Supplementary Figure 1. *EZH2* and MEK-ERK and PI3K/AKT signaling pathway expression in lung adenocarcinoma and HBEC cell lines KRAS wild-type and with different amino acid substitutions in codon 12 KRAS mutants. A, we analyzed a panel of eight lung adenocarcinoma and HBEC cell lines by examining their expression of EZH2, phospho-MEK1/2, MEK1/2, phospho-AKT, AKT, phospho-EZH2, phospho-STAT3 and STAT3 using Western blotting.

Supplementary Figure 2. Sensitivity in vitro to AZD6244 and MK2206 was significantly increased in the presence of highly selective EZH2 inhibitor GSK343, EPZ6438 and GSK126 in NSCLC cells expressing mutant $KRAS^{G12C}$ and $KRAS^{G12D}$, respectively. A, Top, pharmacologic inhibition of EZH2 by treatment with GSK343 decreased slightly the viability of the lung adenocarcinoma cell lines expressing $KRAS^{WT}$ and strongly in $KRAS^{G12C}$ exposed to MEK1 inhibitor AZD6244 according to an MTS assay (data are graphed as the mean percent increase ± percent standard deviation). Treatment with GSK343 caused a 1.9-fold ($P < 0.05$) decrease in the AZD6244 IC50 in H1993 cells expressing $KRAS^{WT}$, and 4.7-fold ($P < 0.03$) decrease in it in H23 cells expressing $KRAS^{G12C}$. Bottom, pharmacologic inhibition of EZH2 by treatment with GSK343 decreased slightly the viability of the lung adenocarcinoma cell lines expressing $KRAS^{WT}$ and strongly in $KRAS^{G12D}$ exposed to AKT inhibitor MK2206 according to an MTS assay. (data are graphed as the mean percent increase ± percent standard deviation). Treatment with GSK343 caused a 2.5-fold ($P < 0.05$) decrease in the MK2206 IC50 in H1993 cells expressing $KRAS^{WT}$, and a 4.4-fold ($P < 0.05$) decrease in

it in HCC461 cells expressing $KRAS^{G12D}$. B, Treatment with EPZ6438 and GSK126 caused a 13-fold and 10-fold, respectively ($P < 0.0001$) decrease in the AZD6244 IC50 in H1993 cells expressing $KRAS^{WT}$, and 15-fold and 63-fold, respectively ($P < 0.0001$) decrease in it in H23 cells expressing $KRAS^{G12C}$, and 13-fold and 14-fold, respectively ($P < 0.0001$) decrease in it in H461 cells expressing $KRAS^{G12D}$. Bottom, Treatment with EPZ6438 and GSK126 caused a 2.5-fold and 6.6-fold, respectively ($P < 0.0001$) decrease in the MK2206 IC50 in H1993 cells expressing $KRAS^{WT}$, and 14-fold and 6.7-fold, respectively ($P < 0.0001$) decrease in it in H23 cells expressing $KRAS^{G12C}$, and 4-fold and 17-fold, respectively ($P < 0.0001$) decrease in it in H461 cells expressing $KRAS^{G12D}$.