**Supplementary Figure legends**

**Supplementary Figure 1. Analysis of CRISPR/CAS9-mediated editing of *Rbms3* in lung tumors initiated in *BC* mice.**

**A:** PCR of *Rbms3* genomic locus is 850 bp, and contains each sgRNA used against the mouse *Rbms3* gene. Digestion of wild-type or mutant duplexed DNA with Surveyor enzyme reveals *Rbms3* locus results in mismatch cleavage fragments below the 850 bp band in lane 10, indicating CRISPR/CAS9-mediated cuts of large tumor DNA. L represents ladder. Numbers represent lanes. C is technical control (lane 1), S represents addition of Surveyor enzyme (lane 2), N is negative control (lane 11) , P is positive or Wild-type *Rbms3* gDNA (lanes 3 and 4), sgRbms3 tumor gDNA (lanes 5-8) and D represents wild-type and sgRbms3 tumor gDNA duplexed with the Surveyor enzyme.

**B**: qRT-PCR indicates significantly lower *Rbms3* mRNA expression in 4 of 6 tumors excised from lung sections of *BC* mice initiated with sgRbms3 virus compared to those initiated with sgNT virus. Mean is graphed, with SEM error bars. Statistical test is a paired T-test. \* = p < 0.05; \*\*= p < 0.01 ; \*\*\*\* = p < 0.0001.

**Supplementary Figure 2. Histological analyses of the grade of lung tumors in *BC* mice either with or without *Rbms3* editing.**

**A-I:** Images of formalin-fixed paraffin-embedded (FFPE) sections of mouse lungs stained with hematoxylin and eosin (H&E).

**A-B:** Tumor bearing lungs from BCmice initiated with sgNT-CRE virus harvested at 13 weeks post-initiation at 40x (**A**) or 400X (**B**) magnification. Shown are typical BRAFV600E-driven benign papillary adenomas with well-circumscribed borders.

**C-D:** Tumor bearing lungs from BCmice 13 weeks post-initiation with sgRbms3-CRE virus harvested at 13 weeks post initiation at 40x (**C**) or 400X (**D**) magnification. Blue arrows indicate micropapillary tufts.

**E-F:** Largest tumor bearing lungs from *BC* mice at 13 weeks post-initiation with sgRbms3-CRE virus harvested at 13 weeks and imaged at 40x (**E**) or 400X (**F**) magnification. Shown here are higher grade adenocarcinoma in a larger tumor with blue arrows indicating complex papillary and micropapillary architecture. The large tumor shown here was validated to have edited *Rbms3* at the DNA and RNA level in Supplemental Figure 2. Scale bars are shown in black in the bottom left corner and are 200 microns (**A**, **C**, **E**) and 20 microns (**B**, **D**, **F**), respectively.

**Supplementary Figure 3. EGFRL858R combined with RBMS3 loss leads to diffuse replacement of lung parenchyma with well-differentiated adenocarcinoma.**

**A-F:** Images of formalin-fixed paraffin-embedded (FFPE) sections of mouse lungs stained with hematoxylin and eosin (H&E).

**A-B:** Tumor bearing lungs from *SPC::CRE-ERT2/+; Rosa26CAGs-LSL-rTTa3;EGFRL858R; H11LSL-CAS9*(*SREC*) mice initiated with sgNT-CRE virus harvested at 11 weeks post-initiation and imaged at 20x (**A**) or 400X (**B**) magnification.

**C-F**: Tumor bearing lungs from *SREC*mice initiated with sgRbms3-CRE virus harvested at 11 weeks post-initiation and imaged at 20x (**C&E**) or 400x (**D&F**) magnification. Representative H&E stained sections of mouse lungs. Left column = 20x magnification, scale bar 500um. Right column = 400x magnification, scale bar 20um.

**G-L**: Representative images of immunohistochemistry on FFPE lung tissue sections from *SREC* mice initiated with either sgNT- or sgRbms3-CRE and then stained to detect expression of Pro-SPC, NKX2.1/TTF-1, or b-Catenin (20x magnification). Scale bar shown in black at the bottom left corner of each image represent 50 microns.

**Supplementary Figure 4. Lung tumors in BC mice, with and without *Rbms3* editing, retain alveolar identity after pathway-targeted inhibition of BRAFV600E or WNT signaling.**

**A-F**: Representative images of Pro-SPC immunohistochemistry in fixed tissue sections of *BC*mice initiated with sgNT-CRE or sgRbms3, treated with: 1. Vehicle; 2. Dabrafenib + Trametinib or D+T, or LGK974 imaged at 20x magnification.

**G-L**: Representative images of immunohistochemical staining for NKX2.1 expression in lung tumors in *BC*mice initiated with sgNT-CRE or sgRbms3, that were treated with vehicle, D+T, or LGK974 at 20x magnifications.

**M-R**: Representative images of immunohistochemical staining for b-Catenin expression in *BC*mice initiated with sgNT-CRE or sgRbms3, treated with vehicle, D+T, or LGK974 at 20x magnifications.

Scale bars are indicated in the bottom left corner of each image.

**Supplementary Figure 5. *RBMS3* is lost frequently in human non-small cell lung cancer patients.**

**A:** Schematic depicting genes located on human chromosome 3p24.1 (not drawn to scale).

**B:**  Quantification of cBioportal analyses of TCGA human lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) patients with identified relative copy number alteration frequences of chromosome 3p either by gain (pink) or deletion (blue) .

**C&D:** Copy number alteration heat mapdepicting chromosome3 gain (blue) or loss (red) (respectively) on both 3p and 3q in **(C)** lung adenocarcinoma (LUAD) or **(D)** lung squamous cell carcinoma (LUSC) patients, respectively. Each row corresponds to a patient.

**E:** Kaplan-Meier survival curve of patient cohorts that either do (orange) or do not (blue) have deletion of chromosome 3p. Deletion was defined to be a copy number threshold of -1 within cBioPortal data.

**(F)** Pie chart with 650 patients from TCGA analyses (n=650) broken down by known oncogenic driver.