SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure S1. Signaling properties of WT PAPSS1. Immunoblotting of lysates from 293H cells transfected with empty vector (1µg) or plasmids encoding BRAF V600E-FLAG (80ng) or WT PAPSS1-FLAG (1µg) demonstrates that WT PAPSS1 does not cause MAPK pathway signaling. kDa, kilodalton.

Supplementary Figure S2. Detection of TRIM24-BRAF. Four representative spanning sequence reads from genotyping of a second "pan-negative" melanoma with the FoundationOne™ assay shows the alignment of *TRIM24* (purple text) to chromosome 7q32-24 and of *BRAF* (dark blue text) to chromosome 7q34. The reads specifically align to intron 9 of *TRIM24* and to intron 8 of *BRAF*, which indicates a coding sequence break between *TRIM24* exon 9 and *BRAF* exon 9. Below are schematics of wild-type BRAF (blue), wild-type TRIM24 (purple), and the fused TRIM24-BRAF proteins. The RING-finger, B-box types 1 and 2, and coiled-coil domains of TRIM24 and the serine/threonine (S/T) kinase domain of BRAF remain intact in the fused protein. WT, wild-type; ex, exon; RBD, Ras-binding domain; CRD, cysteine-rich domain; RKTR, Arg-Lys-Thr-Arg dimerization domain; RING, Really Interesting New Gene, RING-finger domains play key roles in the ubiquitylation pathway; B-box types 1 & 2 are zinc-finger-like domains; PHD, Plant Homeo Domain, binds tri-methylated lysines on histone H3; BROMO, bromodomain, binds acetylated lysines on histones.

Supplementary Figure S3. Signaling and inhibition of TRIM24-BRAF. Immunoblotting of lysates from 293H cells transfected with BRAF V600E-FLAG or TRIM24-BRAF-FLAG show that TRIM24-BRAF activates the MAPK pathway, which can be inhibited by the MEK inhibitor, trametininb (tra), but not the BRAF inhibitor, vemurafenib (vem). Drug dosing: (DMSO vehicle control), 0.1, 0.5, 1 and 5 µmol/L. kDa, kilodalton.

Supplementary Figure S4. Potential TAX1BP1-BRAF and CDC27-BRAF fusions identified in data from The Cancer Genome Atlas. Representative RNA sequencing reads from TCGA skin cutaneous melanoma dataset (SKCM) demonstrate the alignment of paired-end reads mapping to **(A)** exon 11 of BRAF (blue text) and exon 8 of TAX1BP1 (green text), both on chromosome 7 or **(B)** to exon 10 of BRAF (blue text) on chromosome 7 and exon 16 of CDC27 (orange text) on chromosome 17. Below each alignment schematic are diagrams of WT BRAF (blue) and the TAX1BP1-BRAF **(A)** or CDC27-BRAF **(B)** fusion proteins. WT, wild-type; ex, exon; RBD, Ras-binding domain; CRD, cysteine-rich domain; RKTR, Arg-Lys-Thr-Arg dimerization domain.

Supplementary Figure S5. Comparison of reverse phase protein array (RPPA) data in TCGA skin cutaneous melanoma dataset. Both graphs display box and whisker plots based on RPPA data distributions for **(A)** total or **(B)** phosphorylated MEK1/2 protein levels. Samples are divided based on SNaPshot mutation status into "pan-negative" (NEG), BRAF-mutant (includes the non-V600 BRAF alterations listed in Table S1 as well as BRAF N581T, S467L and G466E), NRAS-mutant, KIT-mutant, or GNAQ/11-status. The last two data points in each graph represent the "pan-negative" samples harboring CDC27-BRAF and TAX1BP1-BRAF. Differences in **(A)** total MEK1/2 protein levels are not statistically significant between any of the sample groups, however, **(B)** the phosphorylated MEK1/2 levels between "pan-negative" and BRAF-mutant or NRAS-mutant samples are statistically significant ($p<0.0001$, Student's t-test). Although statistical analyses cannot be performed on single samples, the phosphorylated MEK1/2 levels of the "pan-negative" cases harboring CDC27-BRAF and TAX1BP1-BRAF are similar to, or greater than, the levels observed in BRAF- or NRAS-mutant cases.