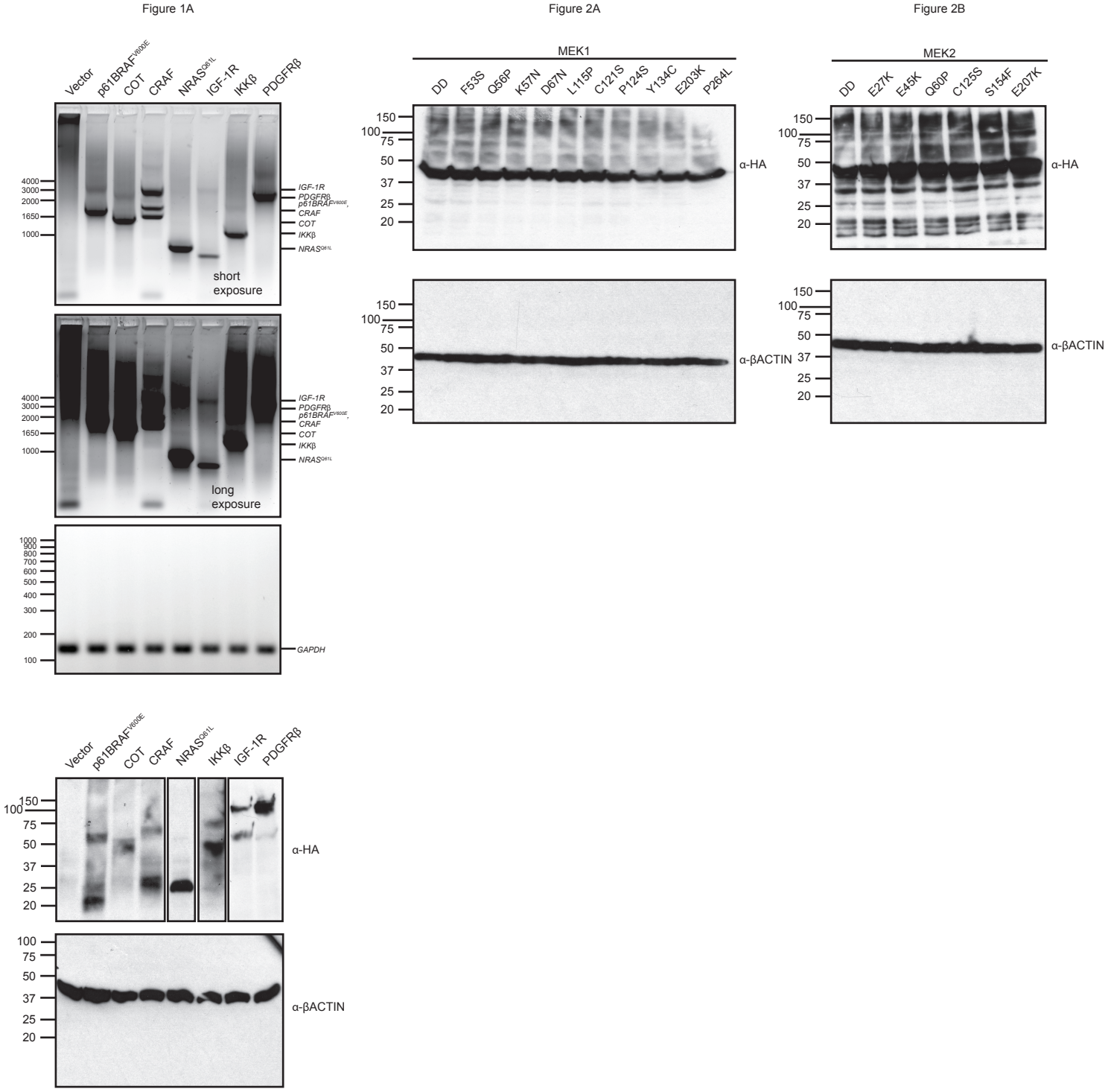


Figure S1. Related to Figures 1,2; Full-length RT-PCR detection of indicated mRNA as shown in Figure 1A or immunoblots of indicated proteins as shown in Figure 1A and Figure 2A,B. GAPDH and βACTIN: loading control.

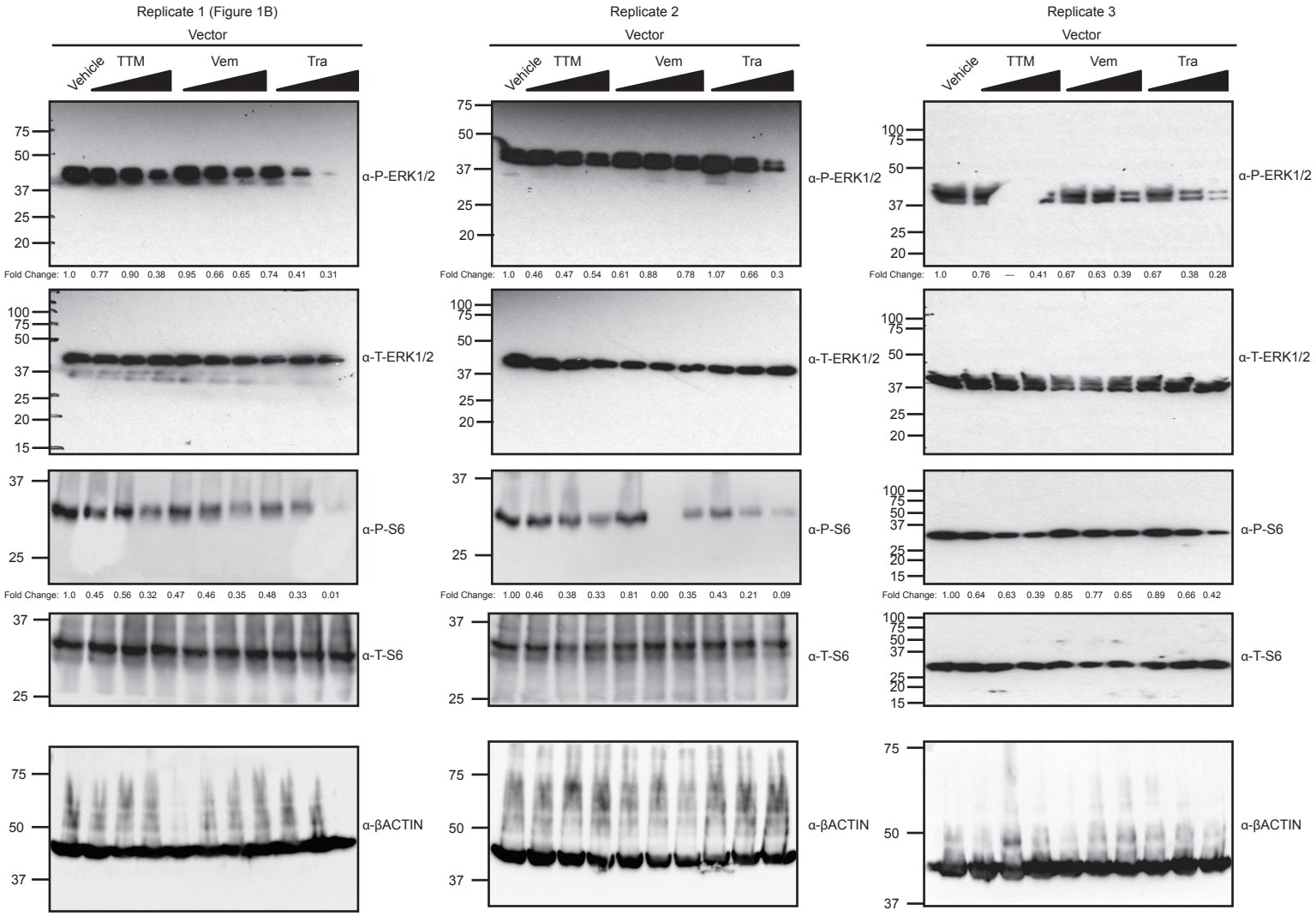


Figure S2. Related to Figure 1; Full length immunoblot shown in Figure 1B as well as two replicates (with quantification).

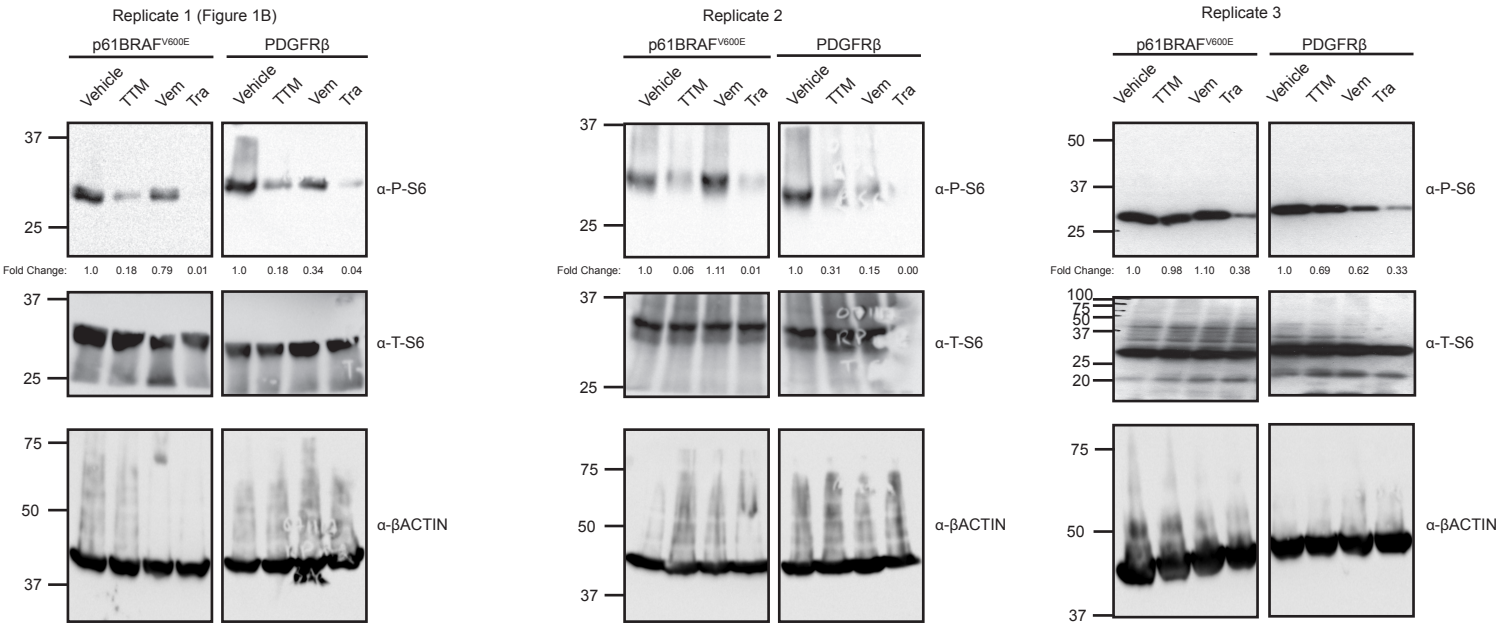


Figure S3. Related to Figure 1; Full length immunoblot shown in Figure 1B as well as two replicates (with quantification).

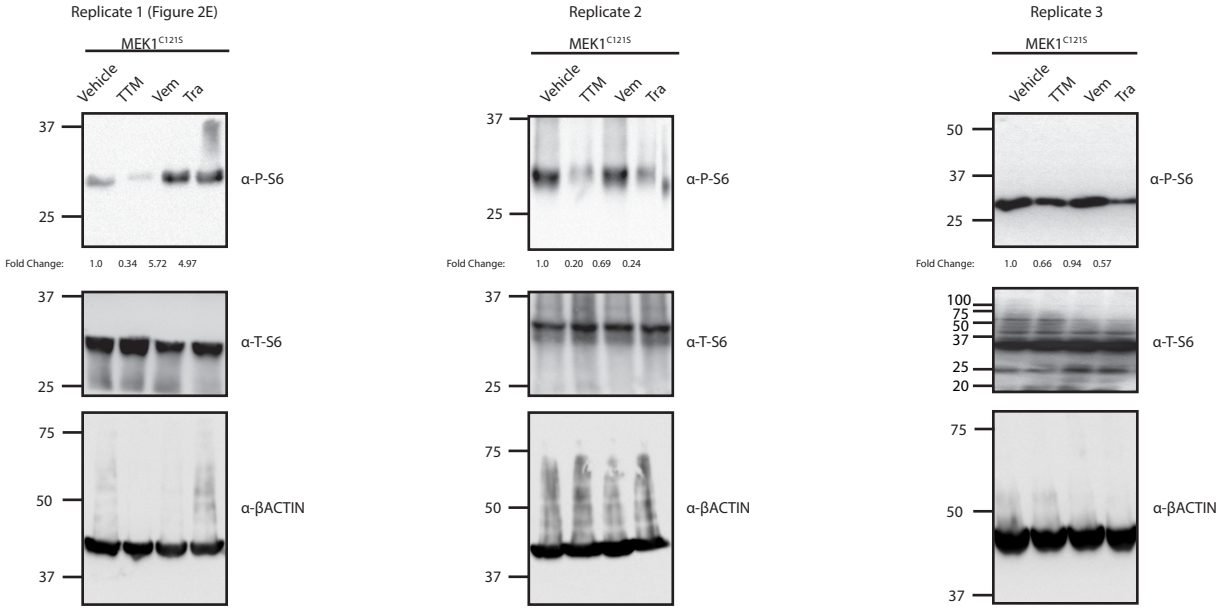


Figure S4. Related to Figure 2; Full length immunoblot shown in Figure 2E as well as two replicates (with quantification).

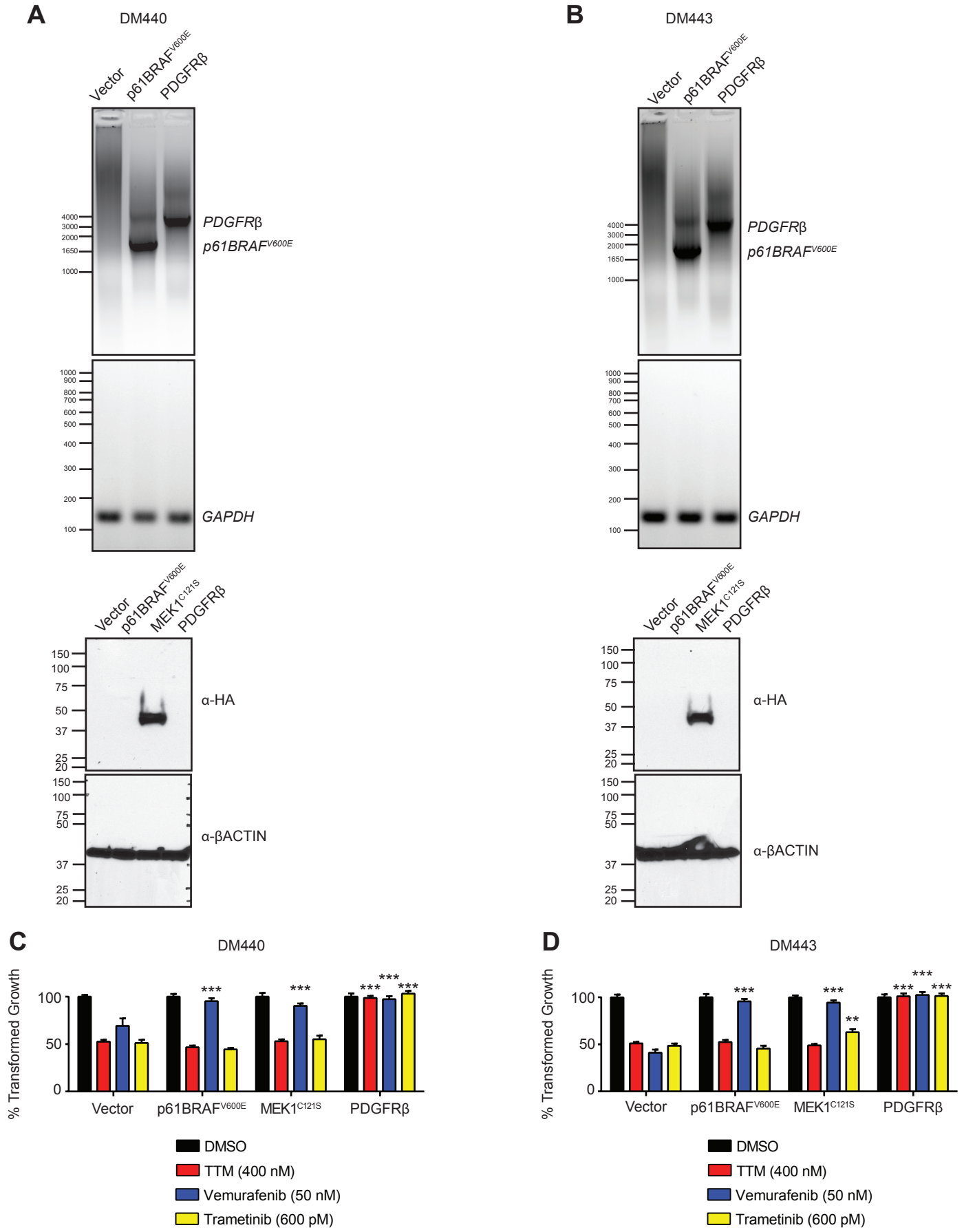
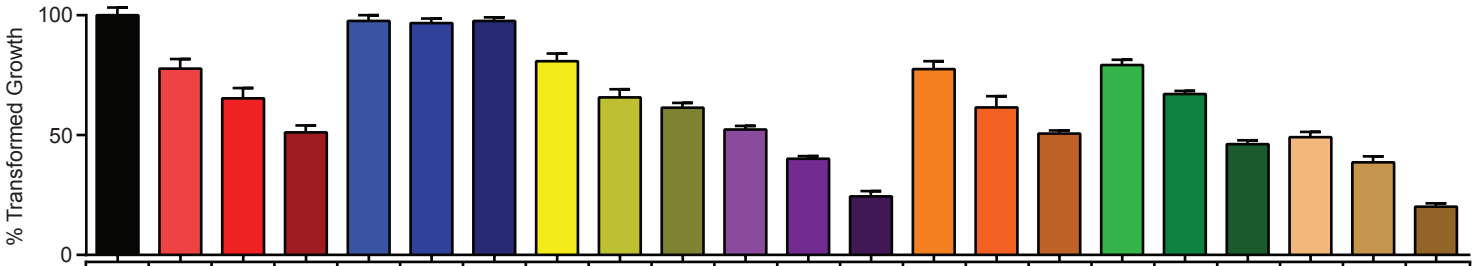


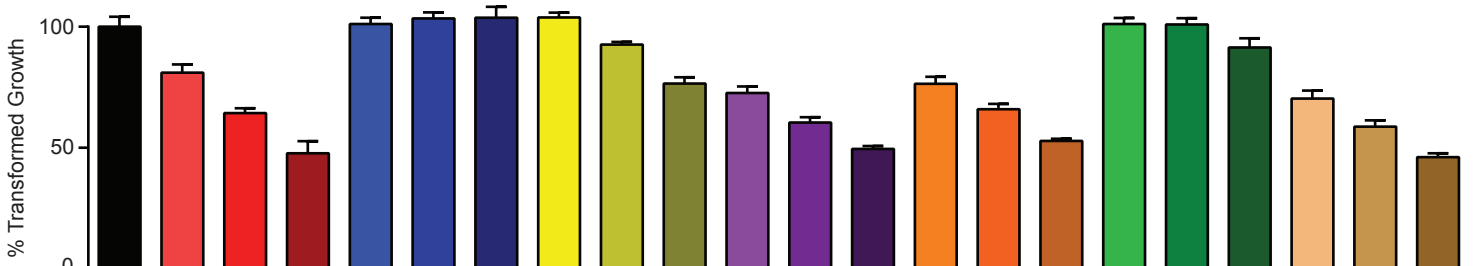
Figure S5. Related to Figures 1,2; (**A, B**) RT-PCR detection of ectopic HA-tagged p61BRAF^{V600E} or PDGFRβ cDNAs or immunoblot detection of ectopic HA-tagged MEK1^{C121S} in (**A**) DM440 or (**B**) DM443 cells. GAPDH and ßACTIN: loading control. (**C, D**) % transformed growth expressed as the normalized % soft agar colony formation (mean ± s.e.m, triplicate samples, three experiments) of (**C**) DM440 or (**D**) DM443 cells stably expressing p61BRAF^{V600E}, MEK1^{C121S}, or PDGFRβ when treated with vehicle (black bar) or the IC50 doses of TTM (red bar), vemurafenib (blue bar), or trametinib (yellow bar). **p<0.001 and ***p<0.0001 versus vector control cells treated with the same drug. Statistical analysis was performed with two-way Analysis of Variance (ANOVA) with a Bonferroni multiple comparisons post test to compare transformed growth of each cell line with vector control cells treated with the same drug.

A



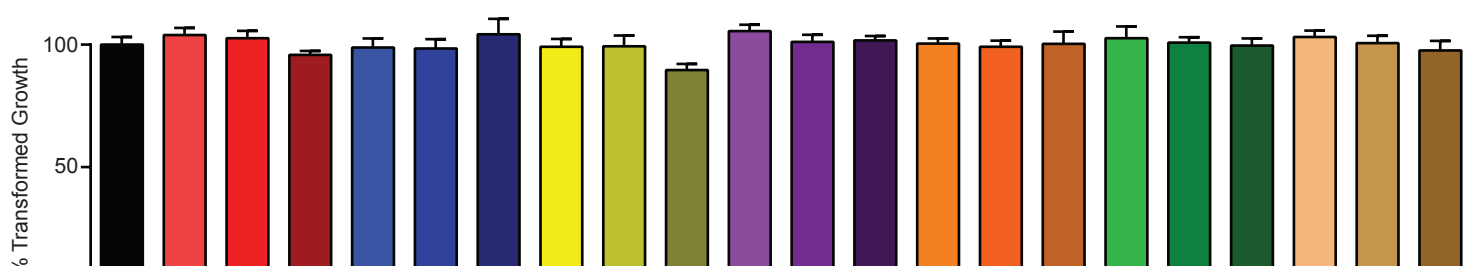
TTM (nM)	-	25	50	100	-	-	-	-	-	-	25	50	100	25	50	100	-	-	-	25	50	100
Vem (nM)	-	-	-	-	3.125	6.25	12.5	-	-	-	3.125	6.25	12.5	-	-	-	3.125	6.25	12.5	3.125	6.25	12.5
Tra (pM)	-	-	-	-	-	-	-	75	150	300	-	-	-	75	150	300	75	150	300	75	150	300

B



TTM (nM)	-	25	50	100	-	-	-	-	-	-	25	50	100	25	50	100	-	-	-	25	50	100
Vem (nM)	-	-	-	-	3.125	6.25	12.5	-	-	-	3.125	6.25	12.5	-	-	-	3.125	6.25	12.5	3.125	6.25	12.5
Tra (pM)	-	-	-	-	-	-	-	75	150	300	-	-	-	75	150	300	75	150	300	75	150	300

C



TTM (nM)	-	25	50	100	-	-	-	-	-	-	25	50	100	25	50	100	-	-	-	25	50	100
Vem (nM)	-	-	-	-	3.125	6.25	12.5	-	-	-	3.125	6.25	12.5	-	-	-	3.125	6.25	12.5	3.125	6.25	12.5
Tra (pM)	-	-	-	-	-	-	-	75	150	300	-	-	-	75	150	300	75	150	300	75	150	300

Figure S6. Related to Figure 3; **(A**, **B**, **C)** % transformed growth expressed as the normalized % soft agar colony formation (mean ± s.e.m, triplicate samples, three experiments) of A375 cells stably infected to express **(A)** p61BRAF^{V600E}, **(B)** MEK1^{C121S}, or **(C)** PDGFRβ when treated with vehicle (black bar), TTM (red bars), vemurafenib (Vem, blue bars), trametinib (Tra, yellow bars), TTM and vemurafenib (TTM+Vem, purple bars), TTM and trametinib (TTM+Tra, orange bars), vemurafenib and trametinib (Vem+Tra, green bars), or TTM, vemurafenib, and trametinib (TTM+Vem+Tra, brown bars) at the indicated doses alone or in fixed-ratio combinations.

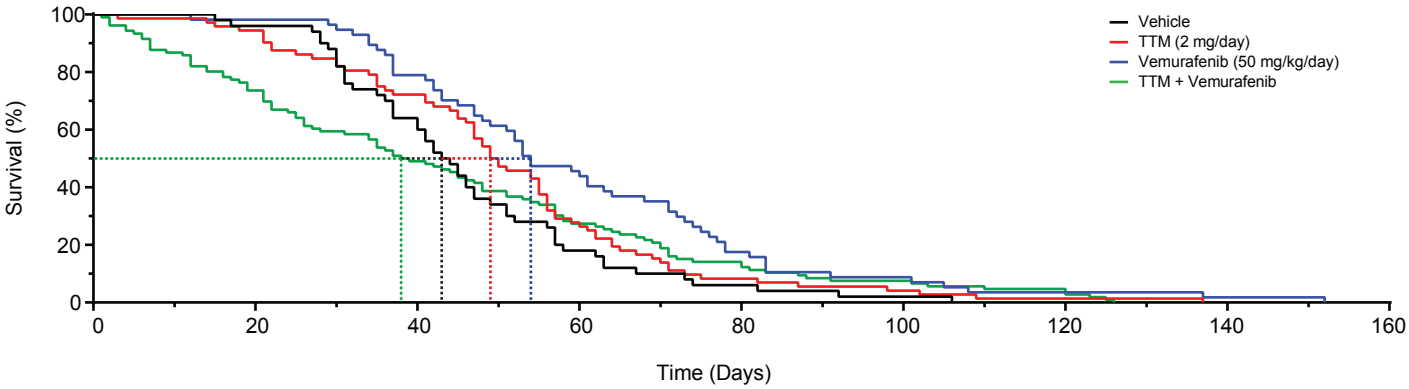


Figure S7. Related to Figure 5; uncensored Kaplan-Meier analysis of BPC mice orally treated daily with vehicle (solid black line, *n*=50, dotted line: 43.5 days median survival), TTM (solid red line, *n*=72, dotted line: 50 days median survival, *p*=0.14 compared to vehicle), vemurafenib (solid blue line, *n*=57, dotted line: 54 days median survival, *p*=0.001 compared to vehicle), or TTM and vemurafenib (solid green line, *n*=106, dotted line: 38.5 days median survival, *p*=0.61 compared to vehicle) from the appearance of a pigmented lesion of all mice that reached endpoint for any reason. Statistical analysis was performed with a Mantel-Cox log-rank method to compare each group to vehicle-treated control mice in a pairwise manner.

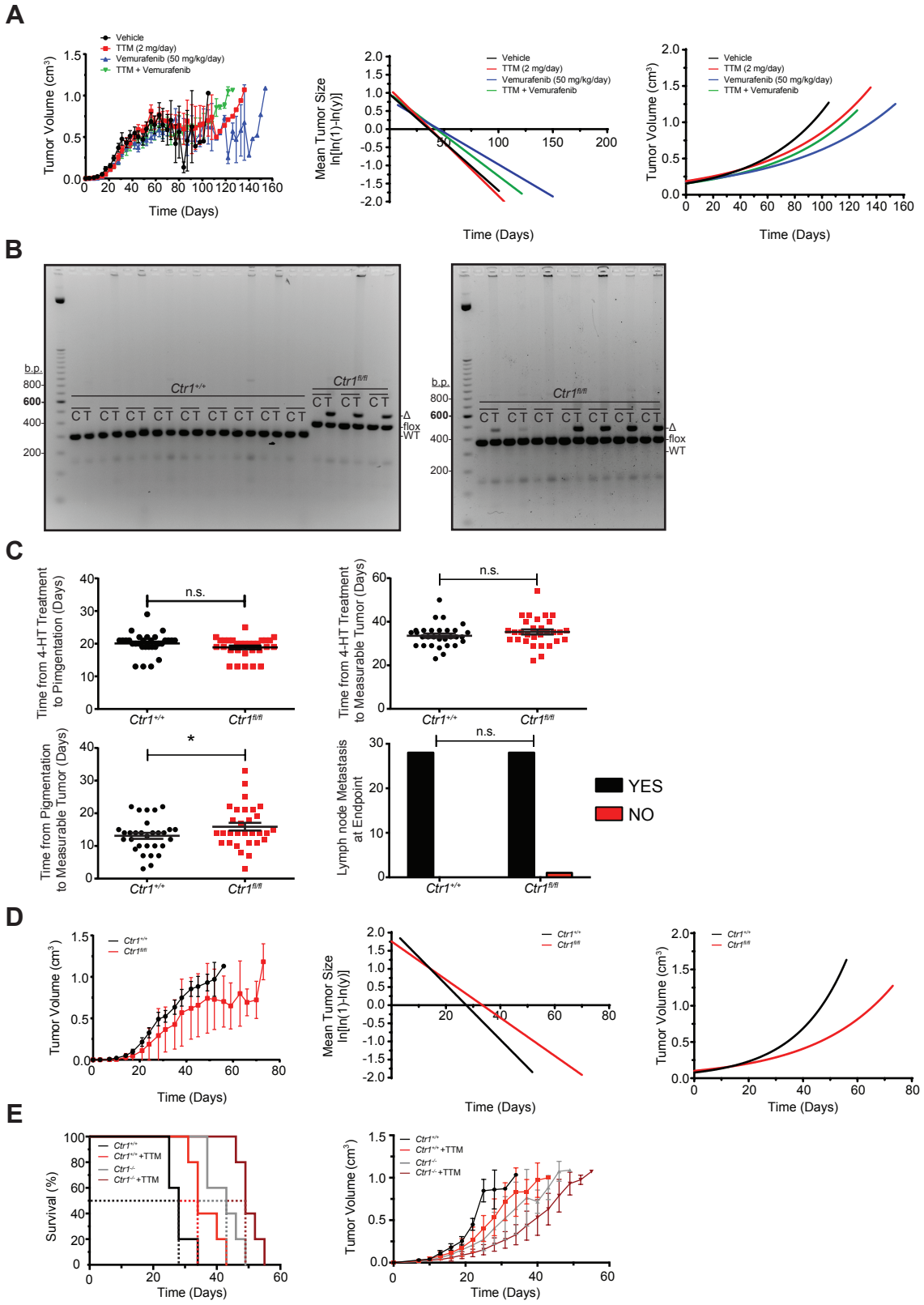


Figure S8. Related to Figures 5,7; growth kinetics, Gompertz transformation, and exponential growth curves for tumors from (**A**) BPC mice treated with vehicle (black line, *n*=48), TTM (red line, *n*=36), vemurafenib (blue line, *n*=51), or TTM and vemurafenib (green line, *n*=51) or (**D**) *Ctr1*$^{+/+}$ (black line, *n*=30) or *Ctr1*$^{fl/fl}$ (red line, *n*=30) BPC mice. (**B**) PCR detection of wildtype (WT), conditional (flox), and the recombined null (Δ) *Ctr1* alleles from *Ctr1*$^{+/+}$ (*n*=9) and *Ctr1*$^{fl/fl}$ (*n*=10) BPC mice from matched normal control tail samples (C) and tumor tissue (T). Left: ladder (b.p., base pairs) (**C**) Scatter dot plot or grouped bar graph of time from 4-HT treatment to appearance of pigmentation, time from 4-HT treatment to appearance of measurable tumor, time from appearance of pigmentation to appearance of measurable tumor, and presence of visible lymph node metastasis at endpoint for *Ctr1*$^{+/+}$ (*n*=30) and *Ctr1*$^{fl/fl}$ (*n*=30) BPC mice. **p*<0.05; n.s., not significant. Statistical analysis was performed with a Student's *t*-test. (**E**) Kaplan–Meier analysis (left) of percentage of mice with tumor volume at least 1.0 cm^3 versus time (right) when injected with BRAF^{V600E}- transformed *Ctr1*$^{+/+}$ MEFs treated with vehicle (solid black line, *n*=5, dotted line: 28 days median survival) or TTM (solid red line, *n*=5, dotted line: 34 days median survival, *p*=0.0249 compared to vehicle) or BRAF^{V600E}-transformed *Ctr1*$^{-/-}$ MEFs treated with vehicle (solid grey line, *n*=5, dotted line: 43 days, *p*= 0.0019 compared to *Ctr1*$^{+/+}$ vehicle) or TTM (solid dark red line, *n*=5, dotted line: 49 days, *p*= 0.0288 compared to *Ctr1*$^{-/-}$ vehicle). Statistical analysis was performed with a Mantel-Cox log-rank method to compare the indicated groups in a pairwise manner.