NRX-0305: A Pan-Mutant BRAF Degrader with Broad Preclinical Efficacy, Brain Penetrance, and Synergistic Potential with MEK Inhibition Across Class 1/2/3 BRAF-Mutant Cancers

1651

Alexandra Borodovsky*, Ya-Wen Lu*, Ge Peng*, Karthik Arumugam, Paul Auger, Robert Cass, Stefan Gajewski, Scott Kimura, Daniel Medina-Cleghorn, Mariah Mesner, Davorka Messmer, Madeleine Nemchek, Prabu Raman, Ryan Rountree, Rusha Sardhara, Sangita Sridharan, Jennifer Stokes, Leslie Tong, Jennifer Tung, Ge Wei, Jeffrey Wu, Jordan Ye, Gwenn M. Hansen
*Co-first authors; Nurix Therapeutics, San Francisco, CA, United States

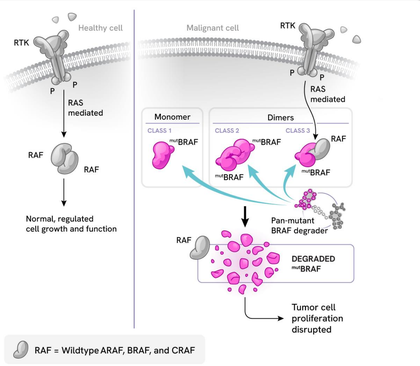
Abstract

Mutations in *BRAF*, a key component of the mitogen-activated protein kinase (MAPK) pathway, drive constitutive pathway activation and oncogenic transformation and are commonly found in a variety of cancers including melanoma, NSCLC and CRC. *BRAF* mutations are categorized into three classes: Class 1 (e.g., V600X), which are RAS-independent and targetable with currently approved BRAF inhibitors (BRAFi); Class 2, which require dimerization; and Class 3, which are kinase-impaired and rely on upstream RAS activation. While approved BRAFi provide significant survival benefit to Class 1 patients, drug durability and efficacy are limited by the emergence of primary and acquired resistance that often involves RAF dimerization and BRAF amplification. Furthermore, patients who have progressed on BRAFi, especially in melanoma, often develop brain metastases, which present limited treatment options due to poor central nervous system (CNS) penetrance of available drugs.

To address this, we developed NRX-0305, a pan-mutant BRAF degrader that selectively degrades mutant BRAF across all classes while sparing wildtype (WT) BRAF. *In vitro*, NRX-0305 potently degrades mutant BRAF protein and suppresses downstream pERK1/2 signaling. NRX-0305 exhibits strong anti-proliferative effects across a panel of Class 1/2/3 BRAF-mutant cell lines including those expressing BRAF splice variants and rare insertion-deletion mutants.

In vivo, daily oral dosing with NRX-0305 induces robust BRAF degradation and exhibits single agent efficacy in several cell line and patient-derived xenograft (PDX) models of Class 1/2/3 BRAF mutant cancers. Notably, NRX-0305 demonstrates robust single agent activity in a BRAFi-resistant Class 1 patient-derived xenograft model and a melanoma brain metastasis cell-derived xenograft (CDX) model, highlighting its brain-penetrant properties. Furthermore, NRX-0305 in combination with MEK inhibition achieves tumor regressions in two Class 3 mouse xenograft models, demonstrating its synergistic potential. These findings establish mutant-specific BRAF degradation as a promising therapeutic strategy, displaying activity across a broad range of mutations and overcoming the limitations of BRAF inhibition in 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

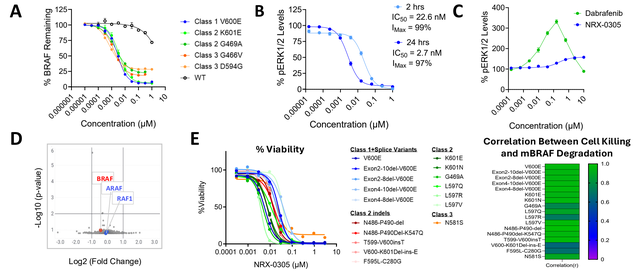


Figure 1. (A) Degradation of Class 1/2/3 mutants and WT BRAF after 24 hours of treatment with NRX-0305. Class 1 V600E A375 and Class 2 K601E WM3130 cell lines contain HiBiT knock-in at the endogenous locus. Class 2/3 G469A, G466V, and D594G are engineered HiBiT overexpression systems in HCT116 *BRAF*$^{-/-}$ 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 (WT BRAF 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 is CNS penetrant and exhibits dose-proportional pharmacokinetics and pharmacodynamics following a single oral dose *in vivo*

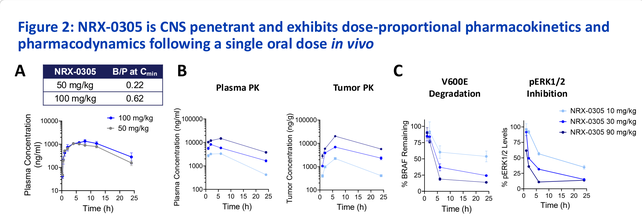


Figure 2. (A) Sprague-Dawley rats were dosed with NRX-0305 (PO, QDx1) and plasma exposures at 50 or 100 mg/kg were evaluated and brain to plasma (B/P) ratios at 24 hours were calculated. **(B)** Mice bearing subcutaneous Class 1 V600E A375 xenografts were dosed once with NRX-0305 (PO, QDx1) at the indicated 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 results in dose-dependent anti-tumor efficacy in Class 1 (V600E) subcutaneous and intracranial melanoma CDX models

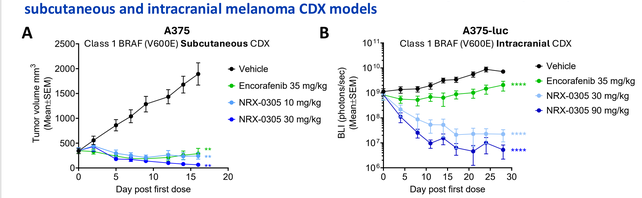


Figure 3. (A) Mice bearing subcutaneous A375 (BRAF V600E) xenografts were dosed daily with NRX-0305 or encorafenib at the indicated doses (PO, QD). Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test. **(B)** Mice bearing A375 (BRAF V600E) luciferase-tagged intracranial xenograft tumors were dosed daily with NRX-0305 (PO, QD). Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test, p value: * <= 0.05, ** <=0.01, *** <=0.001, ****<=0.0001

Figure 4: NRX-0305 exhibits dose-dependent anti-tumor efficacy and BRAF degradation in a Class 2 (K601E) melanoma CDX model

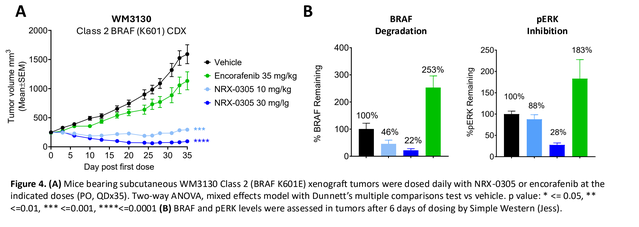


Figure 4. (A) Mice bearing subcutaneous WM3130 Class 2 (BRAF K601E) xenograft tumors were dosed daily with NRX-0305 or encorafenib at the indicated doses (PO, QDx35). Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test vs vehicle. p value: * <= 0.05, ** <=0.01, *** <=0.001, ****<=0.0001 **(B)** BRAF and pERK levels were assessed in tumors after 6 days of dosing by Simple Western (Jess).

Figure 5: NRX-0305 synergizes with MEK inhibitor *in vitro* and exhibits anti-tumor efficacy as single agent and in combination with MEK inhibition in a Class 3 (G466V) NSCLC CDX model

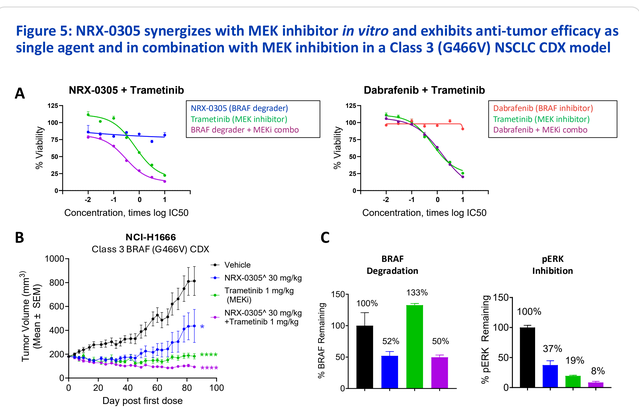


Figure 5: (A) NRX-0305 or dabrafenib was evaluated for dose- and effect-based synergy with MEK inhibitor (MEKi), trametinib, by calculating the change in log IC_{50} in 5-day cell viability assays. **(B)** Mice bearing subcutaneous H1666 Class 3 (BRAF G466V) NSLC PDX tumors were dosed daily with NRX-0305^, trametinib or a combination at the indicated doses (PO, QD). One-way ANOVA with Dunnett's multiple comparison vs vehicle on day 91. p value: * <= 0.05, ** <=0.01, *** <=0.001, ****<=0.0001 **(C)** BRAF and pERK levels were assessed in tumors after 3 days of dosing by Simple Western (Jess). ^ Denotes data from NRX-0305 eutomer.

Figure 6: NRX-0305 is active across a wide range of Class 1 BRAF inhibitor-resistant and Class 2/3 mutant PDX models

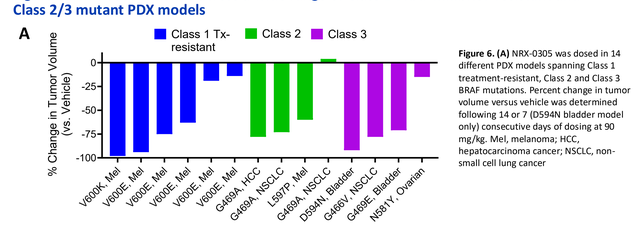


Figure 6. (A) NRX-0305 was dosed in 14 different PDX models spanning Class 1 treatment-resistant, Class 2 and Class 3 BRAF mutations. Percent change in tumor volume versus vehicle was determined following 14 or 7 (D594N bladder model only) consecutive days of dosing at 90 mg/kg. Mel, melanoma; HCC, hepatocarcinoma cancer; NSCLC, non-small cell lung cancer

Figure 7: NRX-0305 results in dose-dependent anti-tumor efficacy as single agent and in combination with MEK inhibitor in a Class 3 (D594N) bladder cancer PDX model

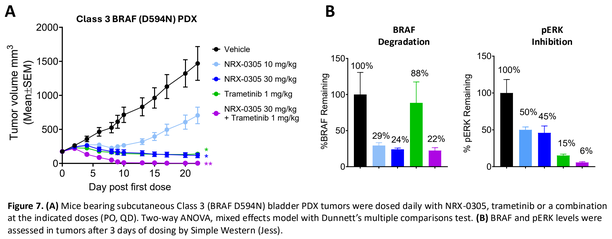


Figure 7. (A) Mice bearing subcutaneous Class 3 (BRAF D594N) bladder PDX tumors were dosed daily with NRX-0305, trametinib or a combination at the indicated doses (PO, QD). Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test. **(B)** BRAF and pERK levels were assessed in tumors after 3 days of dosing by Simple Western (Jess).

Figure 8: NRX-0305 exhibits single agent dose-dependent anti-tumor efficacy in Class 1 treatment-resistant melanoma PDX model

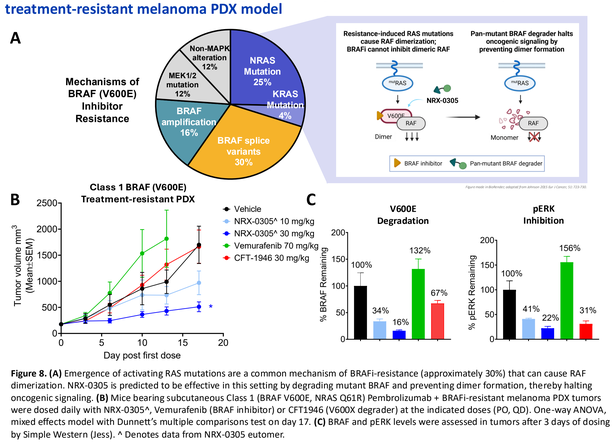


Figure 8. (A) Emergence of activating RAS mutations are a common mechanism of BRAFi-resistance (approximately 30%) that can cause RAF dimerization. NRX-0305 is predicted to be effective in this setting by degrading mutant BRAF and preventing dimer formation, thereby halting oncogenic signaling. **(B)** Mice bearing subcutaneous Class 1 (BRAF V600E, NRAS Q61R) Pembrolizumab + BRAFi-resistant melanoma PDX tumors were dosed daily with NRX-0305^, Vemurafenib (BRAF inhibitor) or CFT1946 (V600X degrader) at the indicated doses (PO, QD). One-way ANOVA, mixed effects model with Dunnett's multiple comparisons test on day 17. **(C)** BRAF and pERK levels were assessed in tumors after 3 days of dosing by Simple Western (Jess). ^ Denotes data from NRX-0305 eutomer.

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 paradoxical activation
- NRX-0305 demonstrates broad anti-tumor efficacy in BRAF Class 1/2/3 and Class 1-treatment resistant CDX and PDX models
- NRX-0305 demonstrates potent combination activity with MEKi to drive tumor regressions in Class 3 BRAF mutant cancers

^ denotes data from NRX-0305 eutomer

Presented at the American Association for Cancer Research, AACR; April 25-30, 2025