

Supplemental Materials:

**A Coding Single Nucleotide Polymorphism in Lysine Demethylase KDM4A Increases
Sensitivity to mTOR Inhibitors**

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FIGURE LEGENDS

Supplementary Figure 1. *KDM4A* SNP-A482 (rs586339) correlates with worse outcome in NSCLC patients. (A) Genotypic frequency of *KDM4A* SNP-A482 in NSCLC and non-NSCLC patients. (B-F) Survival curves plotted based on genotype: wild type (WT) and heterozygous (HET) versus homozygous SNP-A482 (SNP-A482). X axis is the months since diagnosis of NSCLC. Y axis is the probability of survival. (B) Patients with late onset stage 3 cancers. (C) Patients under 64 years of age. (D) Patients with an Adenocarcinoma. (E) Treatment with radiation. (F) Treatment by surgery. (G) Summary of measure of time dependent area under the curve (AUC) for SNP-A482 and clinical information (age, sex, smoking status) or clinical information only, on five subgroups of NSCLC patients.

Supplementary Figure 2. *KDM4A* SNP-A482 associates with increased cellular sensitivity to drugs targeting the mTOR pathway. (A) Relative sensitivity of each lung cancer cell line used in the drug screen to mTOR inhibiting compounds. The genotypic frequency is shown for the cell lines. Cells that are WT are indicated in gray, while heterozygous cells are indicated in blue and homozygous SNP-A482 are indicated in red. In the heat map, green indicates most sensitive and red indicates most resistant. (B) Schematic of the mTOR pathway. The red parentheses indicate the drug targets for which homozygote *KDM4A* SNP-A482 lung cell lines present increased sensitivity, compared to the wild type and heterozygote genotypes (drugs are listed in Figure 3B). (C) Schematic of human *KDM4A* gene indicating the SNPs evaluated in this study: rs586339 (SNP-A482), rs517191 (non-coding SNP1: ncSNP 1) and rs6429632 (non-coding SNP2: ncSNP 2). (D) Stratification for late stage NSCLC patients for *KDM4A* SNPs rs6429632, rs586339 (SNP-A482) and rs517191. The table reports the p value of the significance of association with outcome for each parameter. (E) Comparison of the homozygous SNP status to that of mTOR chemotherapeutic sensitivity. Seventy-five NSCLC

cell lines and 87 compounds were used for these analyses. Green blocks represent increased sensitivity and orange blocks represent increased resistance to each drug.

Supplementary Figure 3. Rapamycin treatment reduces KDM4A protein levels. (A)

Rapamycin causes a selective decrease of SNP-A482 levels versus WT KDM4A. LU99B (KDM4A homozygote WT) and H290 (KDM4A homozygote SNP-A482) cell lines were treated with 100ng/ml of Rapamycin for the indicated period of time. The Y axis represents the ratio of KDM4A relative to time 0, which was normalized to β -actin. The average of three independent experiments is shown. (B) HEK 293T cells transiently overexpressing GFP-WT or GFP-SNP-A482 were treated with 100ng/ml of Rapamycin for the indicated period of time. The Y axis represents the ratio of GFP-KDM4A relative to time 0, which was normalized to β -actin. The average of three independent experiments is shown. (C-D) Western blot representing the knock-down efficiency of the cells used in Figure 4F (C) and Figure 4G (D). All error bars represent the SEM. p values represent two-way ANOVA (significance for overall difference).

Supplementary Table 1. *KDM4A* SNP-A482 associates with cellular sensitivity to drugs targeting the mTOR pathway.

Table summarizes the lung cancer cell line genotypes for *KDM4A* SNP-A482 (WT = homozygote for the major allele, SNP = homozygote for the minor allele, HET = heterozygote), the drugs and concentrations used, the drug sensitivity for each cell line and the statistical tests.

Supplementary Table 2. Lung cell lines homozygotes for *KDM4A* SNP-A482 are not enriched for mutations that could be linked to sensitivity to PI3K/mTOR inhibitors.

Table summarizes the available mutational data for the lung cell lines used in the study.

Supplementary Table 3. List of drugs and primary targets used for the study.