Supplementary Figure 1.

(A) Western blots showing pAMPK, AMPK, and pULK1 levels in vemurafenib-treated $BRAF^{V600wt}$ cancer cells. (B) Uptake of fluorescent glucose analog (2-NBDG) in YUKSI cells treated with DMSO (blue) or 1 μM vemurafenib (red). Data represent mean fluorescence intensity ± S.E.M. for 10^4 events; ****P< 0.0001 Mann-Whitney test.

Supplementary Figure 2.

(A) Fluorescence images showing GFP-LC3B labeled autophagosomes in YUKSI melanoma cells treated with DMSO, vemurafenib, AZD628 or AS703026 for 48 hrs. Inset shows identification of autophagosomes in green by image segmentation analysis. (B) Western blots showing LC3B and pERK1/2 levels in vemurafenib-treated $BRAF^{V600wt}$ cancer cells. (C) p62 and LC3B levels in $BRAF^{V600mut}$ melanoma cells treated with DMSO or vemurafenib for 48 hrs. (D) Fluorescence images showing co-localization of GFP-LC3B labeled autophagosomes with LAMP-1 (top), LAMP-2 (middle), or p62 (bottom) in YUKSI melanoma cells; scale bar 20 μm. (E) Fluorescence images showing GFP-LC3B labeled breast cancer cells, MCF7 and T47D, treated with DMSO or MEKi for 48 hr; scale bar 20 μm. (F) Western blots showing the kinetics of AMPK activation (as gauged by p-AMPK levels), and LC3B-II induction (examined on a 12% Bis-Tris gel) in YUKSI melanoma cells treated with 1 μM vemurafenib for indicated times.

Supplementary Figure 3.

(A) Western blots showing pAMPK and LC3B levels in AS703026 treated KRAS-mut NSCLC cells. (B) YUKSI and YUSIK $BRAF^{V600mut}$ melanoma cells treated with DMSO or 1 μM vemurafenib for 48 hrs were stained with propidium iodide, and analyzed by flow cytometry for cell cycle profiles. (C) Western blot showing levels of pro- and cleaved caspase-3 in YUKSI cells treated with DMSO, vemurafenib or staurosporine (+Cntrl). (D) Western blots showing levels of different ER stress markers (BIP, ATF4 and PERK) in YUKSI cells treated with DMSO, vemurafenib, or thapsigargin (+Cntrl). Thapsigargin activates ER stress as seen by increased expression of BIP and ATF4, and phosphorylation of PERK as seen by mobility shift on SDS-PAGE.

Supplementary Figure 4.

(A) Dose-response curves showing sensitivity to vemurafenib in the absence (blue) or presence of chloroquine (red) or bafilomycin (green). (B) YUKSI melanoma cells expressing shCntrl or shATG5 hairpins were treated with or without vemurafenib. Levels of LC3B, p62 and ATG5 are shown. (C) Dose-response curves for vemurafenib treatment of shCntrl and shATG5 cells. (D) p62 autophagic flux in YUKSI melanoma cells expressing shCntrl, shATG5 or shATG7. (E) Dose-response curves for vemurafenib treatment of shCntrl and shATG7 cells. (F) Data represent average cell viability $\pm$ S.E.M. for DMSO or vemurafenib-treated shCntrl and shATG7 cells. (G) YUSIK melanoma cells were treated with DMSO or vemurafenib, alone or in combination with CQ for 72 hrs. Surviving cells were imaged (left) and quantified (right). Data represent mean $\pm$ S.E.M. across 4 different fields of view.

*$P<0.05$; ****$P<$ 0.0001.

Supplementary Figure 5.

(A) Dose-response curves showing sensitivities of $BRAF^{V600wt}$ YUSIV melanoma cells to vemurafenib (black) and other Ras pathway inhibitors (red); AZD628, AS703026 and AZD6244. (B) YUSIV cells were treated with 1mM AICAR or DMSO for 48 hrs. Left- Western blots showing pAMPK and pULK1 levels; Right- Fluorescence images showing GFP-LC3B labeled autophagosomes. (C) YUSIV cells were treated with 10 nM AS703026 with or without 1mM AICAR ± CQ for 72 hrs. Data shows average cell number ± S.E.M across 4 different fields of view; ***P<0.001, *ns* is not significant. (D) Phase-contrast images showing YUGEN8 $BRAF^{V600mut}$ melanoma cells treated with 1 μM vemurafenib with or without 1mM AICAR for 72 hrs. Data shows average cell count ± S.E.M. for surviving cells from 4 different fields; *** p-value <0.001. (E) pAMPK levels in YUGEN8 cells treated with 1 μM vemurafenib with or without 1mM AICAR for 24 hrs.

Supplementary Figure 6.

(A) Left- Hematoxylin and & eosin stained tumor sections showing regions of necrosis {N}, marked by reduced tissue staining and patches of destroyed tumor architecture, Right- Data represent percentage of necrotic tissue in the different conditions. (B) Left- Images of representative tumors of YUKSI-shCntrl and YUKSI-shATG5 (*hairpin 1)* treated with vemurafenib; scale bar 5 mm, Right- quantification of mean tumor volume and tumor weight ± S.E.M. (n=5 mice per treatment group; **P<0.01 Mann-Whitney test. (C) Heterogeneous YUKSI tumors formed by co-injecting shCntrl (GFP+) cells with

shATG5 (GFP-) cells were treated with vehicle or vemurafenib as indicated. Data represent GFP-negative and GFP-positive tumor fractions in vehicle- vs vemurafenib-treatment; $^{**}P<0.01$. (D) YUSIK $BRAF^{V600mut}$ melanoma cells were injected into mice and allowed to form palpable tumors (4-5 mm). Mice were then treated for 2.5 weeks, daily, with vemurafenib and CQ, singly or in combination, or with a vehicle control. Data shows tumor progression across indicated time interval (each point represents an average of at least 8 tumors); $^{*}P<0.05$ Mann-Whitney test.