SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1: $BRAF^{V600E}/PTEN^{Null}$ and $BRAF^{V600E}/PIK3CA^{H1047R}$ melanomas show similar patterns of expression of melanoma-specific markers and Ki67

Sections of $BRAF^{V600E}/PTEN^{Null}$ or $BRAF^{V600E}/PIK3CA^{H1047R}$ melanomas were stained with antisera against Ki67, S-100 or Tyrosinase as indicated. Ki67 antigen was used as a marker of proliferation, and tumors did not segregate according to number or distribution of proliferating cells. Similarly, melanoma genotypes could not be distinguished based on the staining patterns for S100 or Tyrosinase. Scale bars indicate 100µm.

Supplementary Figure 2: Modest response of $BRAF^{V600E}$/$PIK3CA^{H1047R}$ melanomas to therapeutic AKT inhibition

Since AKT inhibition using MK-2206 was effective at blocking growth of incipient $BRAF^{V600E}$/$PIK3CA^{H1047R}$ melanomas, we tested whether MK-2206 treatment might be effective at suppressing growth of established melanomas. $BRAF^{V600E}$/$PIK3CA^{H1047R}$ melanoma growth was initiated as described. Once average tumor size reached 500mm^3, vehicle (solid line) or AKT inhibitor treatment (dashed line) began, and tumors were measured weekly over the course of 50 days on continuous treatment (displayed as percent change in tumor volume ±SD)

Supplementary Figure 3: Durability of PI3'-kinase→AKT pathway inhibition following addition of inhibitors

$BRAF^{V600E}$/$PTEN^{Null}$ or $BRAF^{V600E}$/$PIK3CA^{H147R}$ mouse melanoma derived cell lines were treated with a single administration of solvent control (DMSO), MK-2206 (5μM), GSK690693 (5μM), BKM-120 (1μM) or GDC-0941 (5μM) to inhibit AKT (MK-2206 & GSK690693) or class 1 PI3'-kinases (BKM-120 or GDC-0941) and incubated for the indicated periods of time from 24-72 hours. Following drug treatment whole cell extracts were prepared for immunoblot analysis with phospho- or backbone specific antisera against various different proteins to determine the durability of the effects of each inhibitor.

Supplementary Figure 4: Analysis of synergy between $BRAF^{V600E}$-specific inhibitor LGX-818 and class I PI3'-kinase inhibitor BKM-120 in melanoma cell lines

(A) Human melanoma-derived 1205Lu cells (Left column) or cells derived from mouse $BRAF^{V600E}$/$PTEN^{Null}$/$CDKN2A^{Null}$ melanomas (center column) or $BRAF^{V600E}$/$PIK3CA^{H1047R}$/$CDKN2A^{Null}$ melanomas (right column) were treated with PI3'-kinase inhibitor (BKM-120) and $BRAF^{V600E}$-specific inhibitor (LGX-818) in combination. For BKM-120, a maximum concentration of 5μM was used (bottom row of wells) and serial 2-fold dilutions of agent were performed, with the top row of wells receiving no BKM-120 (DMSO control). For LGX-818, the maximal concentration was 10μM (right-most column of wells on each plate) and serial 2-fold dilutions of agent were performed with the left-most column of wells receiving no LGX-818. Cells were grown until the DMSO-only well (top left) was confluent, and then stained with crystal violet to visualize cell growth.

(B) Crystal violet staining shown in (A) was quantified and subjected to synergy analysis to calculate interaction indices, using the methods of Chou and Talalay (52). For each cell line, the fractional effect

of treatment with both agents was plotted against the interaction index. Interaction indices <1 indicate a synergistic effect. Error bars are SEM.

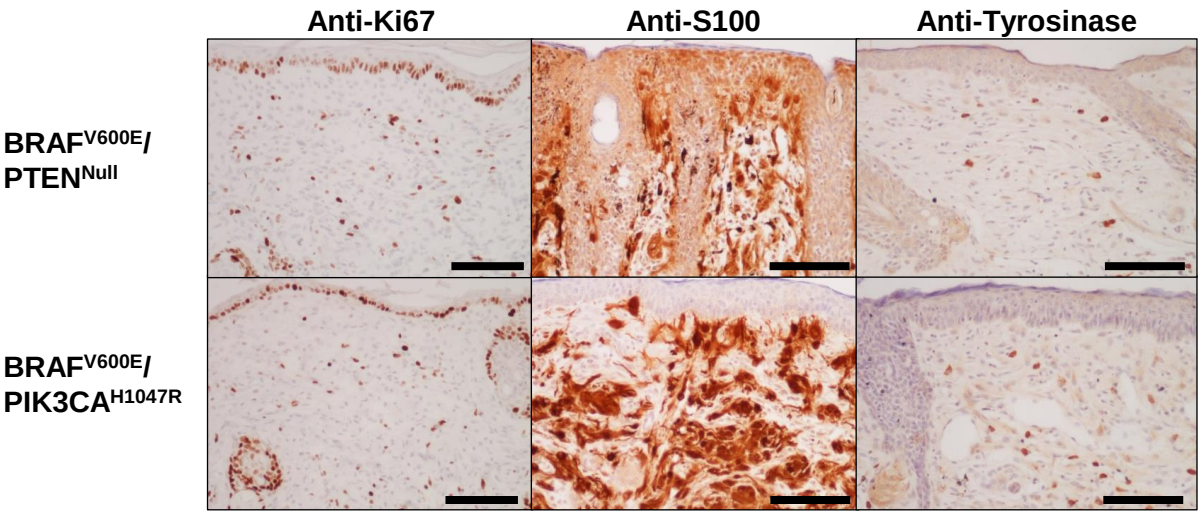
Supplementary Figure 5: Class I PI3'-kinase inhibition does not attenuate growth of autochthonous melanomas or melanoma cell xenografts, or confer increased survival when combined with $BRAF^{V600E}$-specific inhibitor

(A) $BRAF^{V600E}$/$PTEN^{Null}$ or (B) $BRAF^{V600E}$/$PIK3CA^{H1047R}$ melanoma growth was initiated as described. Established, measurable melanomas (~45-60 days after initiation), were treated with either vehicle control (**+VEH**) or with PI3'-kinase inhibitor BKM-120, (**+BKM**) ($BRAF^{V600E}$/$PTEN^{Null}$ + VEH, n=5; $BRAF^{V600E}$/$PTEN^{Null}$ + BKM, n=6; $BRAF^{V600E}$/$PIK3CA^{H1047R}$ + VEH, n=3; $BRAF^{V600E}$/$PIK3CA^{H1047R}$ + BKM, n=4). Melanoma growth was visually assessed. White dashed lines indicate the tumor borders; it should be noted that areas of pigmentation are not necessarily indicative of tumor size and in many cases the depth of the tumor is not readily apparent from the photographs.

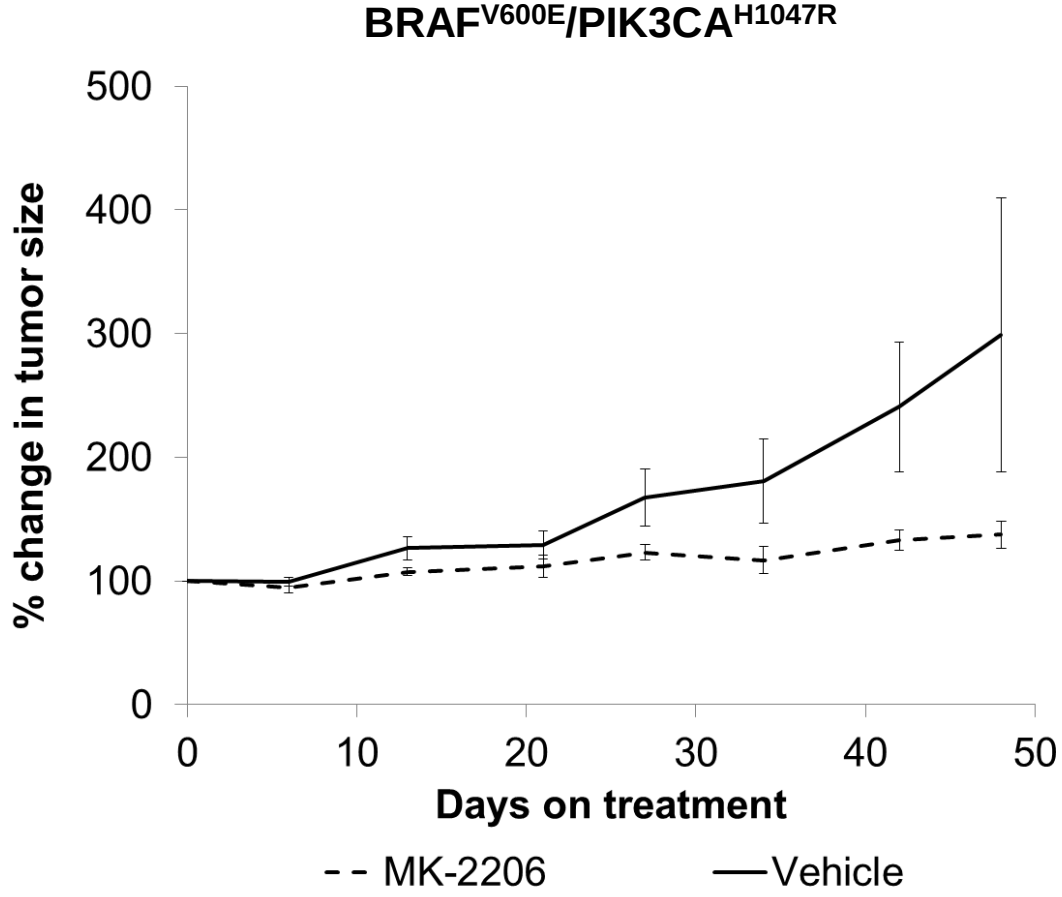
(C) 1205Lu cells were implanted subcutaneously in athymic nude mice ($2.5x10^6$ cells per flank). Once measurable, treatment with vehicle control (solid line) or BKM-120 (Dashed line) was commenced, and tumors measured biweekly over 21 days (displayed as percent change in tumor size ±SD).

(D) Tumor lysates were obtained from 1205Lu cell xenografts 2 hours after final treatment with either vehicle control (VEH) or BKM-120. Lysates were probed with the indicated antisera. Samples were run on the same gel but are non-contiguous.

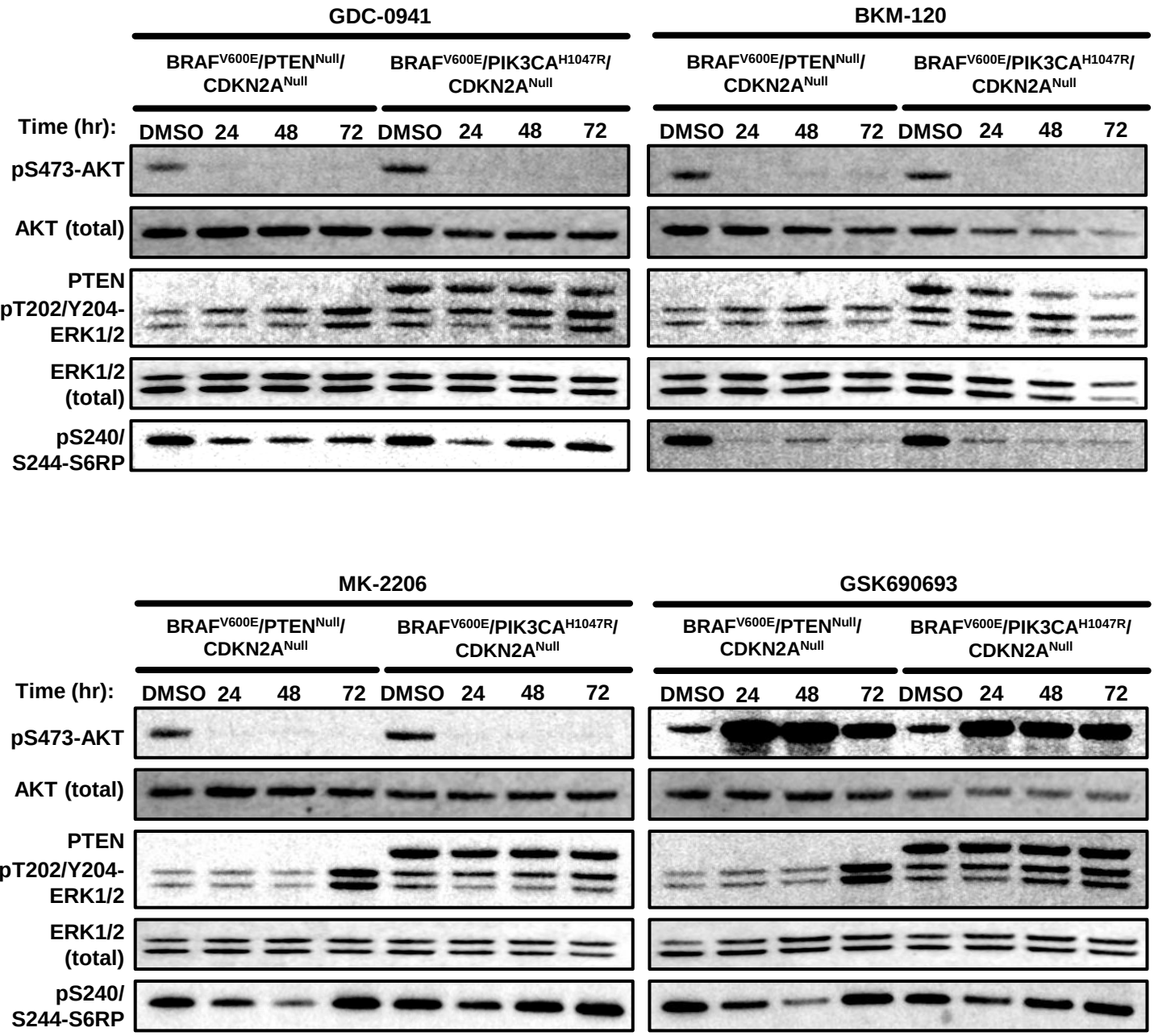
(E) Kaplan-Meier survival analysis of melanoma-bearing mice treated for 50 days with Vehicle (Solid line), BKM-120 alone (dotted line), single-agent LGX-818 (dashed line) or combination LGX-818 plus BKM-120 (dot-dashed line). Treatment was stopped after 50 days, and remaining mice were monitored and tumors measured until experimental endpoints were reached.



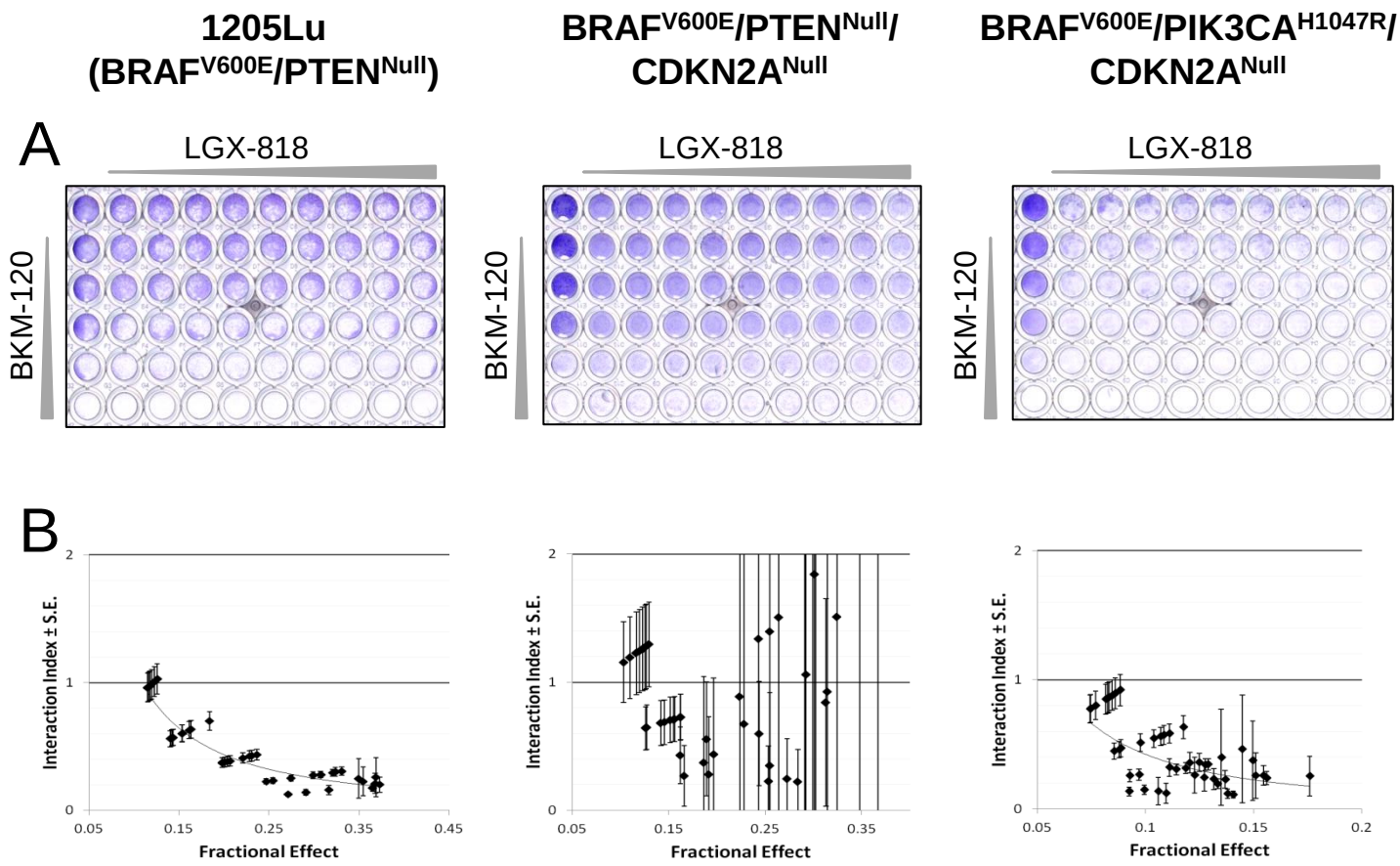
Supplementary Figure 1



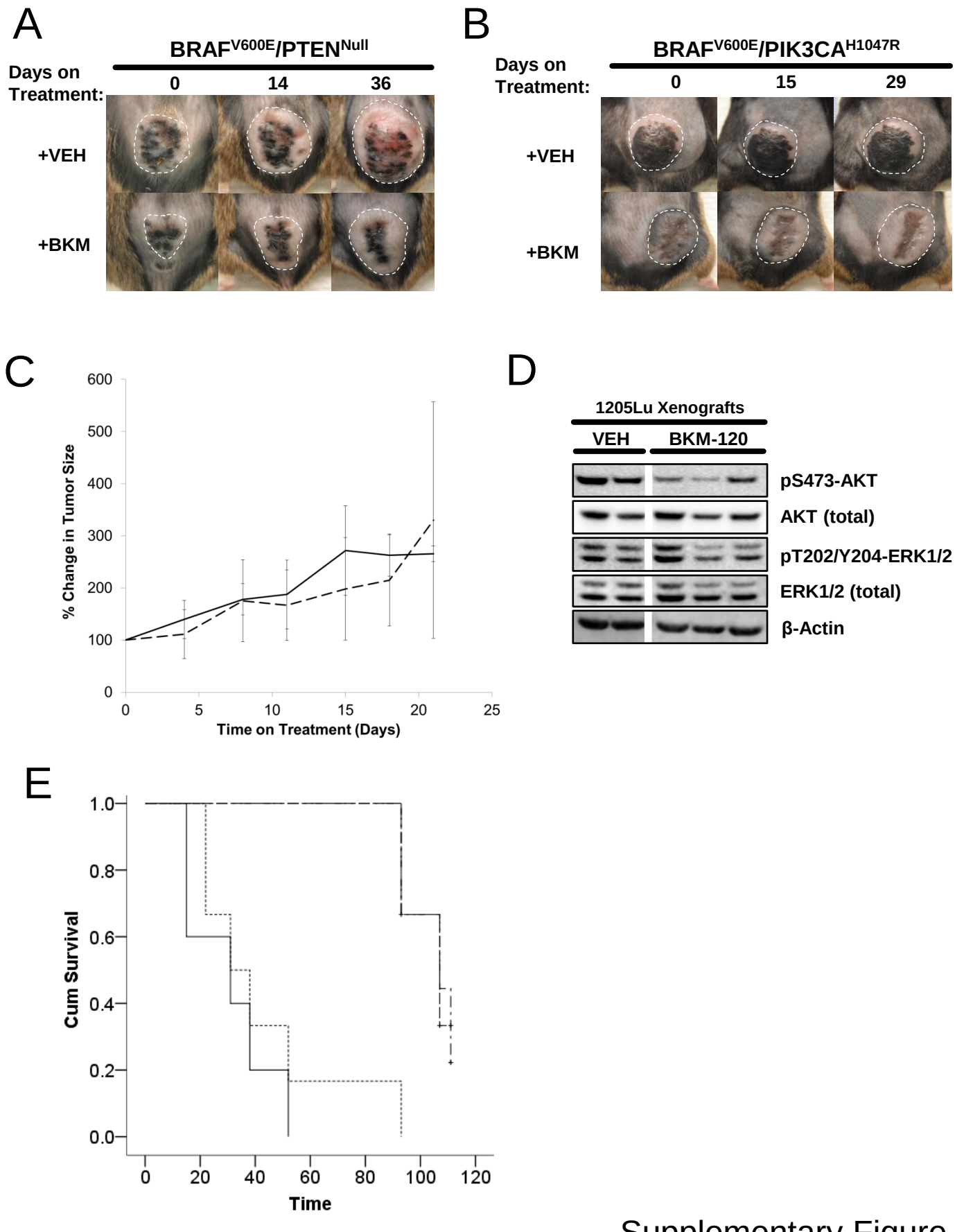
Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5