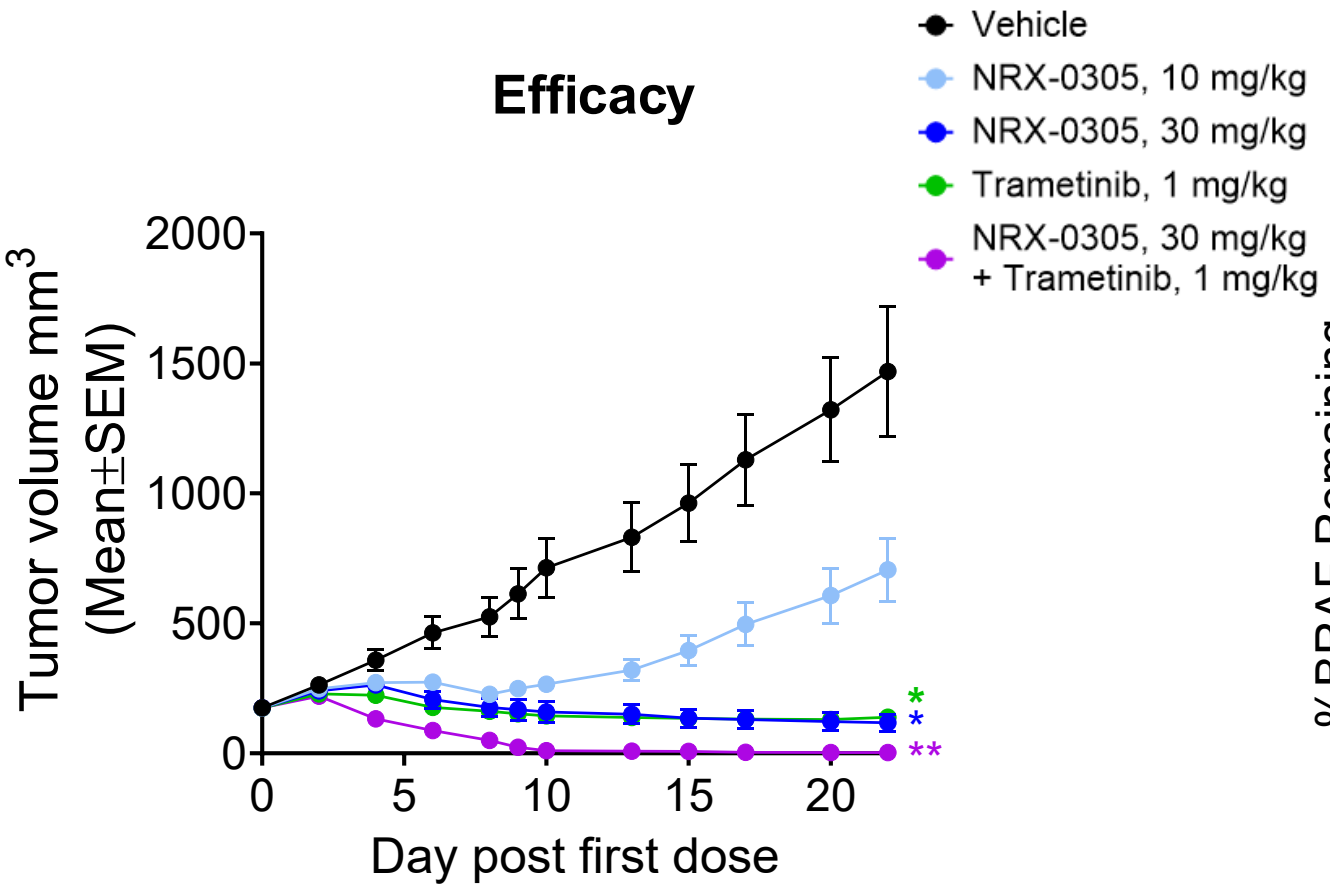


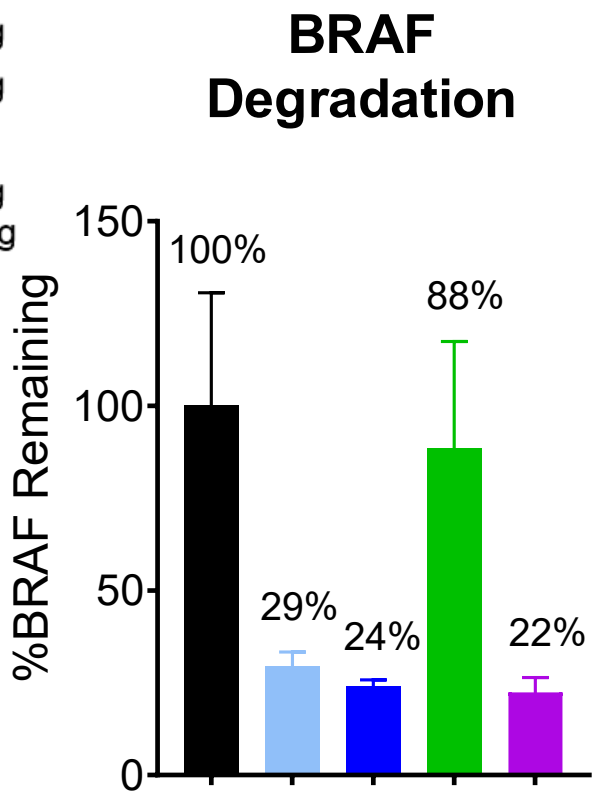
- NRX-0305 demonstrates anti-tumor activity in multiple PDX models in a 14-day exploratory screen

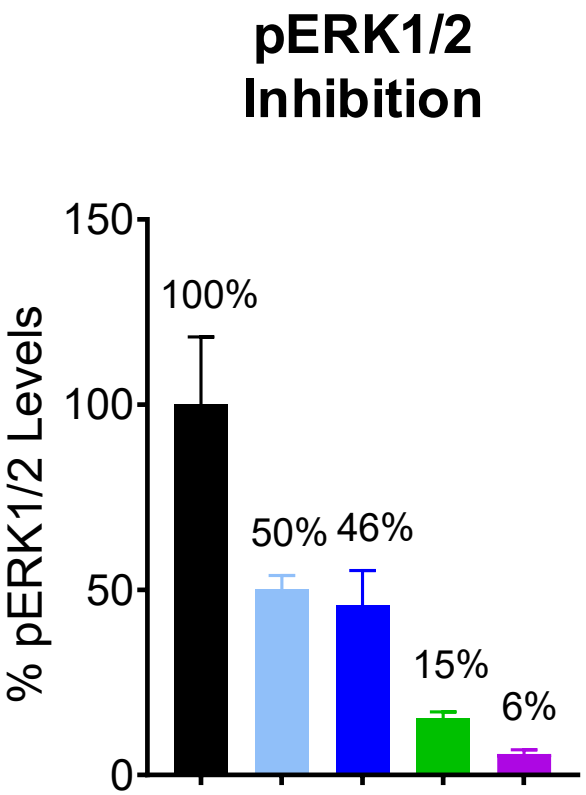
PDX model screening, QDx14 or QDx7 (D594N, Bladder) at 90 mg/kg
Mel, melanoma; HCC, hepatocarcinoma cancer; NSCLC, non-small cell lung cancer

Single Agent Efficacy and MEKi Synergy in Class 3 Bladder Cancer

NRX-0305 and Trametinib in (D594N) Bladder PDX Model







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

PD arm, QDx3

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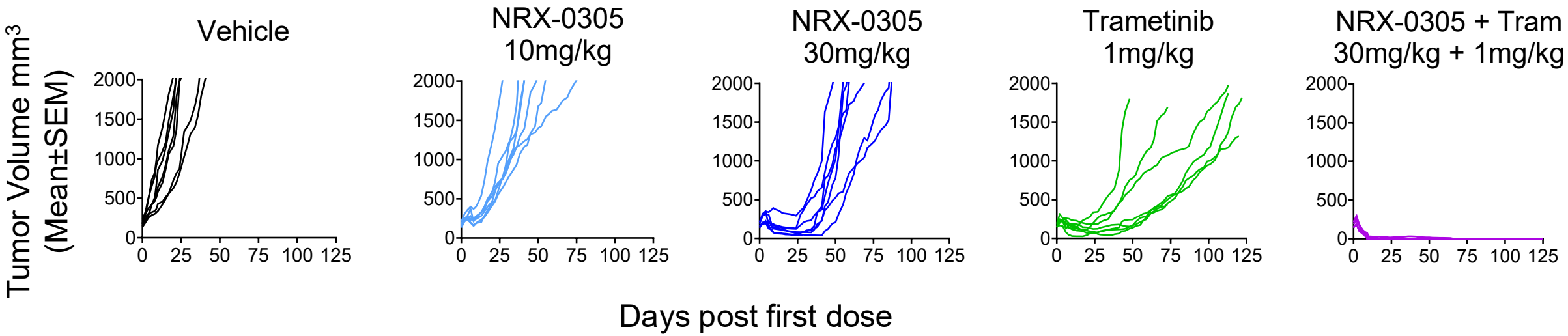
Single Agent Efficacy and MEKi Synergy in Class 3 Bladder Cancer

NRX-0305 and Trametinib in (D594N) Bladder PDX Model

Individual Tumor Volumes

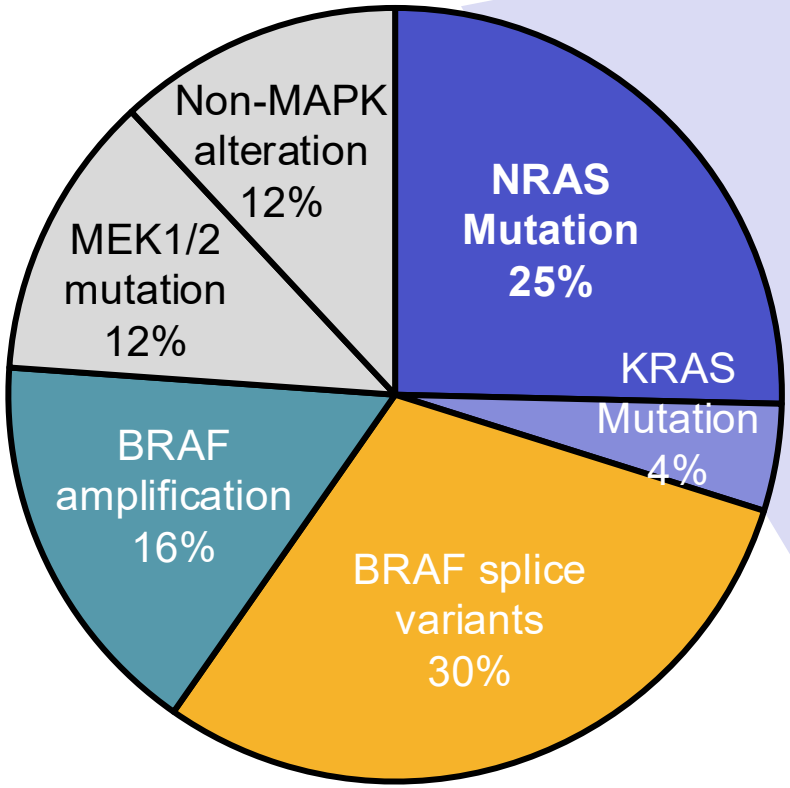


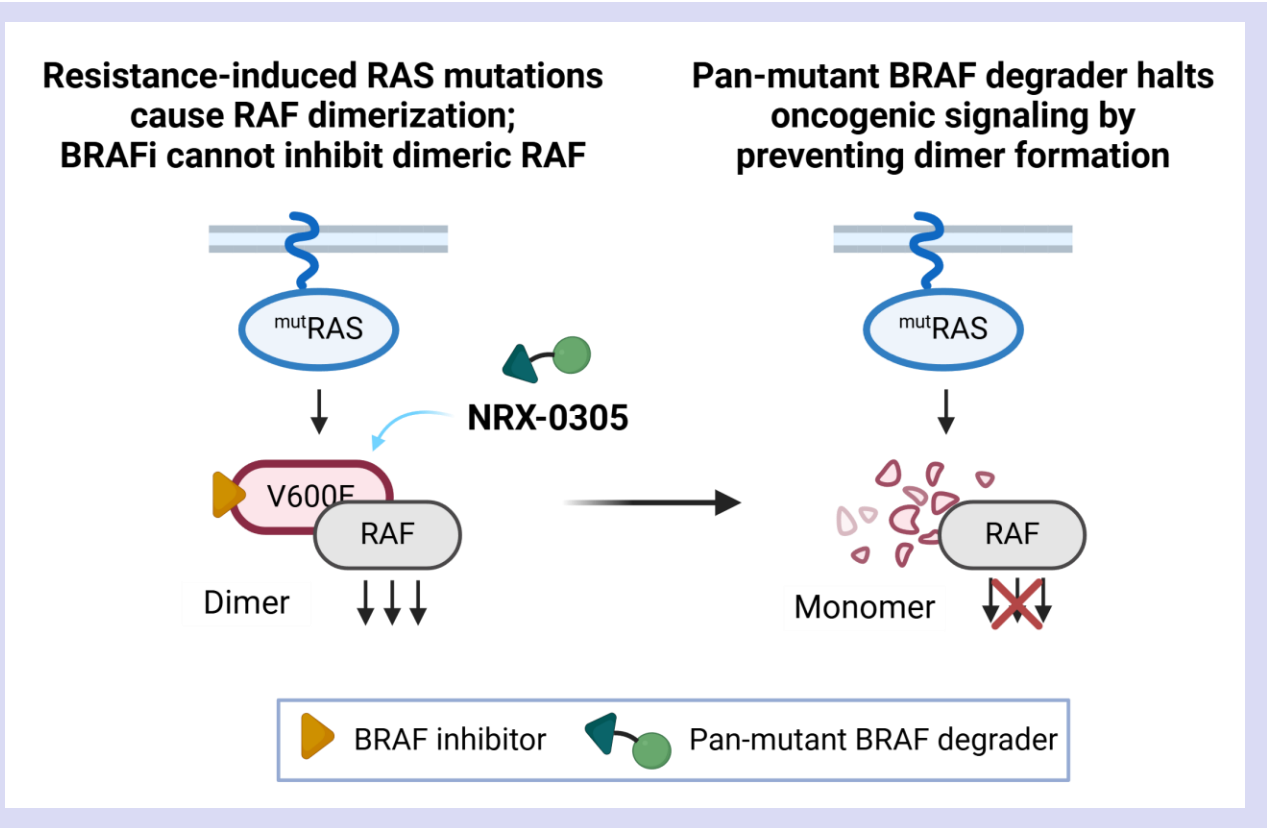
- NRX-0305 in combination with MEK inhibitor, Trametinib, results in complete tumor regressions

Class 3 D594N subcutaneous flank mouse PDX, efficacy arm

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

Mechanisms of B-Raf (V600E) Inhibitor Resistance





- 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.

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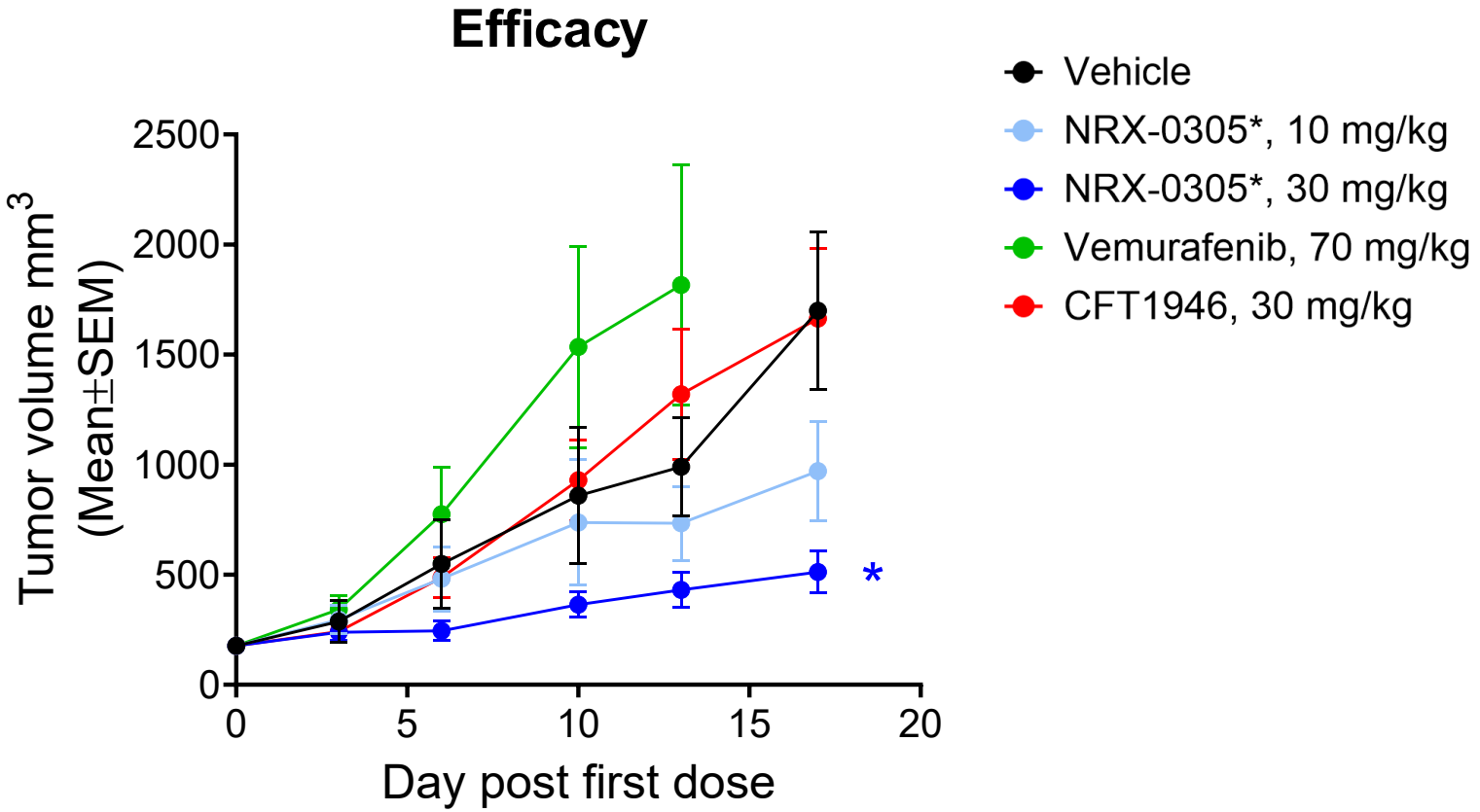
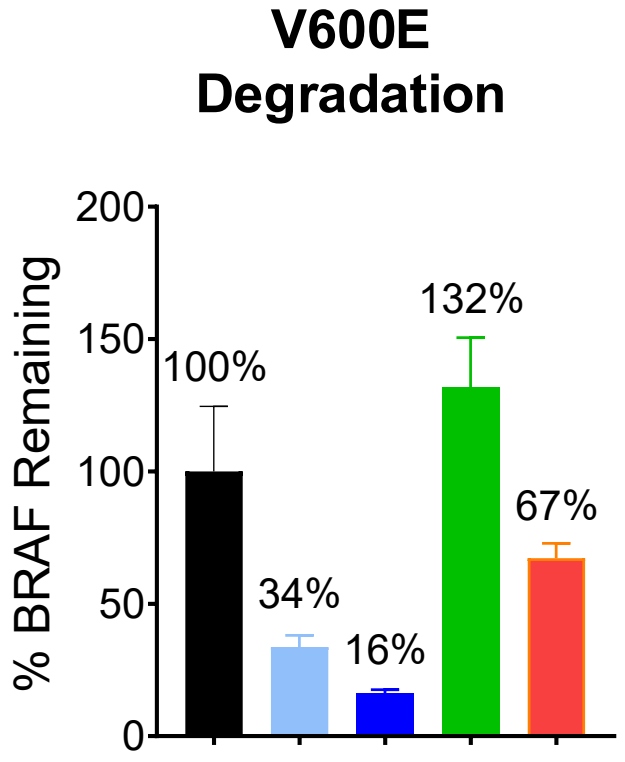
Single Agent Efficacy in Class 1 BRAFi-Resistant Melanoma

NRX-0305 in (V600E, NRAS Q61R) Pembrolizumab+BRAFi resistant PDX Model





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

PD arm, QDx3

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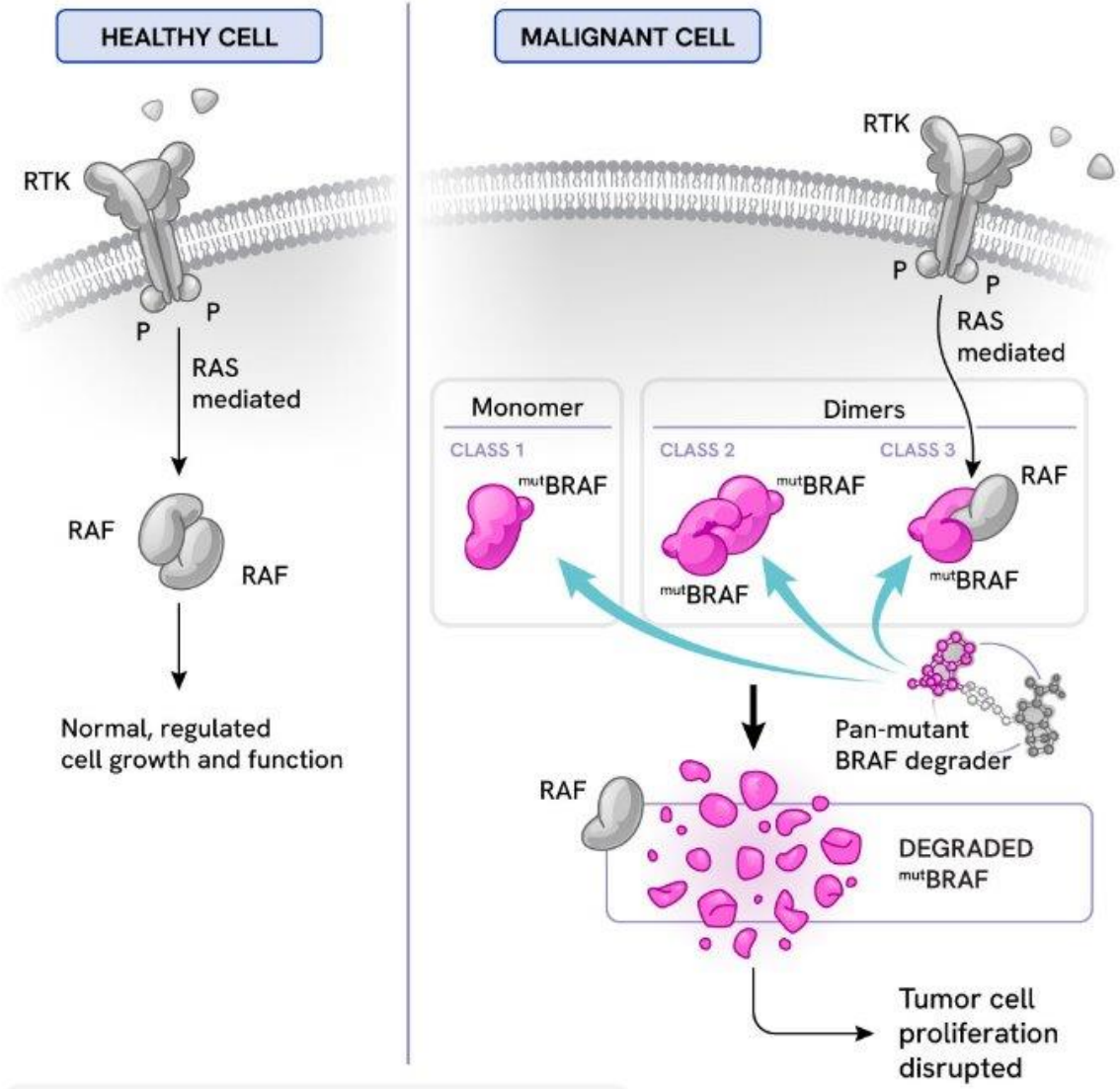
Summary



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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