NRX-0305 is an Orally Bioavailable, Pan-Mutant BRAF Degrader that Exhibits Single Agent and Combination Efficacy with MEKi or anti-EGFR Across Class 1/2/3 BRAF Mutant Cancers

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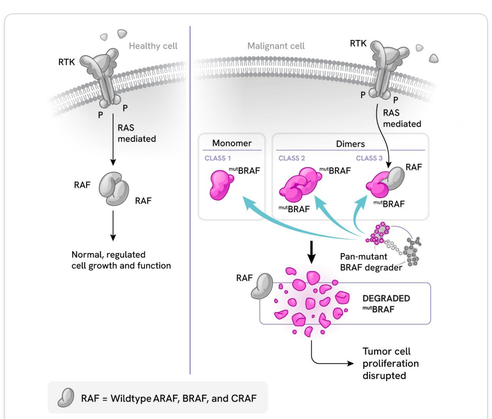
Abstract

Activating mutations in BRAF, a central kinase within the MAPK pathway, promote sustained pathway signaling and drive oncogenic transformation across multiple tumor types including melanoma, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC). BRAF mutations are categorized into three functional classes: Class 1 (e.g., V600X), which are RAS-independent and targetable with approved BRAF inhibitors; Class 2, which signal as constitutive dimers; and Class 3, which are kinase-impaired and depend on upstream RAS activation. While approved BRAF inhibitors provide significant survival benefit to patients with Class 1 mutations, they are ineffective against tumors harboring Class 2 or 3 mutations, which remain refractory to current BRAF-targeted therapies.

Motivated by the lack of therapeutic options for patients with Class 2 and 3 BRAF mutations, we developed NRX-0305, a potent and orally bioavailable pan-mutant BRAF degrader that selectively eliminates mutant BRAF while sparing the wild-type (WT) protein. *In vitro*, NRX-0305 potently degraded Class 1/2/3 mutant BRAF and suppressed downstream pERK1/2 signaling, resulting in strong antiproliferative effects across a diverse panel of Class 1/2/3 BRAF-mutant cell lines, including those expressing BRAF fusion proteins. *In vivo*, daily oral administration of NRX-0305 induced robust, dose-dependent BRAF degradation and pathway inhibition, producing marked single-agent efficacy in multiple Class 1/2/3 cell lines-derived xenograft and patient-derived xenograft models. Furthermore, combination studies of NRX-0305 with MEK inhibitor or anti-EGFR demonstrated enhanced antitumor activity, supporting its potential use in clinically relevant combination regimens.

Collectively, these studies demonstrate NRX-0305 is a potent, mutant-selective BRAF degrader that can overcome the limitations of approved BRAF inhibitors, offering broad therapeutic potential both as a single agent and in combination with MEKi or anti-EGFR antibodies across Class 1/2/3 BRAF-mutant cancers.

Rationale



Results

Figure 1: NRX-0305 is a potent and selective pan-mutant BRAF degrader with broad coverage of clinically relevant BRAF mutations

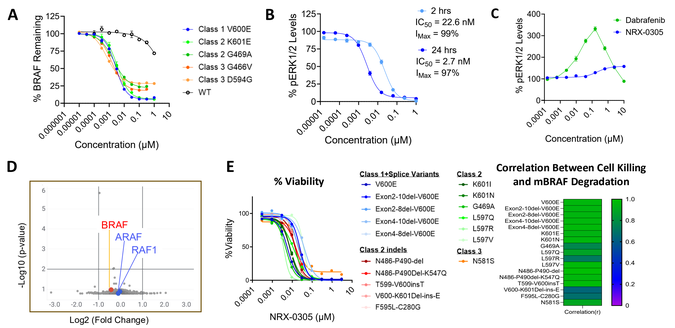


Figure 1. **(A)** Degradation of Class 1/2/3 mutants and WT BRAF after 24 hours of treatment with NRX-0305. Class 1 V600E A375 and Class 2 K601E WM3130 cell lines contain HiBiT knock-in at the endogenous locus. Class 2/3 G469A, G466V, and D594G are engineered HiBiT overexpression systems in HCT116 *BRAF*$^{-/-}$ cell lines. WT BRAF degradation was assessed in human peripheral mononuclear cells (PBMC). **(B)** pERK levels were measured in Class 1 V600E A375 cells following treatment with NRX-0305 for 2 or 24 hours. **(C)** Paradoxical activation was assessed in HCT116 (WT BRAF with KRAS G13D) after 24 hours drug treatment **(D)** Global proteomics in human IMR-90 (BRAF^{WT} lung fibroblast cells) after 24 hours treatment with NRX-0305 at 50x DC_{50} (potency in A375), 50% change, 1% FDR. **(E)** Ba/F3 cells with the indicated mutations were treated with NRX-0305 for 5 days. Cell viability was measured by Cell-Titer Glo and BRAF degradation was evaluated with Western blot. Pearson r values were calculated by correlating NRX-0305 concentrations of viability and mutant (m)BRAF degradation. Heatmap color reflects correlation strength (scale bar, right).

Figure 2: NRX-0305 exhibits dose-proportional pharmacokinetics and pharmacodynamics following a single oral dose *in vivo*

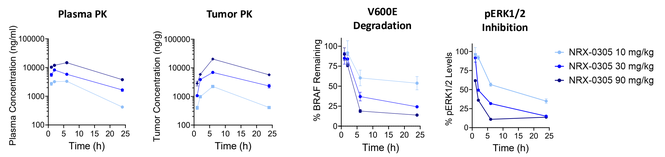


Figure 2. Mice bearing subcutaneous Class 1 V600E A375 xenografts were dosed once with NRX-0305 (PO, QDx1) at the indicated dose levels. Plasma and tumor PK were assessed at indicated timepoints. **(C)** BRAF and pERK levels in the implanted tumor were assessed by Simple Western (Jess) 24 hours after dosing.

Figure 3: NRX-0305 induces stronger anti-tumor effects as a single agent or in combination with MEK inhibition versus Encorafenib in Class 1 (V600E) subcutaneous melanoma CDX model

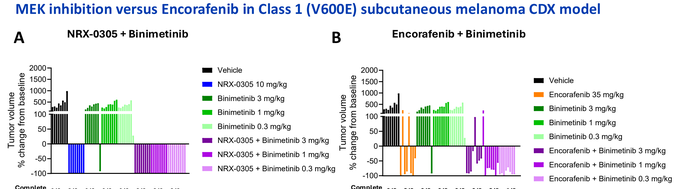


Figure 3. **(A)** Mice bearing subcutaneous Class 1 V600E A375 xenografts were dosed daily with NRX-0305^ (PO, QD) or Binimetinib (PO, BID) as single agents or in combination at the indicated doses (QDx100). **(B)** Mice bearing Class 1 V600E A375 xenografts were dosed daily with Encorafenib (PO, QD) or Binimetinib (PO, BID) as single agents or in combination at the indicated doses. Note that **(A)** and **(B)** are from the same study with a shared vehicle group and tumor volume changes on day 50 or last measured timepoint.

Figure 4: NRX-0305 is efficacious in Class 1 (V600E) CRC subcutaneous xenograft model as a single agent and demonstrates enhanced anti-tumor activity in combination with anti-EGFR, Cetuximab

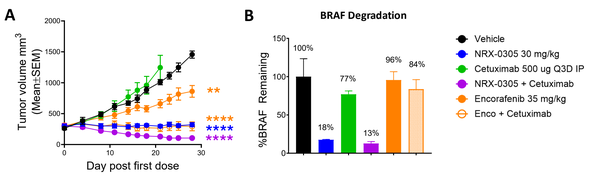


Figure 4. (A) Mice bearing subcutaneous Class 1 V600E HT-29 xenograft tumors were dosed daily with NRX-0305^, Cetuximab, Encorafenib as single agents or in combination at the indicate doses (PO, QDx28 or IP, Q3D). Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test vs vehicle. p value: ** ≤ 0.01, *** ≤ 0.001, **** ≤ 0.0001. **(B)** BRAF levels were assessed in tumors collected 4 hours after the third dose by Simple Western (Jess).

Figure 5: NRX-0305 demonstrates anti-tumor activities across a wide range of Class 1 BRAF inhibitor-resistant and Class 2/3 mutant PDX models

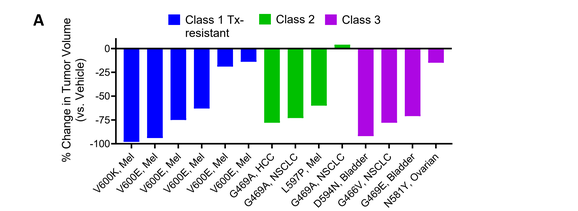
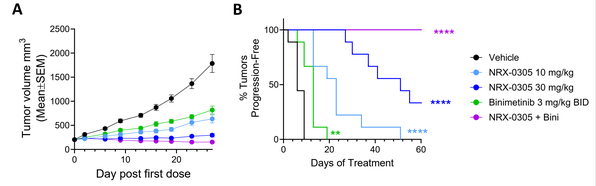


Figure 5. (A) NRX-0305 was dosed in 14 different PDX models spanning Class 1 treatment-resistant, Class 2 and Class 3 BRAF mutations. Percent change in tumor volume versus vehicle was determined following 14 or 7 (D594N Bladder model only) consecutive days of dosing at 90 mg/kg. Mel, melanoma; HCC, hepatocarcinoma cancer; NSCLC, non-small cell lung cancer

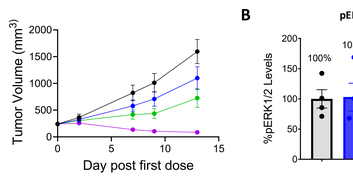
Figure 6: NRX-0305 exhibits anti-tumor efficacy as a single agent and in combination with MEK inhibition in a Class 2 (G469A) KRAS (Q61H) HCC subcutaneous PDX model



Comparison	NRX-0305 (10 mg/kg)	NRX-0305 (30 mg/kg)	NRX-0305 + Bini (10 mg/kg + 3 mg/kg BID)	Binimetinib (3 mg/kg BID)
TGI	64%	83%	91%	54%
vs Vehicle	***	***	***	**
vs Bini (3 mg/kg BID)	NS	***	***	-

Figure 6. (A) Mice bearing subcutaneous Class 2 G469A patient-derived xenografts were dosed daily with NRX-0305^ or binimetinib as single agents or in combination at the indicated doses (PO, up to QDx27). Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test vs vehicle or binimetinib. **(B)** Progression free survival was calculated and significance calculated by Log-Rank (Mantel-Cox) test vs vehicle up to day 83.

Figure 7: NRX-0305 is efficacious in a Class 3 (G466V) NRAS (Q61R) NSCLC subcutaneous PDX model as a single agent and in combination with MEKi, Trametinib



Comparison	NRX-0305 (10 mg/kg)	NRX-0305 + Tram (10 mg/kg + 0.3 mg/kg)	Trametinib (0.3 mg/kg)
TGI	31%	95%	55%
vs Vehicle	NS	**	*
vs Tram (0.3 mg/kg)	NS	*	-

Figure 7. (A) Mice bearing subcutaneous Class 3 G466V NSCLC PDX tumors were dosed daily with NRX-0305^, trametinib or a combination at the indicated doses (PO, QDx13). Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test, days 0-13. **(B)** pERK levels were assessed in tumors collected 4 hours after the third dose by Simple Western (Jess).

Figure 8: NRX-0305 synergy with MEK inhibition is maintained at lower Trametinib dose levels in Class 3 (D594N) subcutaneous bladder cancer PDX model

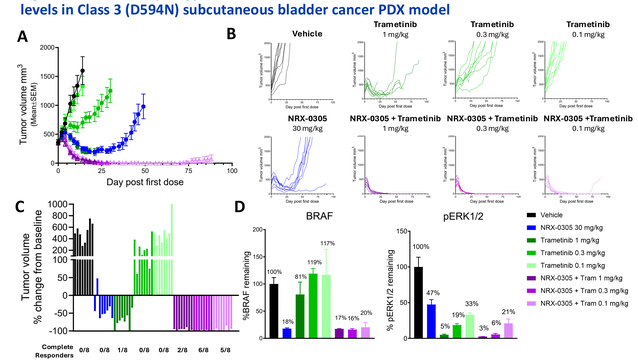


Figure 8. (A) Mice bearing subcutaneous Class 3 (BRAF D594N) bladder PDX tumors were dosed daily with NRX-0305^, trametinib or a combination at the indicated doses (PO, up to QDx89). Grey shading indicates dosing interval. **(B)** Spider plots associated with each of the dosing groups. **(C)** Mean tumor volume percent change from baseline for each dosing group at day 28 of the study or the last measured timepoint (for animals that came down before day 28). **(D)** BRAF and pERK levels were assessed in tumors collected 4 hours after the third dose by Simple Western (Jess).

Conclusion

- NRX-0305 is an orally bioavailable and CNS-penetrant Class 1/2/3 pan-mutant BRAF degrader sparing wildtype BRAF
- Potent BRAF degradation by NRX-0305 prevents dimer formation and avoids BRAFi/RAFi-induced paradoxical activation of dimers
- NRX-0305 demonstrates broad anti-tumor efficacy in BRAF Class 1/2/3 and Class 1-treatment resistant CDX and PDX models as a single agent
- NRX-0305 demonstrates potent combination activity with MEKi and anti-EGFR to drive tumor regressions in Class 1/2/3 BRAF mutant cancers

^ denotes data from NRX-0305 eutomer; NRX-0305 and associated eutomer are non-optimized leads, optimized lead data confidential

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