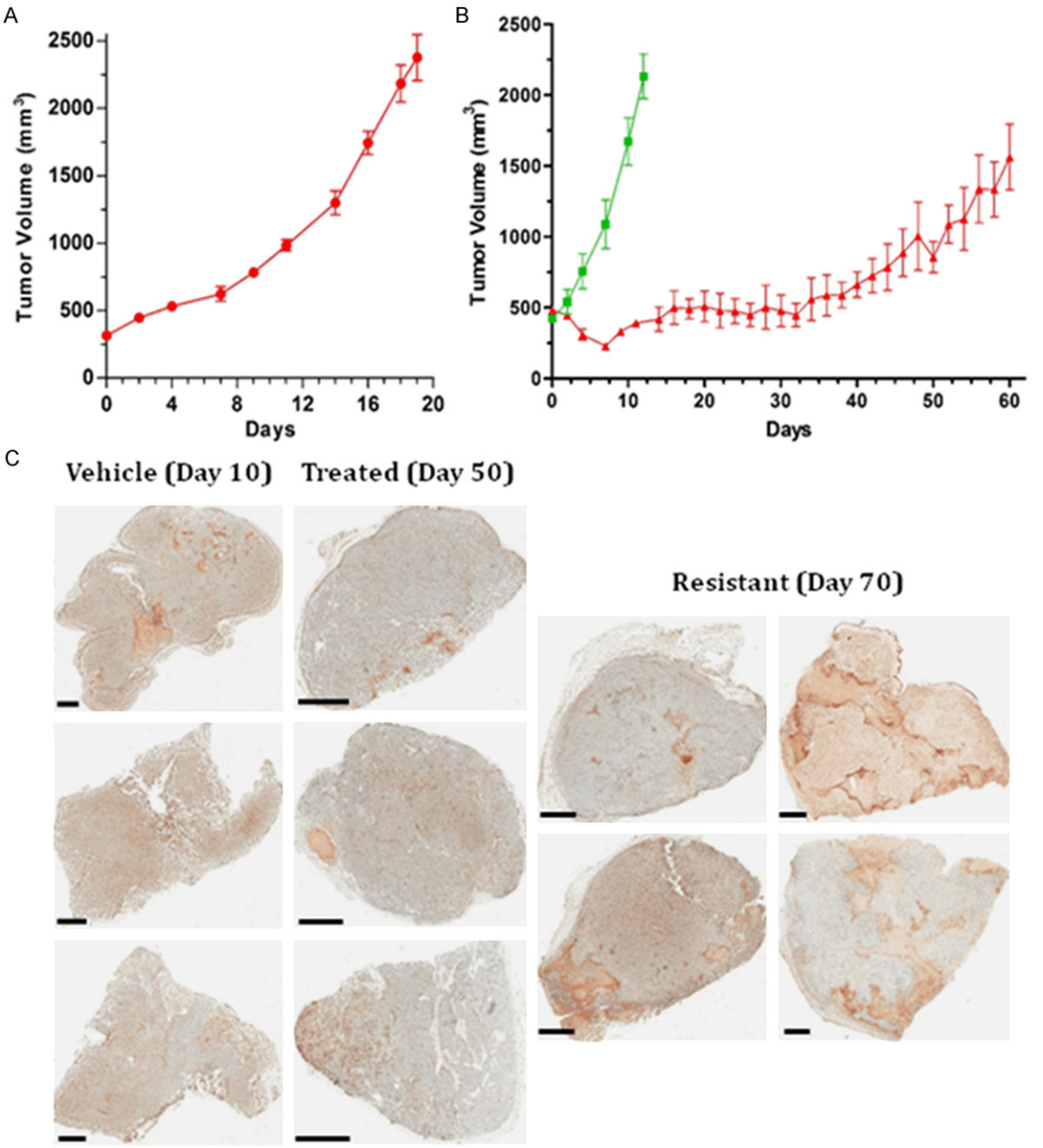
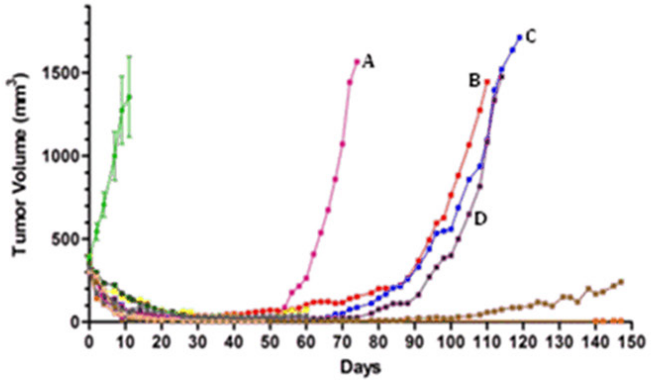
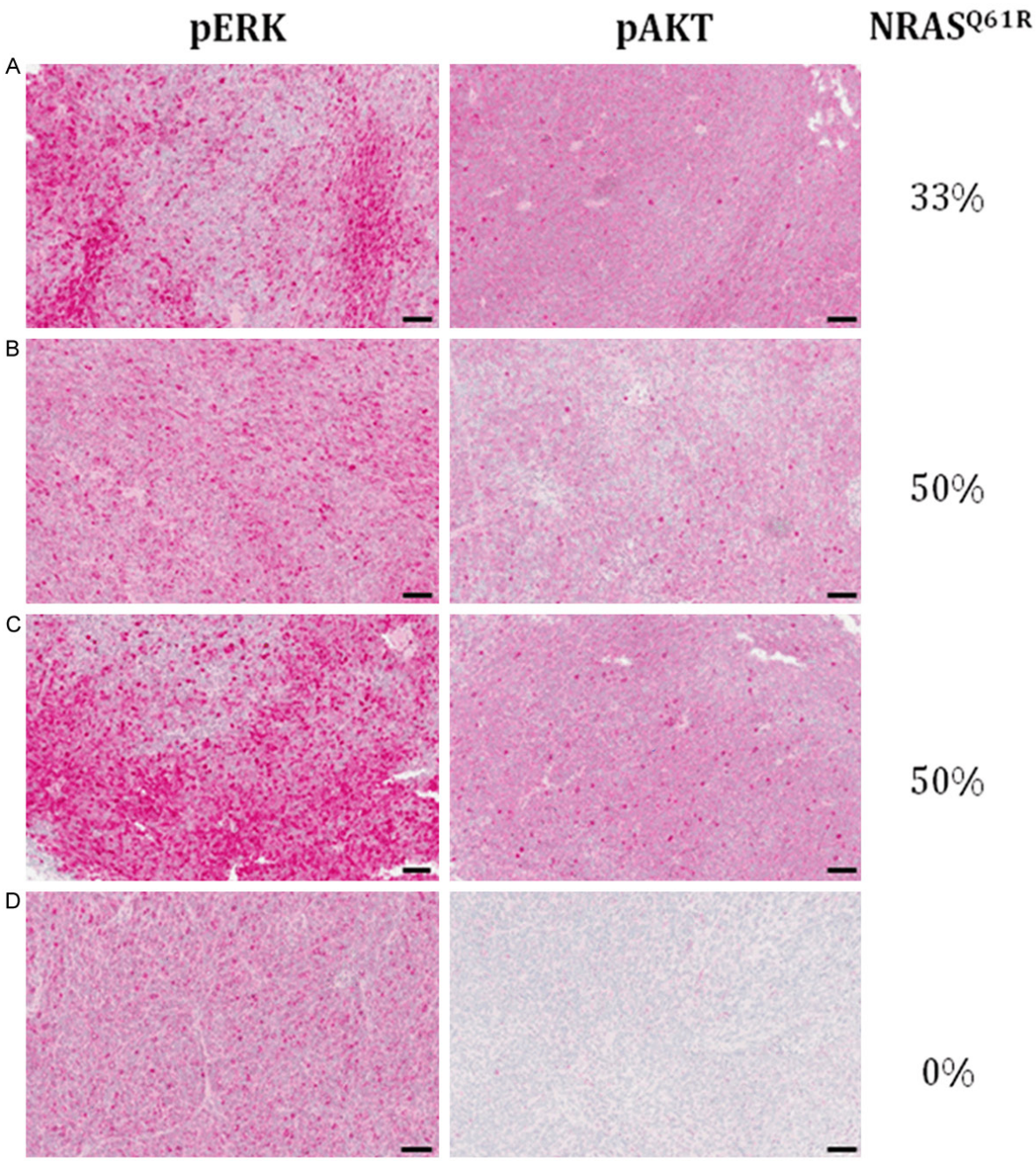
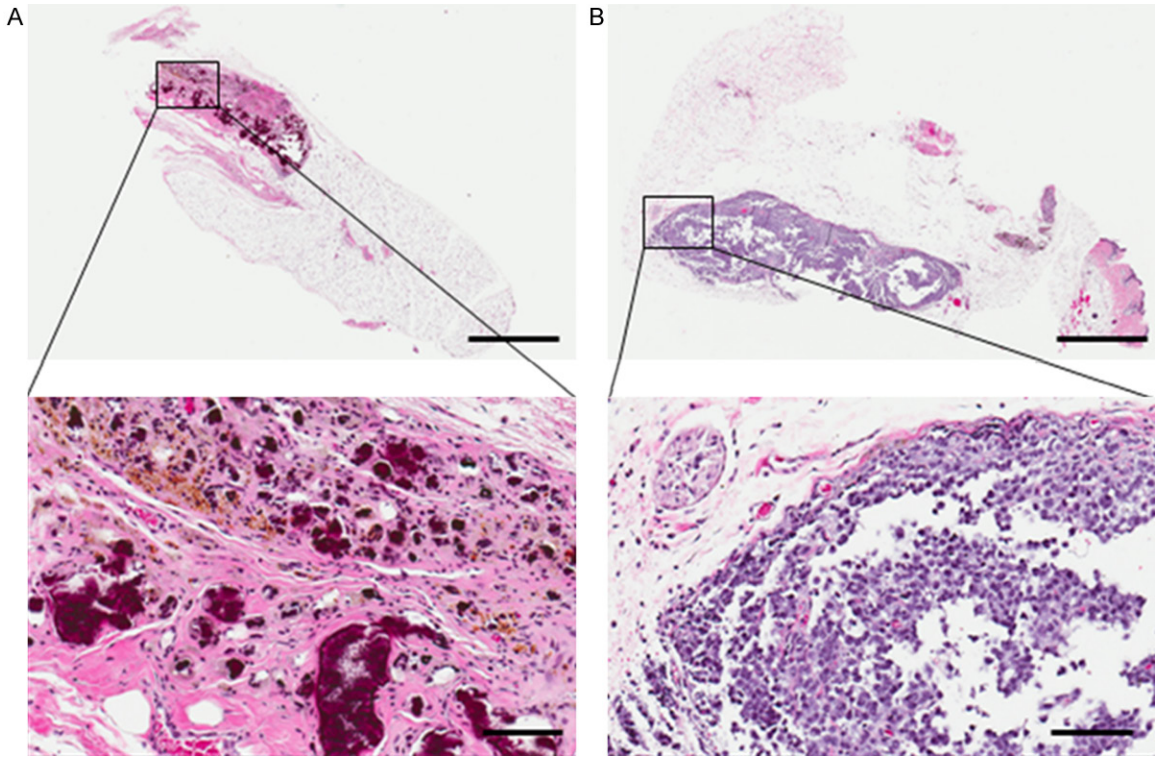


Supplementary Figure 1. Transplantation of Vemurafenib-resistant and Ki-67 IHC-based staining profiles. A. Patient 1 Vemurafenib-resistant tumors harvested on day 70 were re-engrafted in new recipient mice and maintained rapid growth phase in presence of Vemurafenib (50 mg/kg orally, twice a day, 5 d on, 2 d off). B. Patient 1 PDX model tumor responses to Vemurafenib (50 mg/kg orally, twice a day, 5 d on, 2 d off) are reproducible; compare this graph to **Figure 1A**. C. Staining for the proliferation-associated marker Ki-67 in whole mounts of tumors from mice exposed to vehicle alone for 10 d or Vemurafenib (50 mg/kg orally, twice a day, 5 d on, 2 d off) for 50 d; resistant tumors after 70 d of Vemurafenib exposure are also shown. Ki-67 levels were higher in vehicle-treated tumors and in Vemurafenib-resistant tumors. Scale bars indicate 1 mm.


Tumor Volume (mm³)
1500
1000
500
0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
Days
A
B
C
D


pERK
pAKT
NRAS^{Q61R}
A
33%
B
50%
C
50%
D
0%

Supplementary Figure 2. Patient 2 Vemurafenib-resistant xenograft samples show similar IHC staining for pERK despite differences in resistance mechanisms linked to either NRAS or BRAF alternate splicing. Panels are labeled A through D to indicate the tumorgrafts from which they were derived in the top panel. pAKT staining is markedly reduced in the tumor (D) lacking the activating NRAS mutation. Scale bar indicates 100 μm.



Supplementary Figure 3. Histological appearance of two different tumor sites from day-100 mice chronically exposed to Vemurafenib and PD0325901 (see **Figure 4A**). In panel A, no viable metastatic melanoma cells could be identified among the fibrocalcific nodules. In panel B, only a small cluster of viable residual metastatic melanoma cells was apparent; they had a high nuclear: cytoplasmic ratio and a relatively undifferentiated appearance. Note scale bar indicates 1 mm.