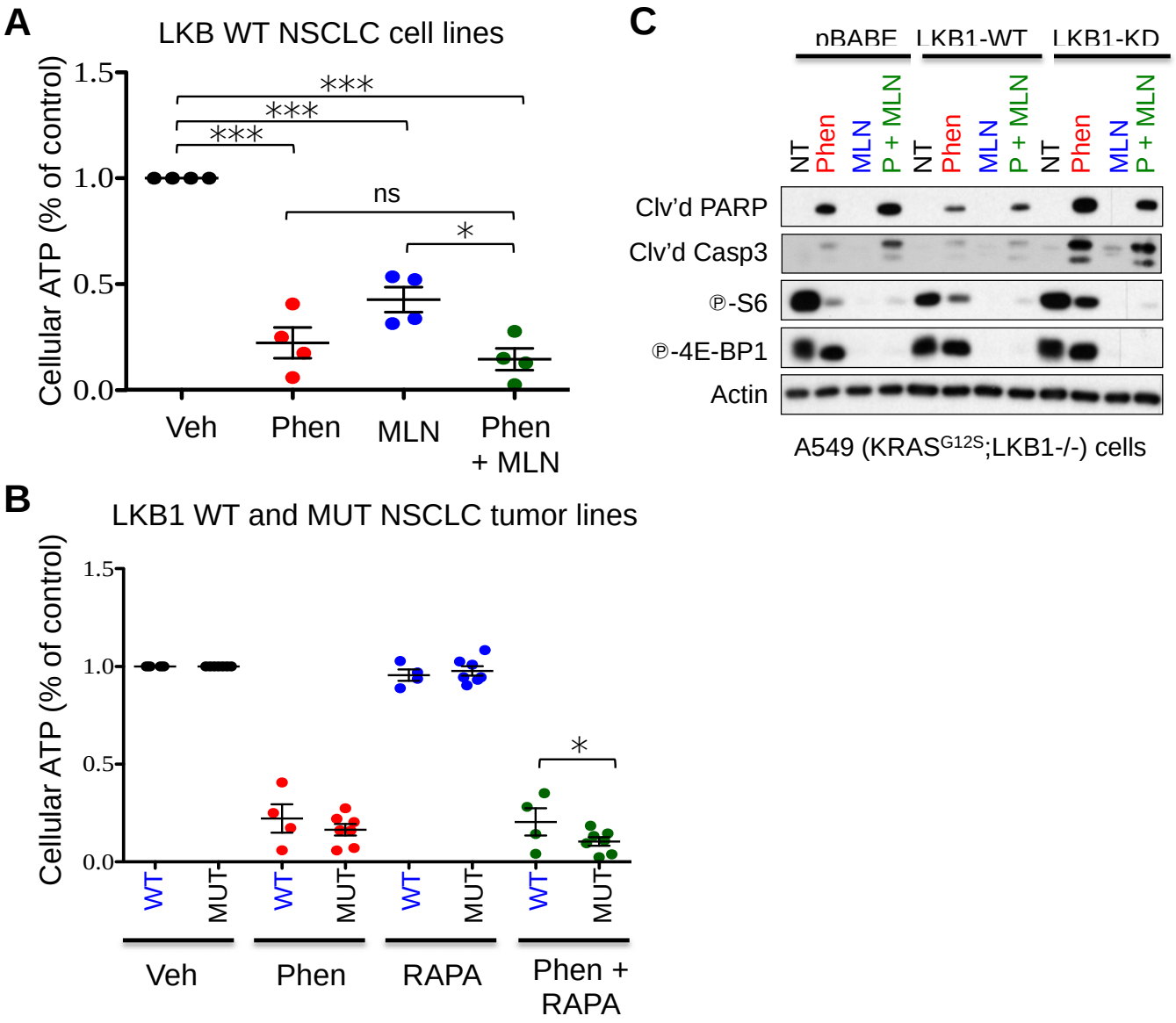
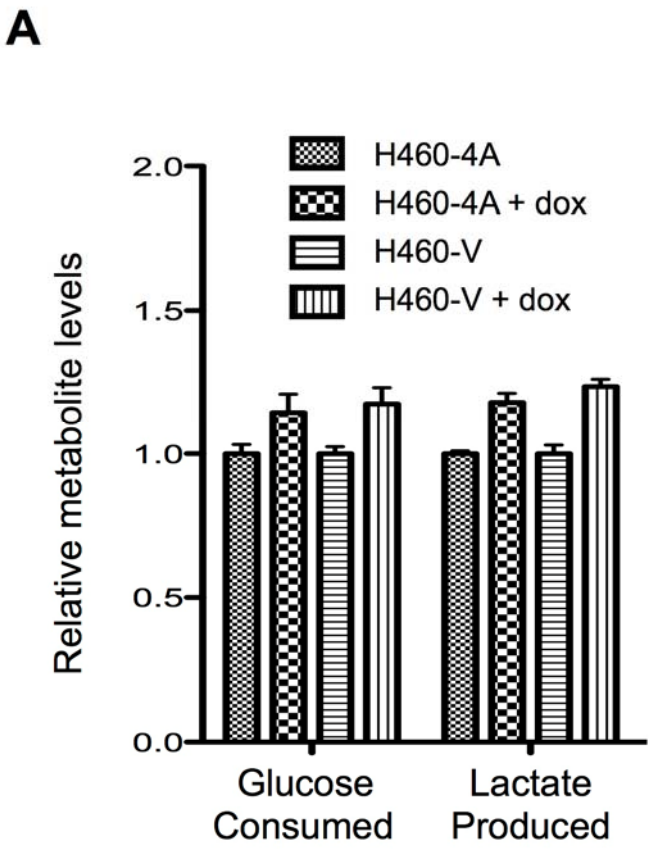
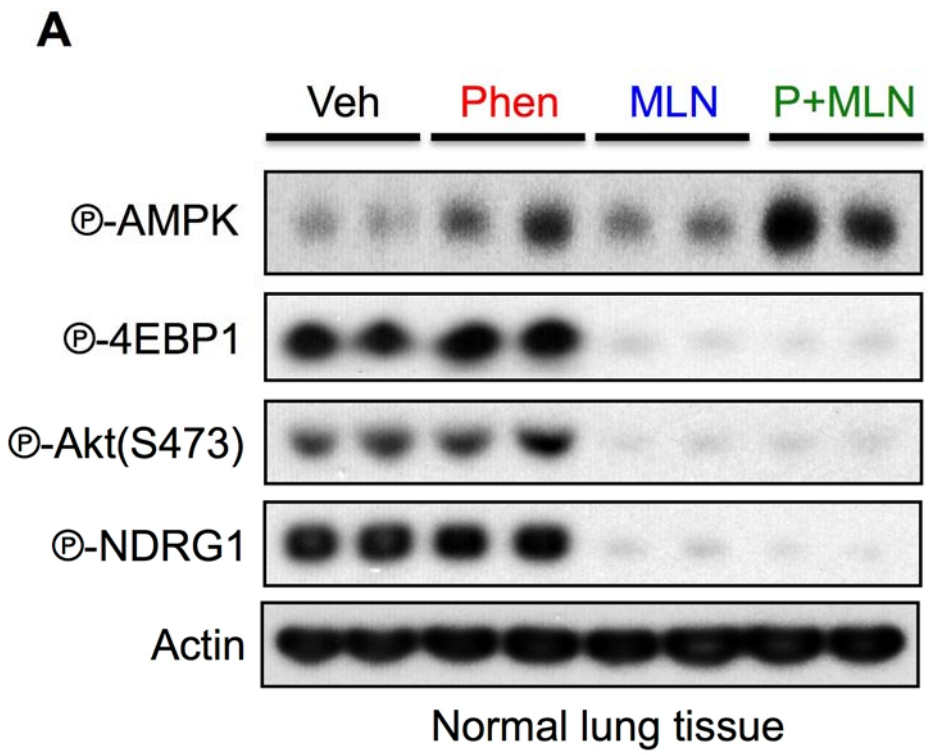
Supplemental Figures



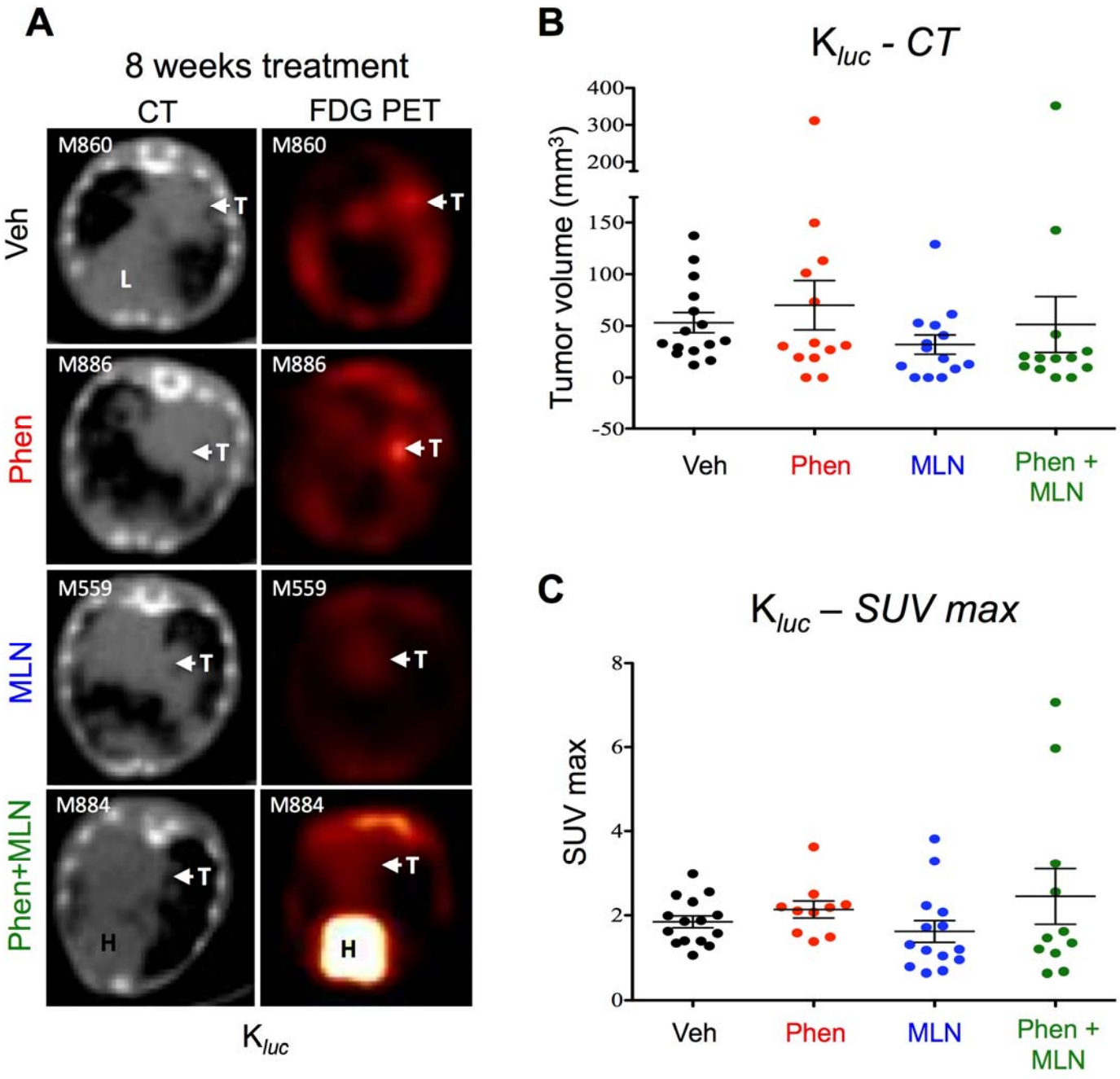
Supplementary Figure 1: **Treatment of LKB1 mutant and LKB1 wildtype NSCLC lines with phenformin, MLN0128 or combination leads to loss of cellular ATP.** (A) Cellular ATP measurement of LKB1 wildtype NSCLC tumor lines H441, SW900, H1703, and H226 (n= 4). (B) Cellular ATP measurement of $KRAS^{MUT}$ and $KRAS/LKB1^{MUT}$ tumor cell lines as described above and in figure 1. $KRAS^{MUT}$ and $KRAS/LKB1^{MUT}$ tumor cell lines (A549, H596, H838, RH2, HeLa, H460, H441, SW900, H1703, and H226) were treated with DMSO (NT), phenformin (2mM), rapamycin (50nM) or phenformin + rapamycin for 24 hours and were analyzed by cell titer glo. (C) Immunoblot analysis of A549 cells expressing pBABE vector (B), wildtype LKB1 (WT) or kinase dead LKB1 (KD) that were treated with DMSO (NT), phenformin (2mM), MLN0128 (2μM) or phenformin + MLN0128 for 24 hours. Immunoblots were probed with the indicated antibodies.



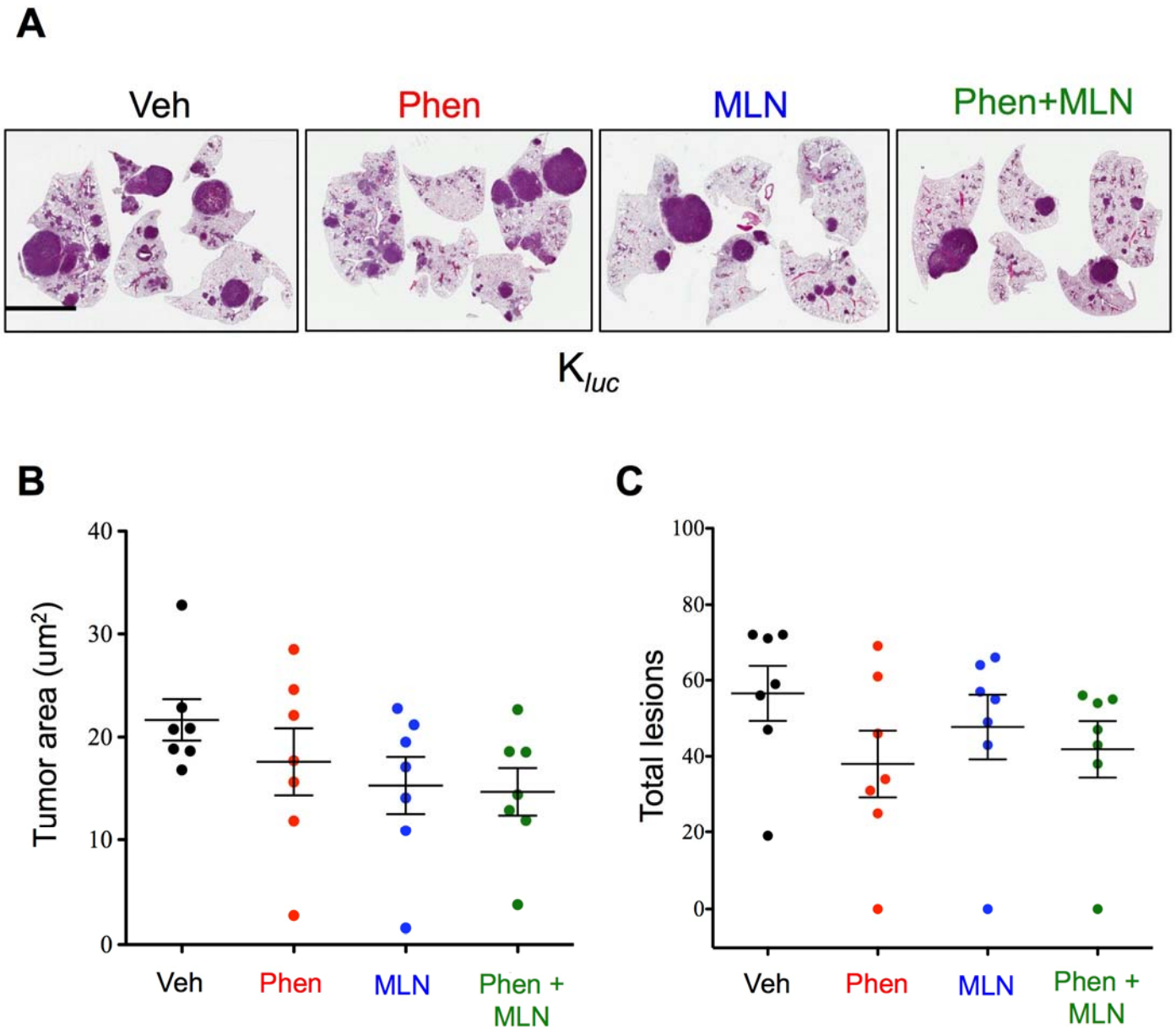
Supplementary Figure 2: **Metabolite analysis of NSCLC human cell line expressing dox inducible 4E-BP1 4Ala protein and control vector.** (A) Relative levels of glucose consumption and lactate production in H460-V and H460-4A cells untreated or treated with dox for three days.



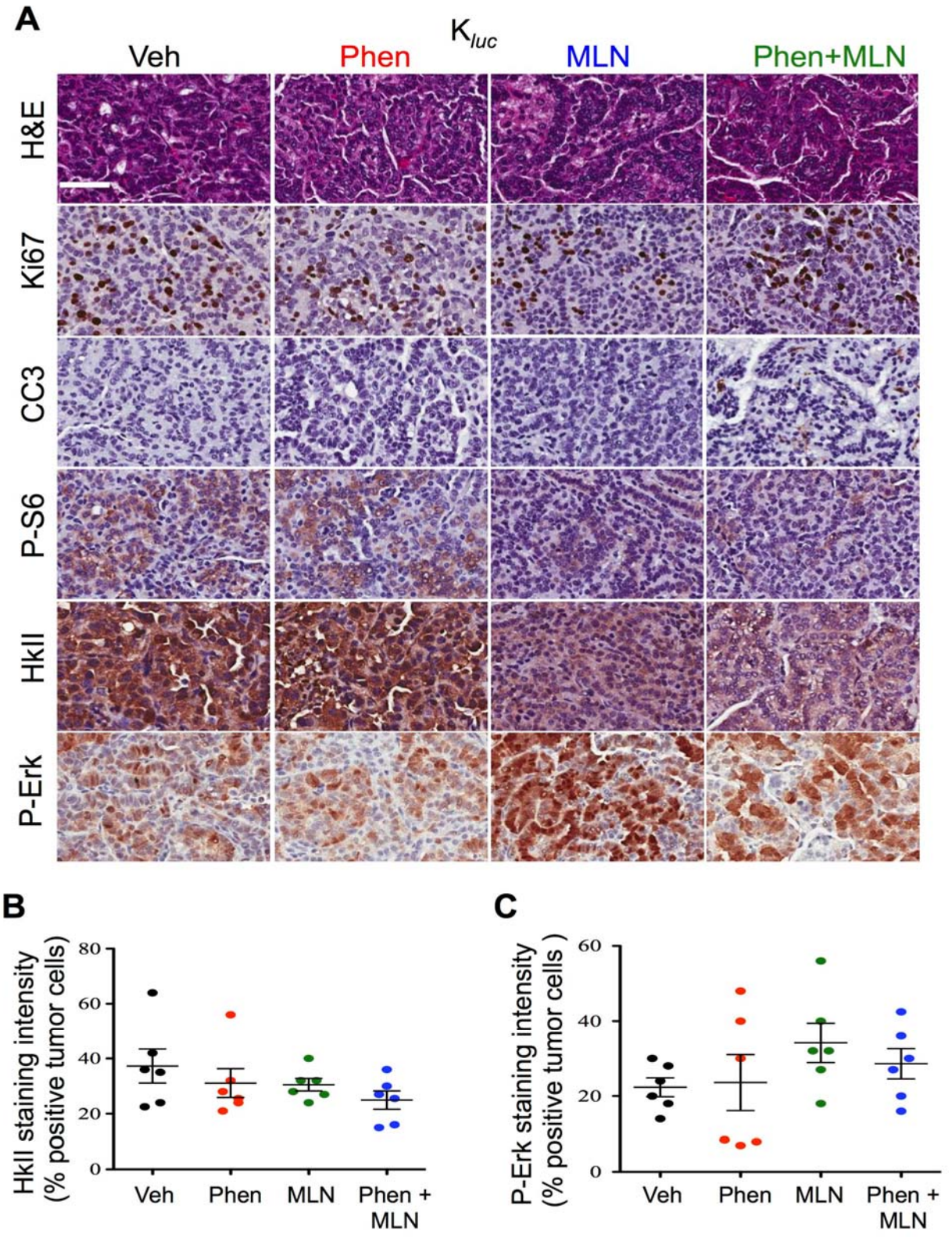
Supplementary Figure 3: **Biomarker analysis of normal lung tissue in response to drug treatments.** (A) Normal lung tissue lysates from FVB mice treated with vehicle (PEG/NMP), Phenformin (1.8mg/mL ad lib), MLN0128 (1.0mg/kg/q.d. by i.p. injections) or MLN0128 + Phenformin for three weeks. Immunoblots were probed for the indicated antibodies.



Supplementary Figure 4: **Treatment of K_{luc} mice with phenformin, MLN0128 or combination does not result in therapeutic benefit.** (A) 18F-FDG-PET and CT images of K_{luc} mice at 8 weeks post treatment with vehicle, phenformin, MLN0128 or phenformin + MLN0128. (B) Quantitative measure of tumor volume by CT of K_{luc} mice at 8 weeks post treatment. **(**C) Quantitative measure of SUVmax by 18F-FDG PET of K_{luc} mice at 8 weeks post treatment. There was not statistical significance detected for S4B or S4C. Statistical significance (p-values: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001) was calculated using a non-parametric one-way ANOVA (Tukey test). The data are represented as the mean ± SEM. Error bars represent the ± S.E.M.

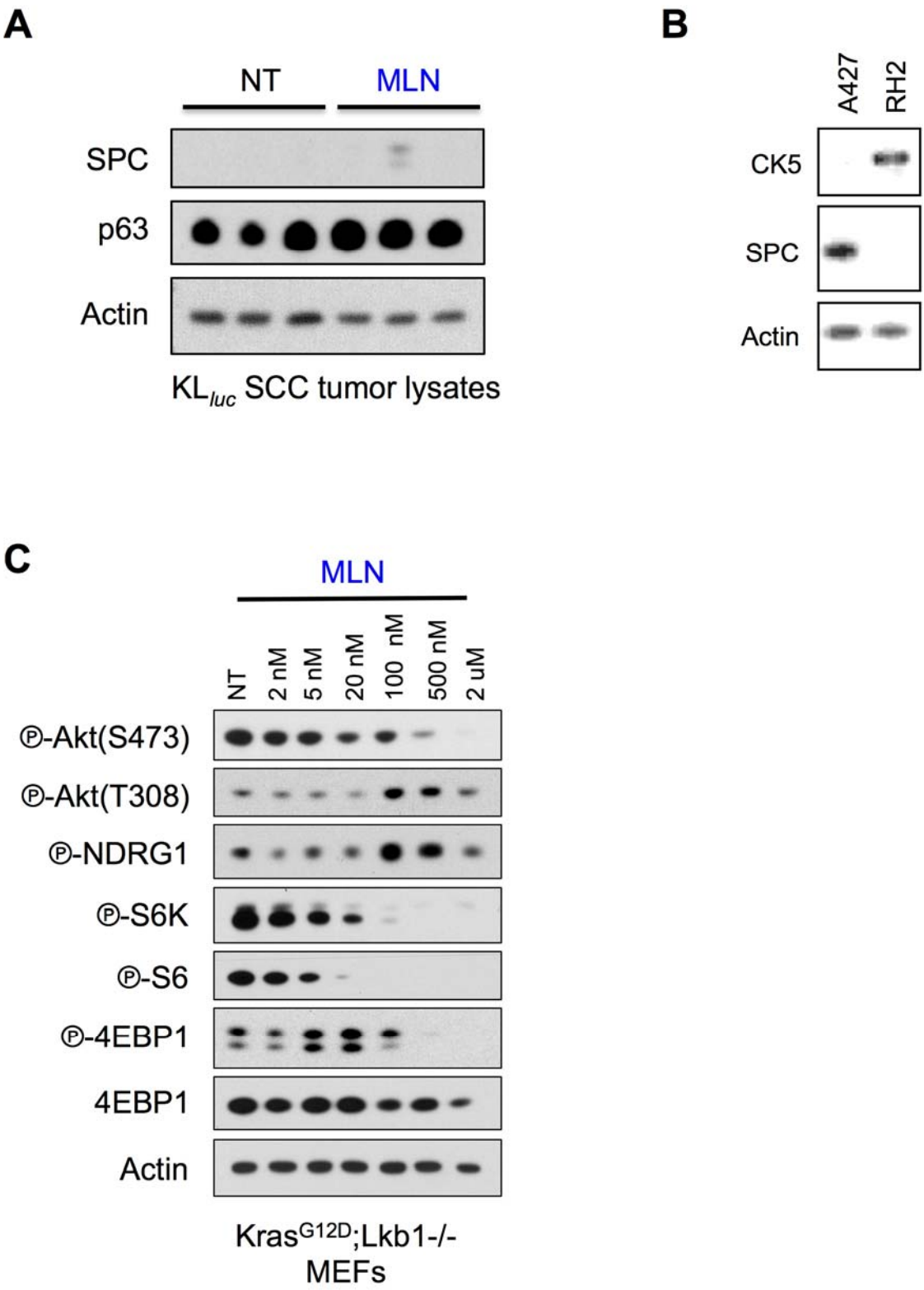


Supplementary Figure 5: **Tumor burden does not decrease in response to phenformin, MLN0128 or combination therapy in K_{luc} mice.** (A) Representative H&E images of K_{luc} whole lungs following 8 weeks treatment with vehicle, phenformin, MLN128 or phenformin + MLN0128 combination therapy. Scale bars (black) = 4mm. (B) Quantitative histology analysis of lung tumor area from H&E stained whole lung sections of K_{luc} mice using morphometric analysis software. (C) Total lesion counts in whole lung sections of K_{luc} mice. Statistical significance (p-values: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001) calculated using a non-parametric one-way ANOVA (Tukey test). The data are represented as the mean ± SEM. Error bars represent the ± S.E.M.



Supplementary Figure 6: **Biomarker analysis in tumors treated with phenformin, MLN0128 or combination.** (A) Immunohistochemical analysis of lung tumors from K_{luc} mice following 8 weeks of treatment. Whole lung sections were stained with H&E or the indicated antibodies: Ki67, cleaved caspase 3 (CC3), P-S6, HkII or P-Erk. Scale bars (white) = 50μM. (B and C) Quantitative IHC analysis of whole lung sections from K_{luc} mice stained with (B) HkII and (C) P-Erk. Statistical significance (p-values: * < 0.05; ** < 0.01; *** < 0.001) calculated using a non-parametric one-way

ANOVA (Tukey test). The data are represented as the mean ± SEM. Error bars represent the ± S.E.M..



Supplementary Figure 7: **Biomarker analysis of mouse tumors lysates, human NSCLC cell lines and mouse embryonic fibroblasts.** (A) Immunoblots of KL$_{luc}$ SCC mouse lung tumor lysates described in Figure 7 and probed with the indicated antibodies. Surfactant protein c (Spc) is a marker of adenocarcinoma and p63 is a marker of squamous cell carcinoma. (B) Immunoblots of A427 and RH2 cells probed for cytokeratin 5 (CK5) a squamous cell marker and SPC. (C) Immunoblots of

whole cell lysates from Kras G12D;Lkb1-/- mouse embryonic fibroblasts treated with increasing concentrations of MLN0128 for 72hr. Immonoblots were probed with indicated antibodies.