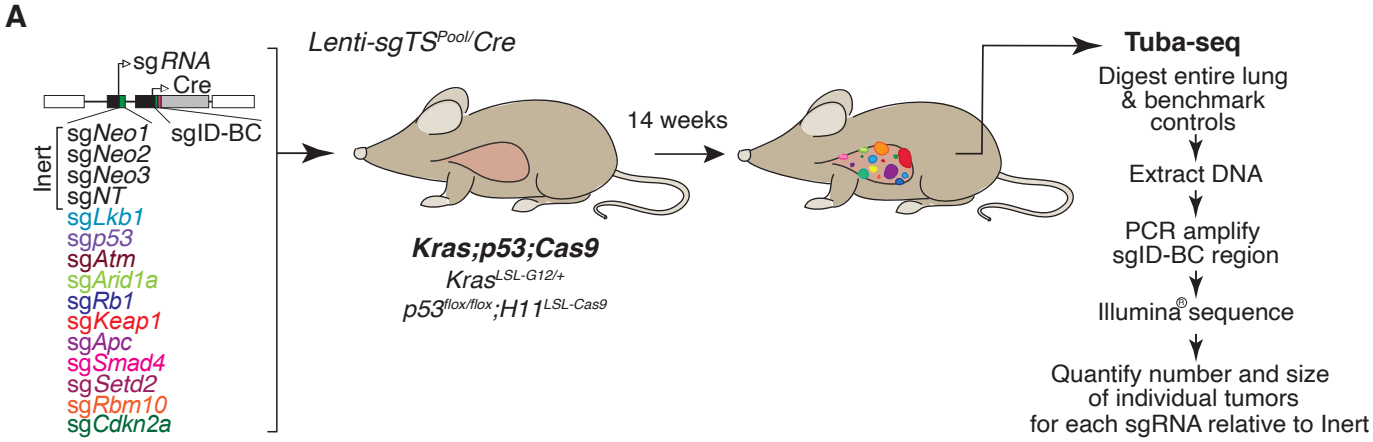
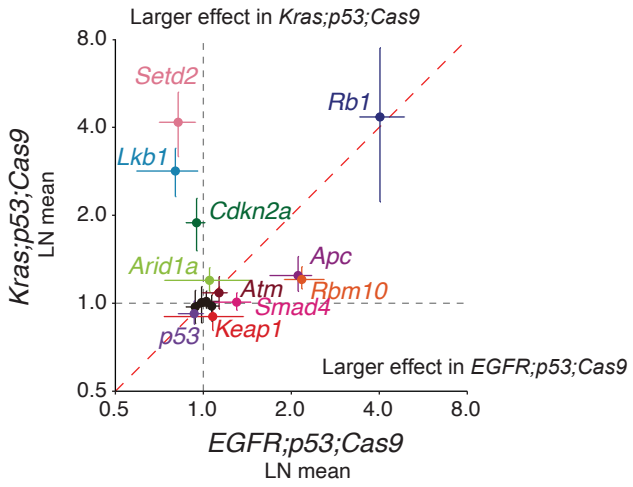
**A**




**B**




**C**

*LKB1*

| | wt | mut | |
|---|---|---|---|
| *EGFR*$^{onc}$ | 542 | 8 | 1.5% |
| *KRAS*$^{onc}$ | 1436 | 319 | 18.2% |

Odds ratio = 15.05
*P* = 1.7x10$^{-30}$

*RBM10*

| | wt | mut | |
|---|---|---|---|
| *EGFR*$^{onc}$ | 250 | 33 | 11.7% |
| *KRAS*$^{onc}$ | 621 | 81 | 11.5% |

Odds ratio = 0.99
*P* = 1.00

*SETD2*

| | wt | mut | |
|---|---|---|---|
| *EGFR*$^{onc}$ | 390 | 13 | 3.2% |
| *KRAS*$^{onc}$ | 1148 | 75 | 6.1% |

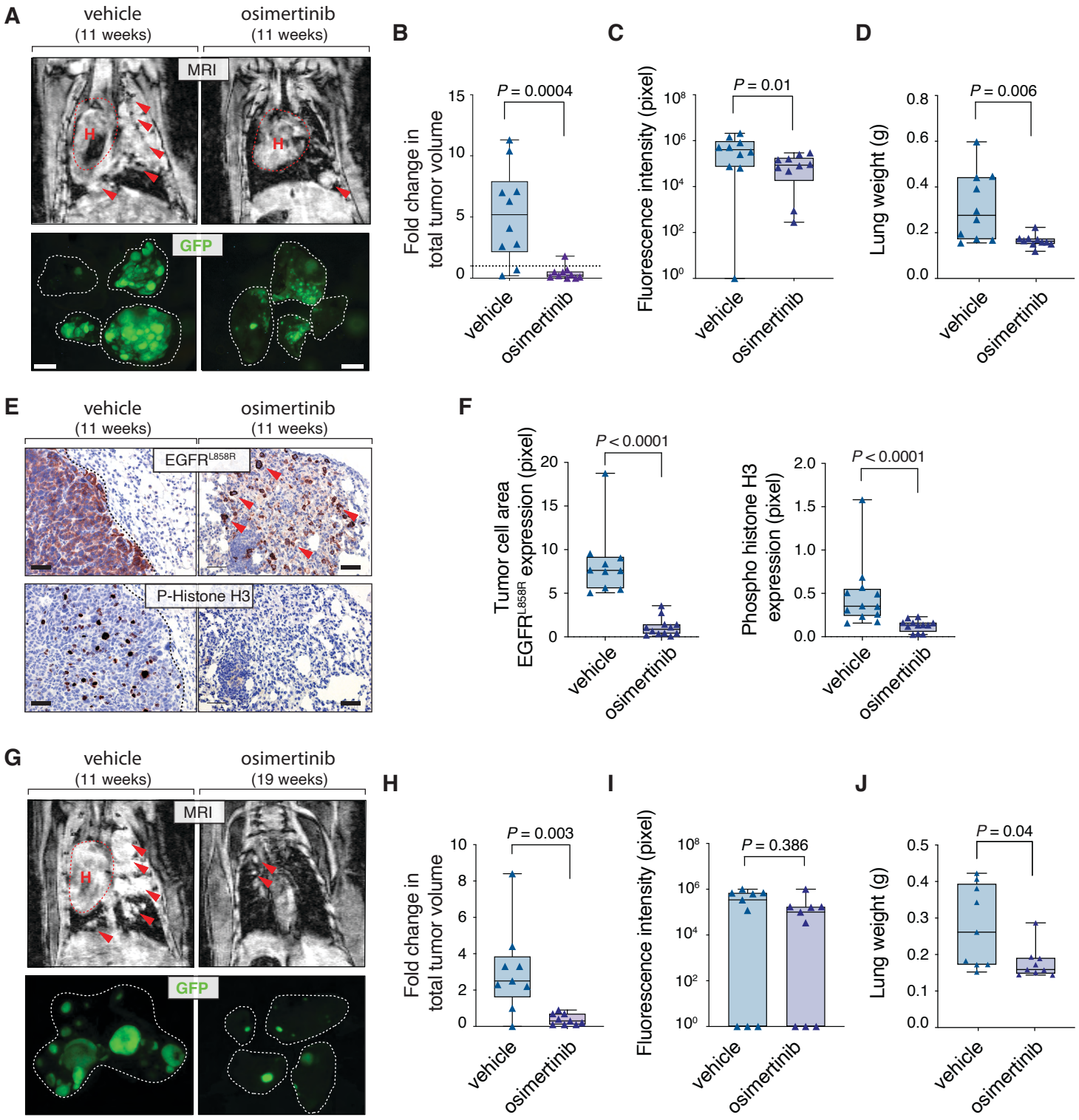
Odds ratio = 1.96
*P* = 0.03

*APC*

| | wt | mut | |
|---|---|---|---|
| *EGFR*$^{onc}$ | 527 | 23 | 4.2% |
| *KRAS*$^{onc}$ | 1680 | 75 | 4.3% |

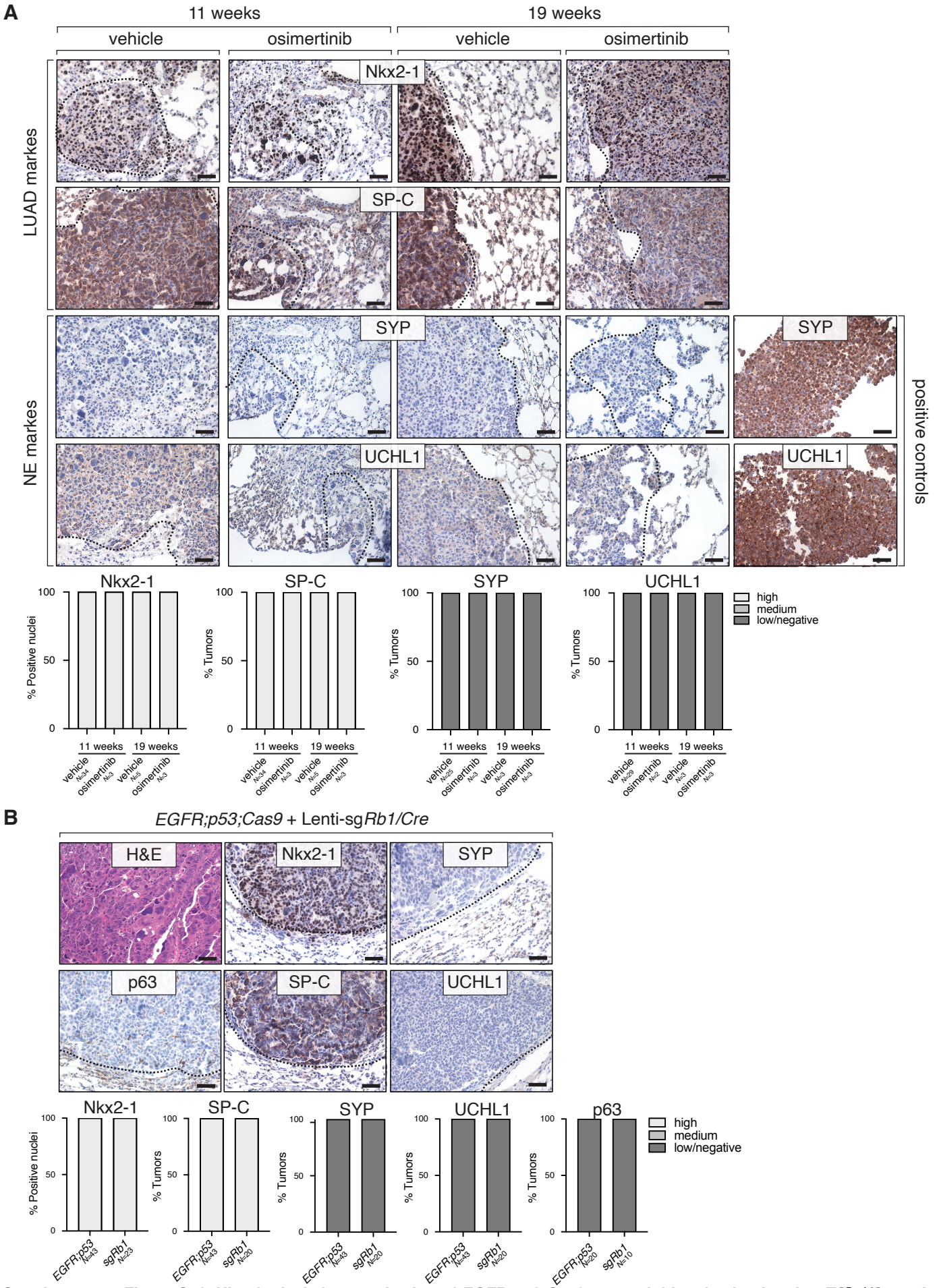
Odds ratio = 1.02
*P* = 1.00

**Supplementary Figure S8. Oncogenic drivers dictate the fitness landscape of tumor suppression.**
**A.** Tumors were initiated in *Kras;p53;Cas9* mice with Lenti-sg*TS*$^{Pool}$*/Cre* virus (2.2x10$^4$ ifu) and collected for Tuba-seq 14 weeks after tumor initiation (*N* = 6).
**B.** LN mean for different tumor suppressor genes in *EGFR;p53;Cas9* and *Kras;p53;Cas9* mice. *P*-values were calculated from bootstrapping. Confidence intervals are shown.
**C.** Frequency of co-occurrence of *LKB1, RBM10, SETD2* and *APC* alterations with *EGFR*$^{onc}$ and *KRAS*$^{onc}$ alterations in human lung adenocarcinomas. The odds ratios represent a measure of the strength of the frequency of co-occurring tumor suppressor gene alterations with *KRAS*$^{onc}$ compared to *EGFR*$^{onc}$ cases. *P*-values were calculated using a Fisher's exact test.




**Supplementary Figure S9. Strong therapeutic response to the 3rd generation TKI, osimertinib at 11 and 19 weeks after tumor initiation.**

**A.** *EGFR*-driven lung adenocarcinomas and early-therapeutic response to osimertinib. Tumor burden visualized using MRI and GFP fluorescence after two weeks of osimertinib treatment (25 mg/kg 5 days/week) at 11 weeks after tumor initiation compared to vehicle. Scale bars = 2.5 mm.
**B-D.** Overall response to osimertinib treatment at 11 weeks of tumor initiation. Therapeutic response is measured as (**B**) the fold change in total tumor volume relative to baseline (by MRI quantification), (**C**) change in GFP fluorescence, and (**D**) weight of tumor-bearing lungs after treatment with vehicle or osimertinib. *P*-values were calculated using the Mann-Whitney U test. Horizontal lines show the median.
**E.** Immunostaining and relative quantification of mutant EGFR positive cells and phospho-histone H3 positive tumor cells showing that tumors treated with osimertinib are less proliferative compared to tumors treated with vehicle. The black dashed lines indicate tumor area (left panels) and the red arrows indicate residual tumor cells (top right panel). Scale bars = 100 μm.
**F.** Quantification of mutant EGFR positive and phospho-histone H3 positive tumor cells in vehicle- and osimertinib-treated tumors after 11 weeks of tumor initiation. Each triangle represents a tumor area in a histological lung section. *P*-values were calculated using the Mann-Whitney U test. Horizontal lines indicate the median.
**G.** Tumor burden visualized by MRI and GFP fluorescence after two weeks of treatment with vehicle or osimertinib 17 weeks after tumor initiation.
**H-J.** Overall response to osimertinib at 19 weeks of tumor initiation measured as (**H**) the fold change in total tumor volume relative to baseline, (**I**) change in GFP fluorescence and (**J**) a change in the weight of tumor-bearing lungs. *P*-values were calculated using the Mann-Whitney U test. Horizontal lines indicate the median.




**Supplementary Figure S10. Histological characterization of *EGFR;p53;Cas9* tumors initiated using Lenti-sg*TS*$^{Pool}$*/Cre* or Lenti-sg*Rb1/Cre* virus.**

**A.** Immunohistochemical staining showing tumors positive for TTF-1/Nkx2-1 and SP-C in *EGFR;p53;Cas9* mice after two weeks of treatment with either vehicle or osimertinib, after 11 or 19 weeks of tumor initiation with Lenti-sg*TS*$^{Pool}$*/Cre* virus. None of the tumors are positive for staining for NE markers SYP or UCHL1. The dashed lines indicate tumor areas, Scale bars = 50 μm. Histograms show quantification of the staining (high, medium or low/negative). The positive control was the H69 SCLC cell line (SYP and UCHL1).
**B.** H&E showing a representative *EGFR/Tp53/Rb1* tumor in *EGFR;p53;Cas9* mice after 17 weeks of tumor initiation with Lenti-sg*Rb1/Cre* virus. Immunohistochemical staining showing a tumor positive for adenocarcinoma markers (Nkx2-1 and SP-C) and negative for either NE (SYP and UCHL1) or SCC (p63) markers. The dashed lines indicate tumor areas, Scale bars = 50 μm. Histograms show quantification of the staining (high, medium or low/negative).