

NRX-0305: an Orally Bioavailable, CNS Penetrant, Pan-Mutant BRAF Degradер Demonstrates Robust Efficacy in Intracranial Models of Melanoma Brain Metastasis and Primary Glioma

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Abstract

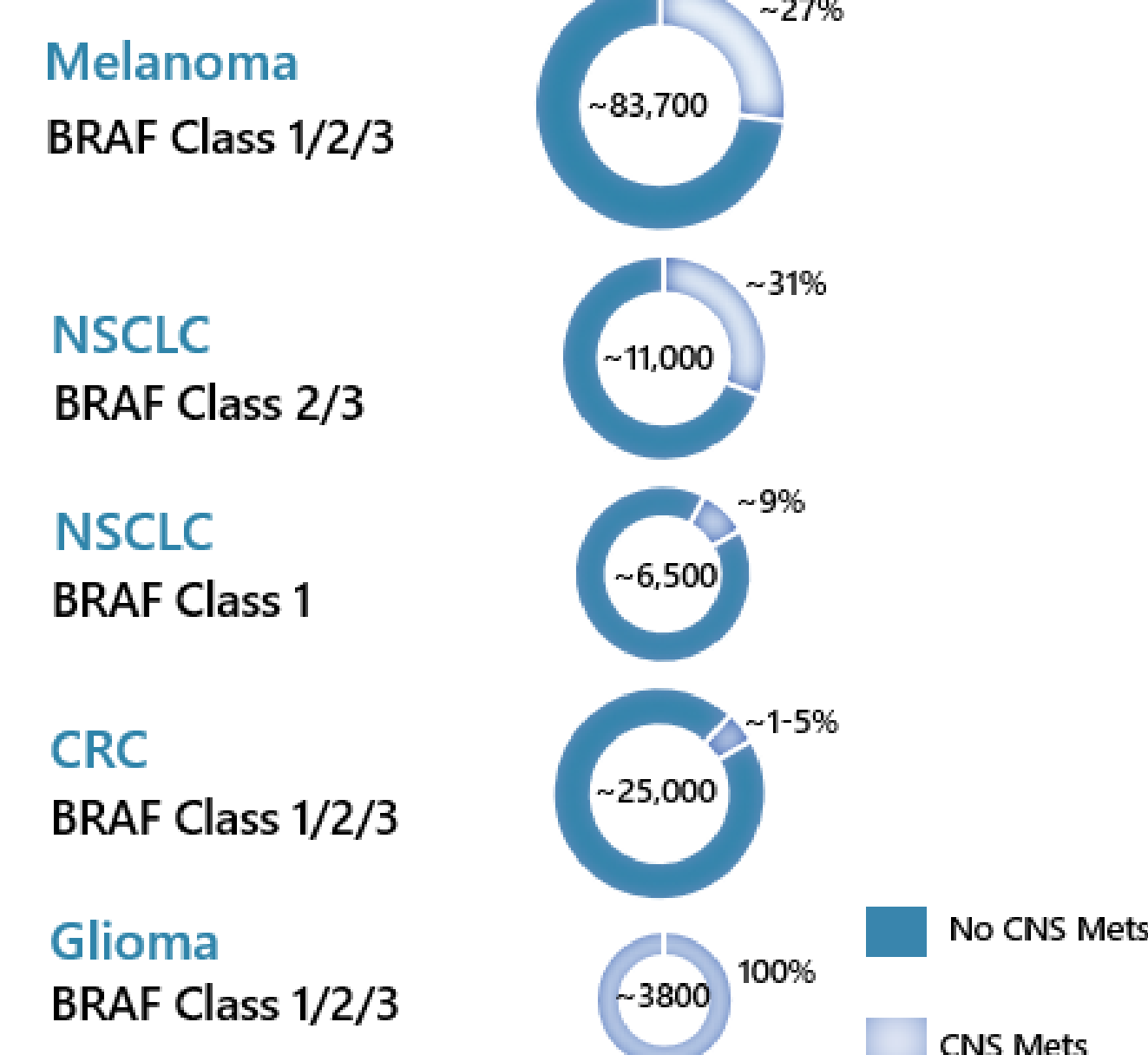
Mutations in BRAF, a key component of the MAPK pathway, drive constitutive pathway activation and oncogenic transformation across multiple tumor types. BRAF V600 mutations occur in approximately 40–50% of cutaneous melanomas, of which 30–50% develop brain metastases during disease. CNS progression is common following acquired resistance to BRAF inhibitor (BRAFi) and MEK inhibitor combination therapy, with 40–60% of patients experiencing intracranial relapse despite initial systemic response. BRAF mutations are also detected in ~5–8% of primary gliomas, predominantly in pediatric and epithelioid subtypes. Although approved BRAFi provides meaningful benefit to patients with Class 1 mutations, there is a high unmet need for patients with brain involvement due to limited CNS activity of existing therapies.

We developed NRX-0305, a CNS-penetrant, pan-mutant BRAF degrader designed to selectively degrade mutant BRAF across Class 1/2/3 mutant tumors while sparing wildtype BRAF. Pharmacokinetic and pharmacodynamic studies following oral dosing confirmed brain exposure, robust BRAF degradation, and pathway inhibition. Daily oral administration of NRX-0305 demonstrated potent single-agent efficacy in multiple intracranial models of BRAF-mutant melanoma and glioma. In a BRAFi-resistant melanoma brain metastasis PDX model, NRX-0305 achieved dose-dependent efficacy and significantly improved survival relative to vehicle and dabrafenib treatment, demonstrating superiority to clinically approved BRAF inhibitors.

These findings establish pan-mutant BRAF degradation as a promising therapeutic strategy for BRAF-mutant CNS malignancies and highlight NRX-0305's potential to overcome the limited CNS activity and treatment-emergent resistance associated with BRAF targeted therapies.

Rationale

Total Patients* across indications and respective frequency of CNS tumors/ metastases



* Total pts/year in US+EU5

Results

Figure 1. NRX-0305 demonstrates selective binding to mutant BRAF without the liabilities associated with paradoxical activation or WT MAPK pathway inhibition

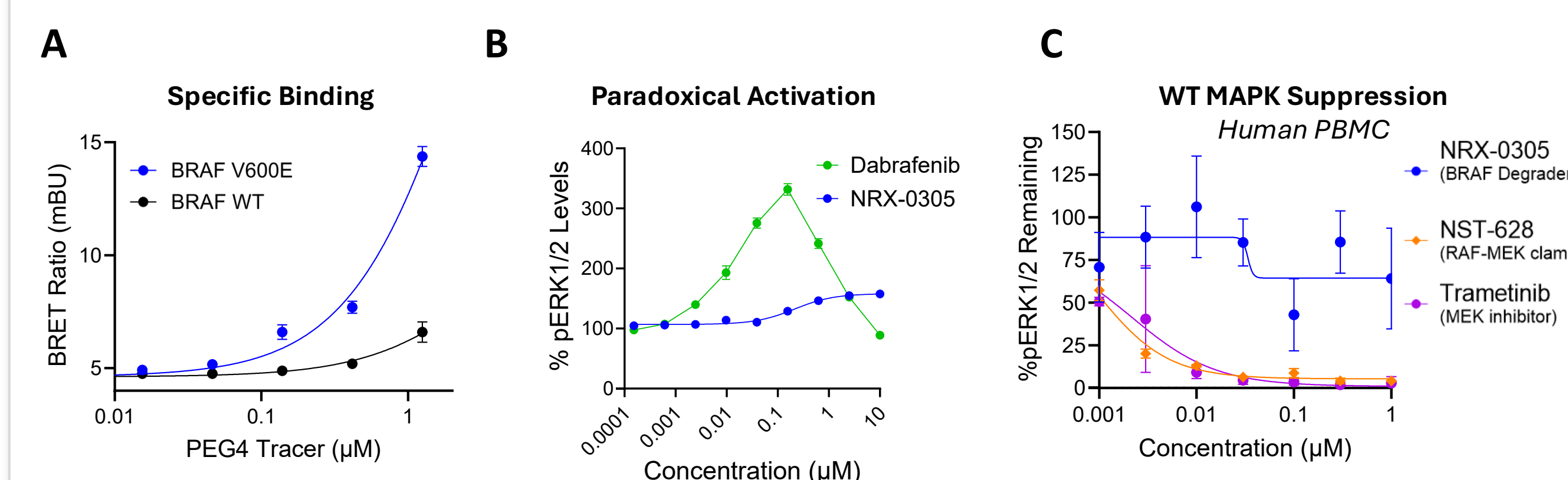


Figure 1. (A) NanoBRET target engagement specific binding assay. HEK293T cells were transiently transfected with NanoLuc-BRAF constructs. The transfected HEK293T cells were treated with a warhead-derived PEG4 fluorescent tracer for 2 h. Data are represented as BRET ratio in mBU (mean ± SD). **(B)** Paradoxical activation was assessed in HCT116 (WT BRAF with KRAS G13D) by measurement of pERK1/2 levels after 24 hours drug treatment by HTRF. **(C)** Human PBMCs (3 donors) were treated with NRX-0305, NST-628 (RAF-MEK clamp) and trametinib (MEK inhibitor) for 24h and pERK1/2 was measured in lysates by Simple Western (Jess).

Figure 2. NRX-0305 is CNS penetrant and exhibits dose-proportional pharmacokinetics and pharmacodynamics at steady state in vivo

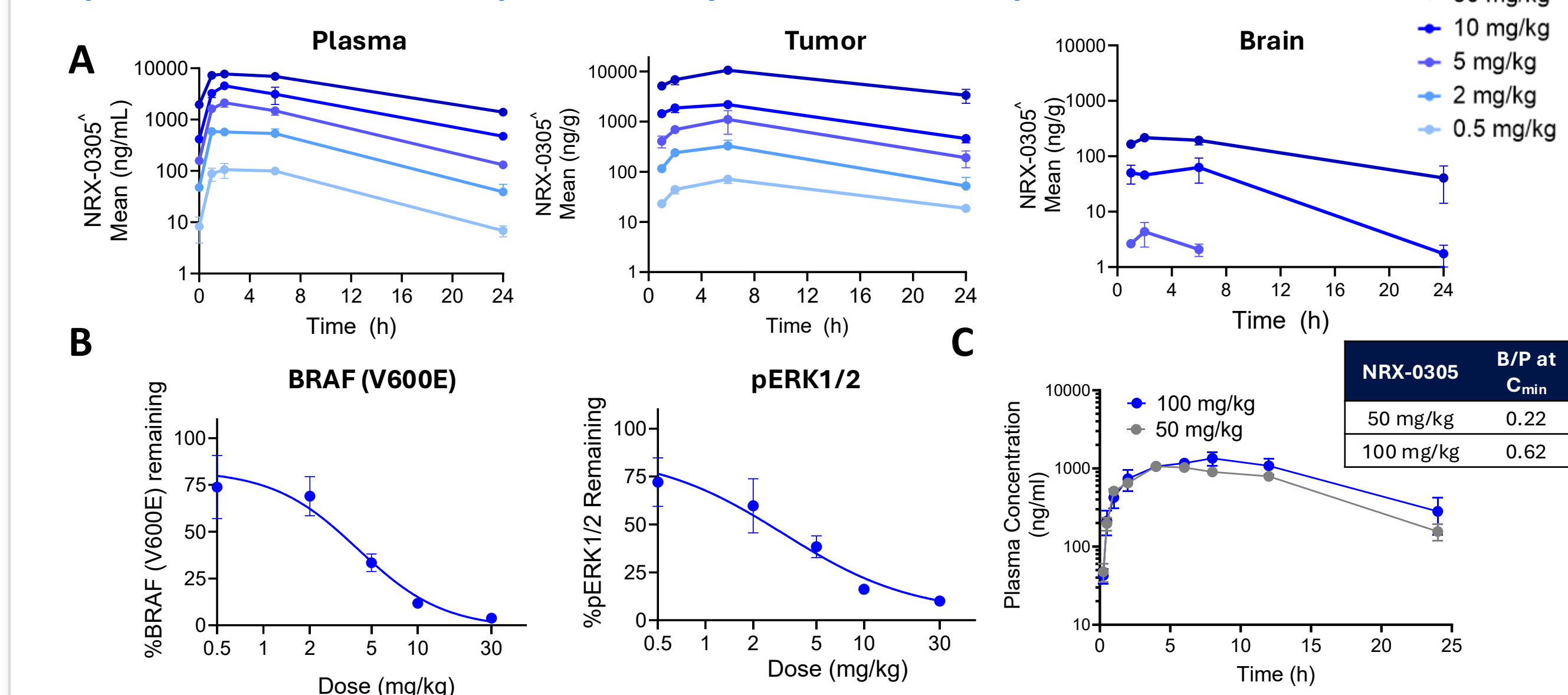


Figure 2. (A) Mice bearing subcutaneous Class 1 V600E A375 xenografts were dosed with NRX-0305* (PO, QDx4) at the indicated dose levels. Plasma, brain and tumor PK were assessed at indicated timepoints following the final dose. **(B)** BRAF (V600E) and pERK levels in the implanted tumor were assessed by Simple Western (Jess) at 6 hours following the final dose. **(C)** Sprague-Dawley rats were dosed with NRX-0305 at the indicated doses and plasma and brain exposures were calculated.

Figure 3. NRX-0305 results in dose-dependent anti-tumor efficacy in Class 1 (V600E) intracranial glioma CDX model

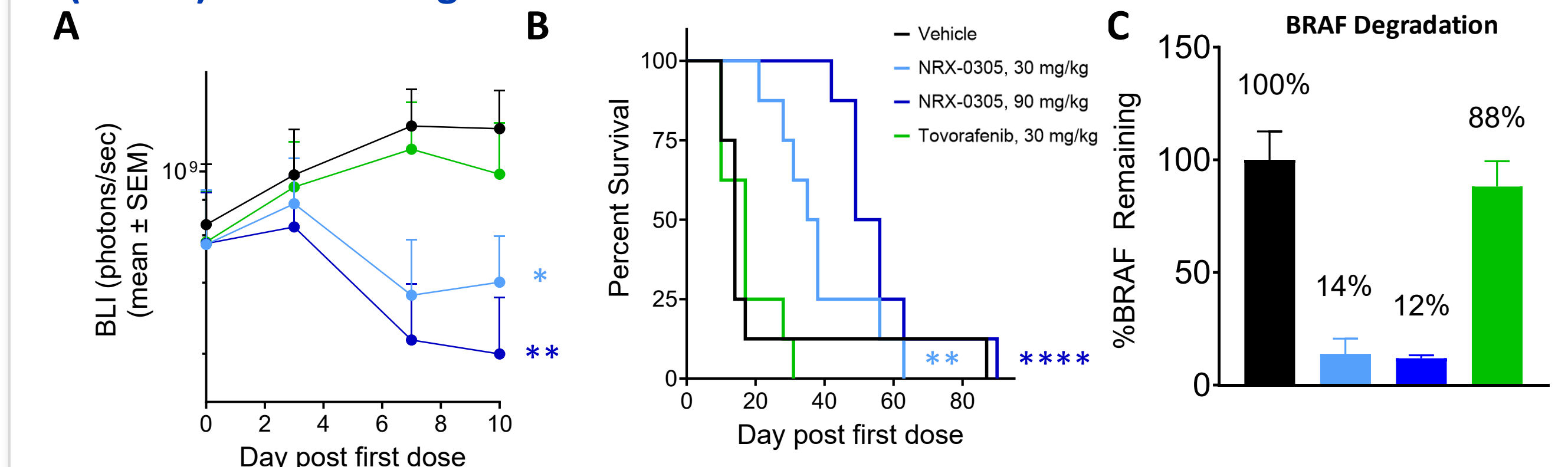


Figure 3. (A) Mice bearing AM38 (BRAF V600E) luciferase-tagged intracranial xenografts were dosed daily with NRX-0305* or tovorafenib at the indicated doses (PO, QDx100). One-way ANOVA with Dunnett's multiple comparisons test at day 10. **(B)** Survival was assessed by Kaplan-Meier survival analysis compared to vehicle across the treatment period. **(C)** BRAF (V600E) degradation was measured in isolated, purified tumor cells following 3 days of treatment, 2 hours post last dose by Jess Simple Western. Statistical significance * p < 0.05, ** p < 0.01, **** p < 0.0001

Figure 4. NRX-0305 treatment demonstrated dose-dependent, anti-tumor activity in an intracranial, Class 1 BRAF (V600E) melanoma CDX model

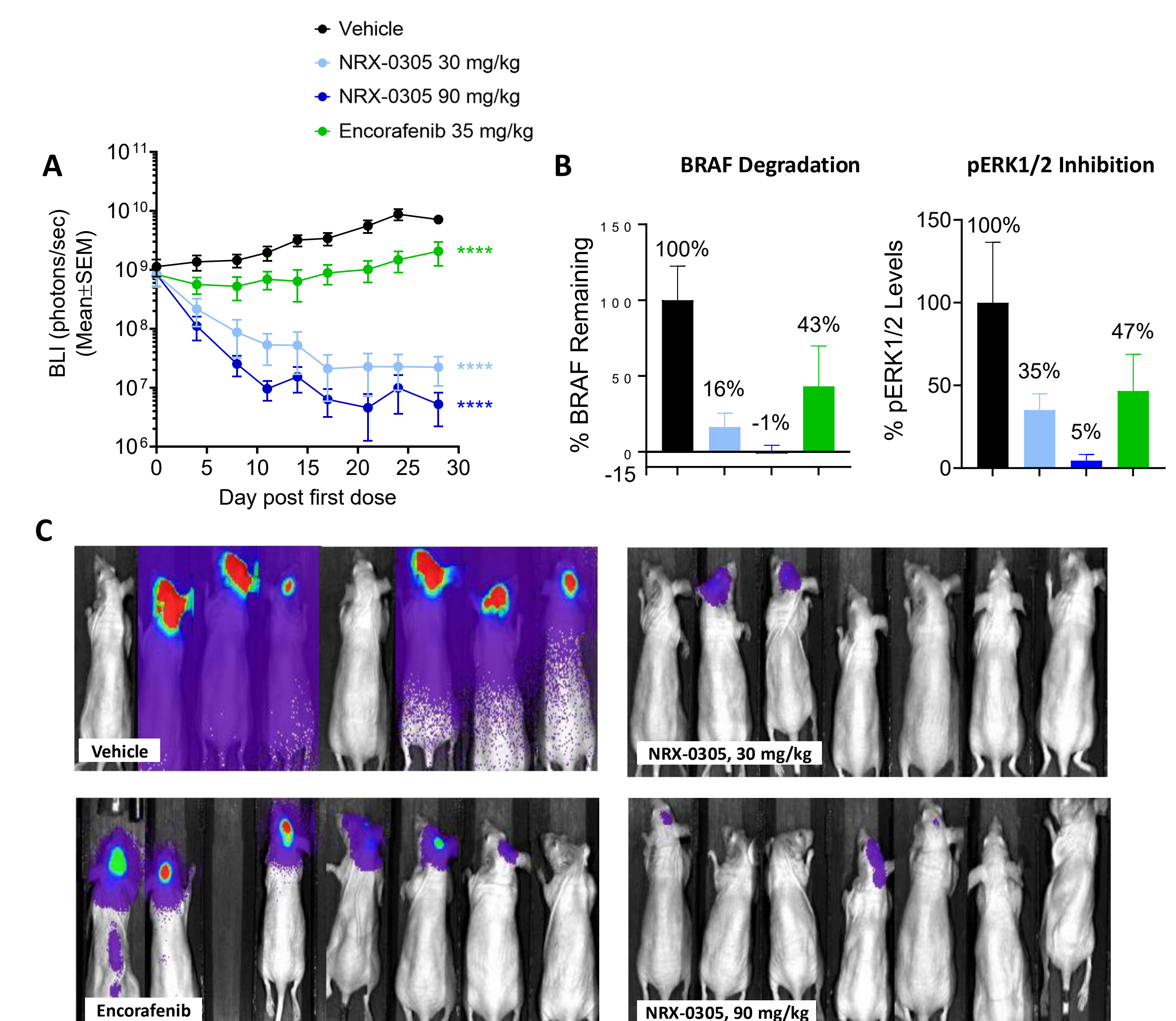


Figure 3. (A) Mice bearing A375 (BRAF V600E) luciferase-tagged intracranial xenograft tumors were dosed daily with NRX-0305 or encorafenib (PO, QDx28). Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test. **(B)** BRAF (V600E) degradation and pERK1/2 inhibition was measured in isolated, purified tumor cells following 4 days of treatment 2 hours post last dose by flow cytometry. **(C)** Tumor bioluminescence (BLI) was measured by AMI-HTX imaging system. Representative pseudocolor images from day 21. Statistical significance: **** p < 0.0001

Figure 5. NRX-0305 demonstrates anti-tumor efficacy in a subcutaneous Class 1 (V600K) PDX model derived from melanoma brain metastasis

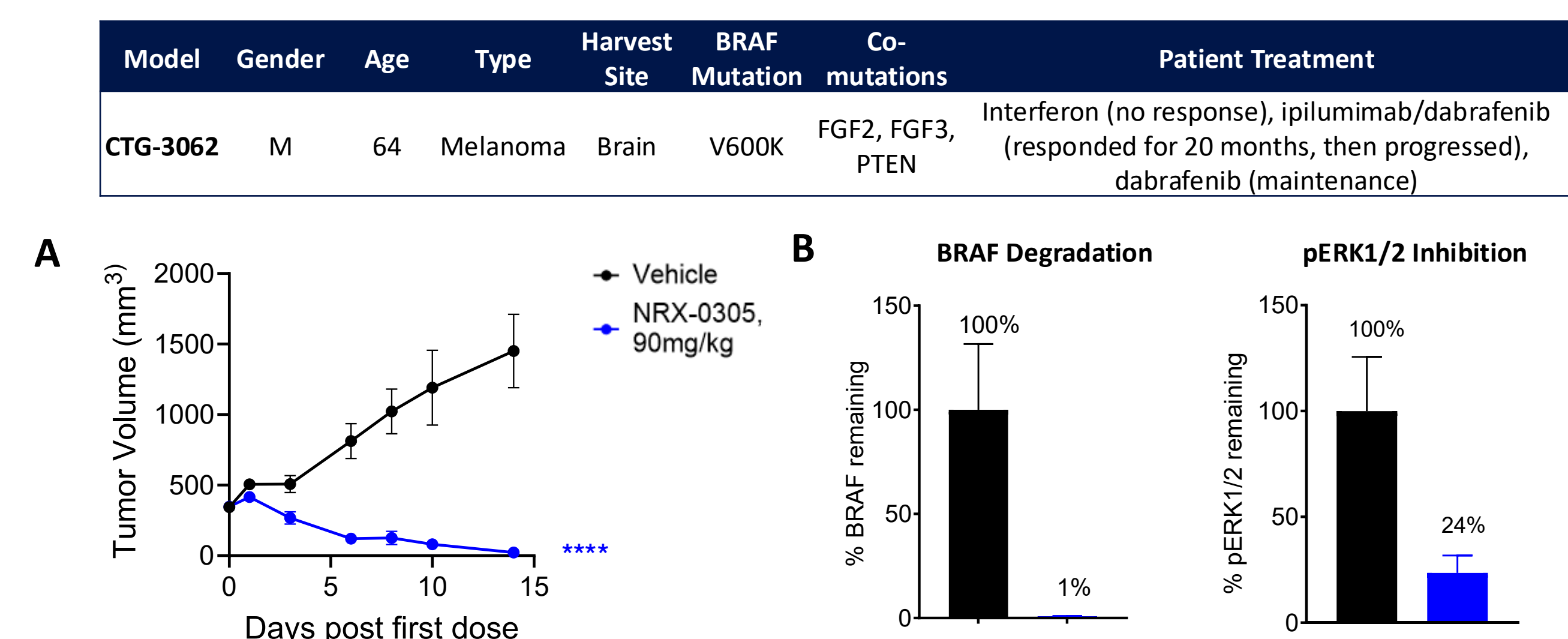


Figure 5. (A) Mice bearing subcutaneous CTG-3062 Class 1 (V600K) melanoma PDX were dosed with NRX-0305 (90mg/kg, QDx14). Two-way ANOVA, mixed effects model with Dunnett's multiple comparisons test vs vehicle. Statistical significance ****p < 0.0001 **(B)** BRAF and pERK levels were assessed in xenografts after 14 days of dosing, 24 hours post last dose by Simple Western (Jess).

Figure 6. Development and characterization of a clinically relevant BRAFi resistant intracranial melanoma metastasis PDX model

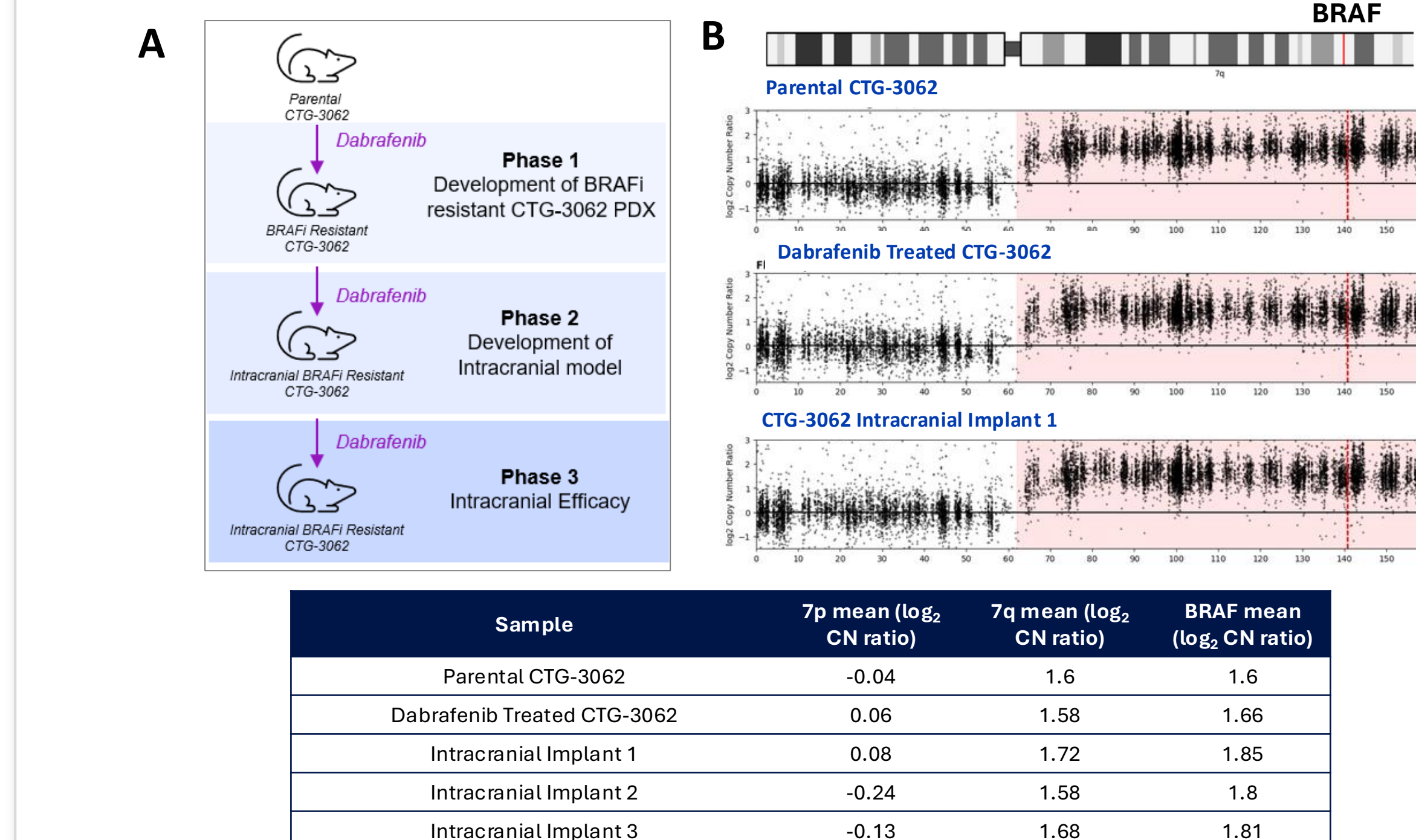


Figure 6. (A) Scheme for the development of intracranial, BRAFi resistant CTG-3062. **(B)** WES analysis (Monoceros Biosystems) identifies persistent 7q amplification during evolution of the BRAFi resistant CTG-3062 PDX model. Chromosome 7 copy number profiles are shown for the resistant parental tumor and subsequent resistant passages. Points indicate CNVkit bin-level log₂ tumor-to-normal copy number ratios relative to diploid baseline. A value of 0 represents two copies, with gains and losses reflected by positive and negative values, respectively. Observed log₂ ratios of ~1.6-1.8 correspond to approximately 6-7 genomic copies under a diploid assumption.

Figure 7. NRX-0305 extends survival in a BRAFi resistant intracranial melanoma metastasis PDX model

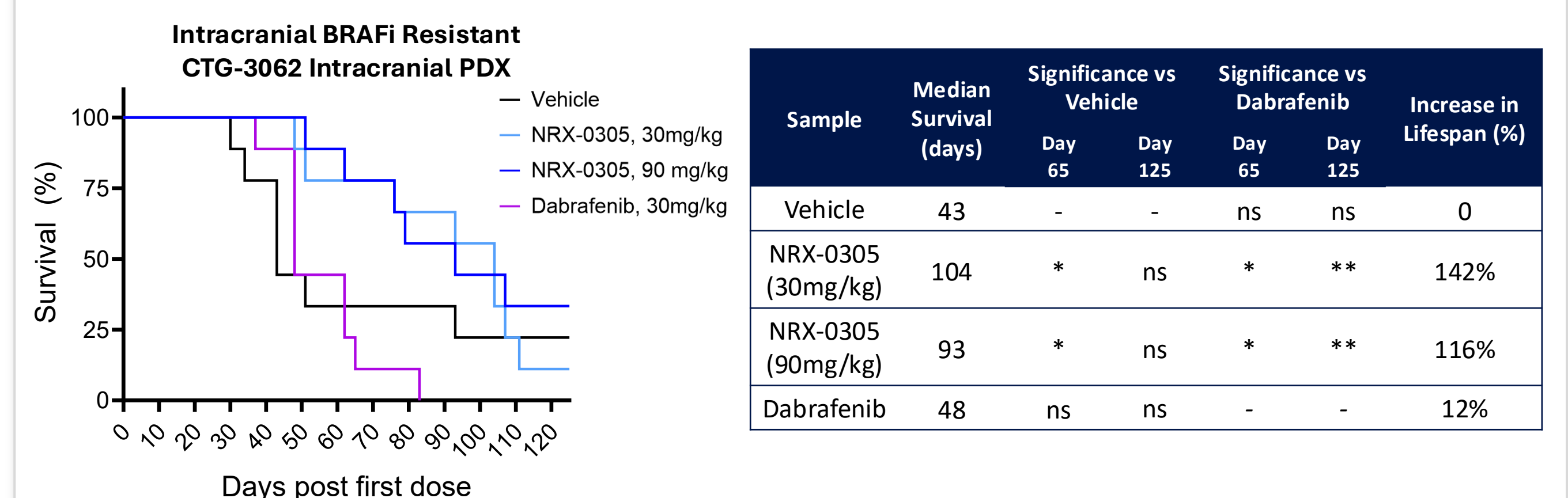


Figure 7. Mice bearing intracranial BRAFi resistant CTG-3062 PDX tumors were dosed once daily with NRX-0305* or dabrafenib at the indicated doses (PO, QDx125). Kaplan Meier survival analysis was performed, and significance was calculated by Log-Rank (Mantel-Cox) test vs vehicle or Dabrafenib at days 65 and 125. Percent increase in lifespan was calculated by the following formula: [Median survival (treated)-median survival (control)]/median survival (control)x100. Statistical significance: *p < 0.05, ** p < 0.01, ns=not significant.

Conclusion

- NRX-0305 is a potent and selective pan-mutant BRAF degrader, which spares wildtype BRAF and lacks paradoxical activation
- NRX-0305 demonstrates dose proportional pharmacokinetics in plasma, tumor and brain leading to robust BRAF degradation and pERK1/2 inhibition in tumor tissue
- NRX-0305 demonstrates dose dependent anti-tumor efficacy across intracranial CDX and PDX models of BRAF mutant glioma and melanoma metastases
- The unique combination of pan-mutant BRAF degradation, CNS penetration, and lack of WT inhibition and paradoxical MAPK activation positions NRX-0305 to expand the treatable patient population capturing BRAF-mutant patients with CNS involvement