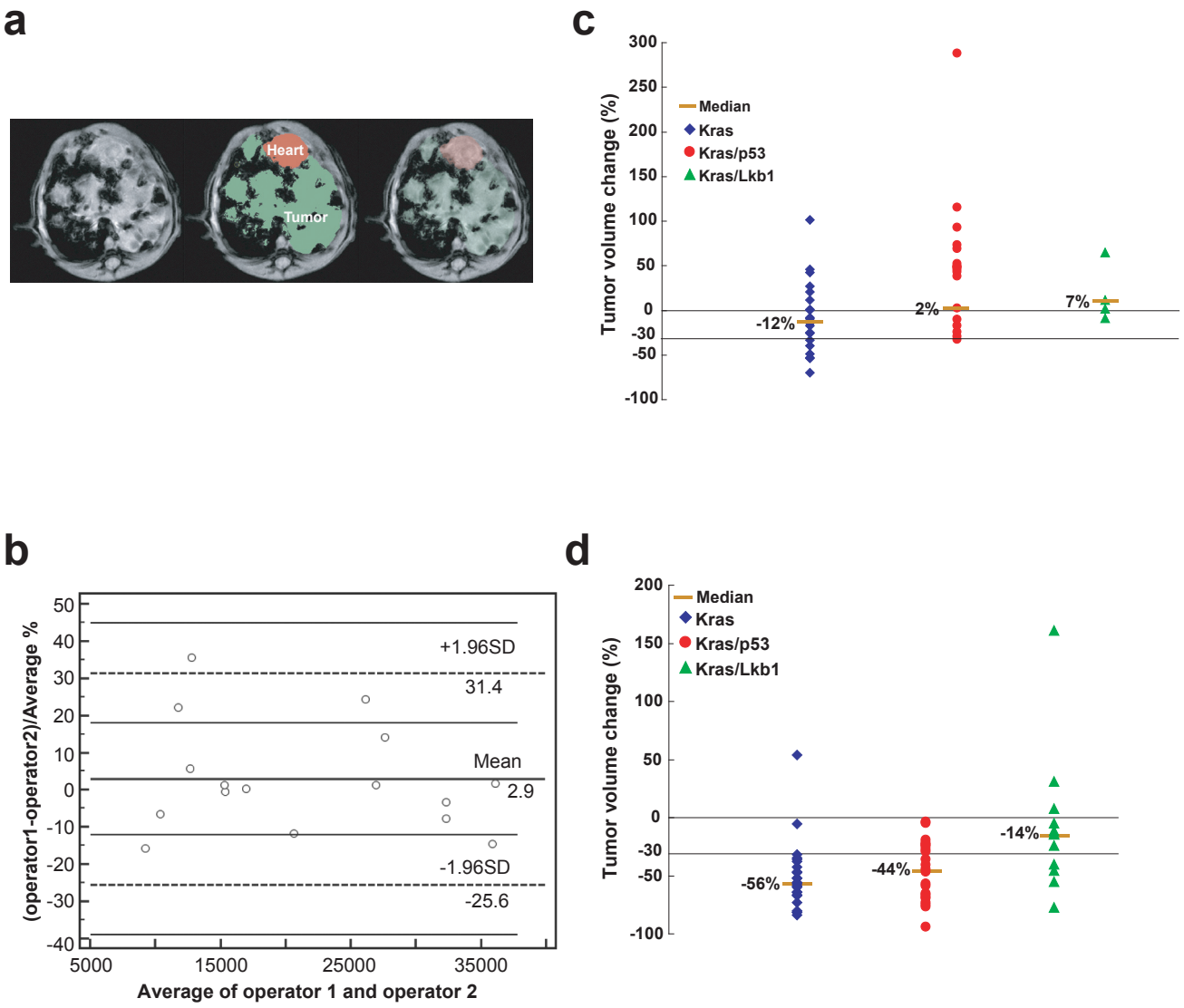
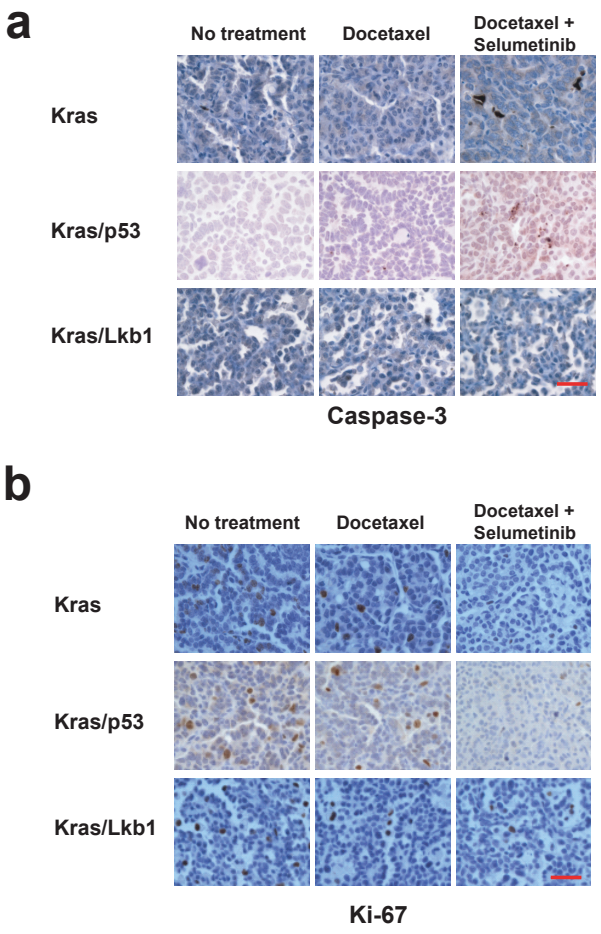
doi:10.1038/nature10937



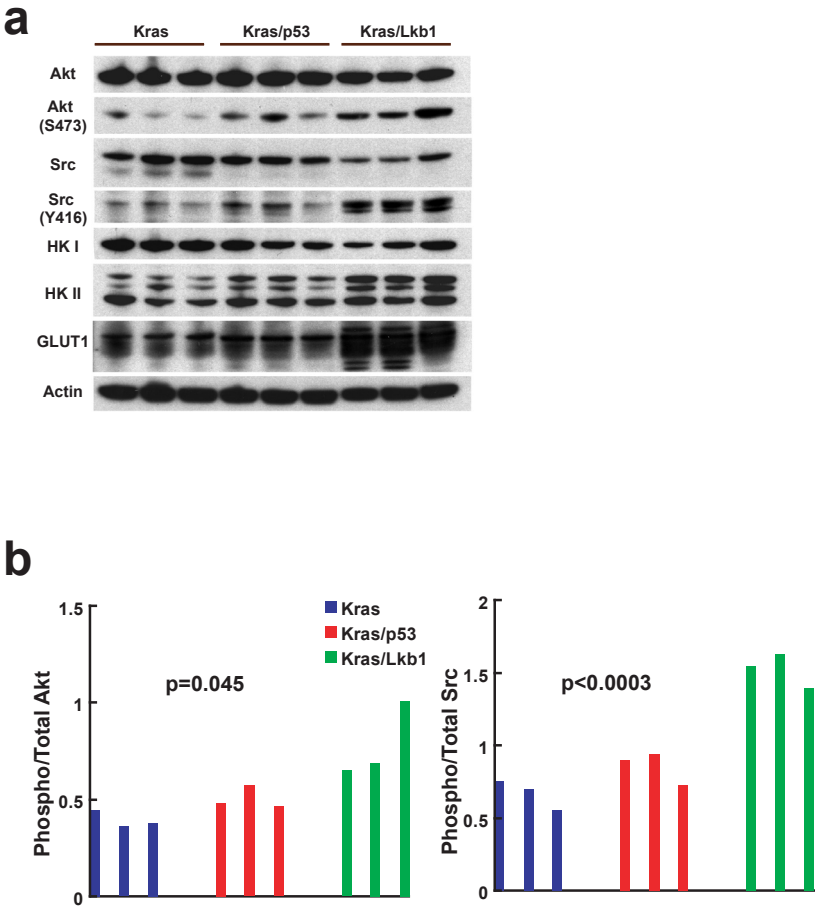
Supplementary Figure 1. Quantification of mouse lung cancers

a, Volumetric quantification of MRI scans using 3D Slicer software. Left, one axial slice of MRI scan; Middle, segmentation of tumor using thresholding and manual adjustment of regions of interest; green=tumor, red=heart; Right, fused image. **b,** Bland-Altman plot for reproducibility between two independent operators. Horizontal lines are drawn at the mean difference (+2.9%) and the 95% confidence interval for both lower (-25.6%) and upper (+31.4%) limits of agreement. **c,** Distribution of tumor response in different genotypes after 2 weeks of docetaxel treatment. Lines indicate median response value for each genotype. **d,** Distribution of tumor response in different genotypes after docetaxel plus selumetinib treatment. Line indicates median response value for each genotype.

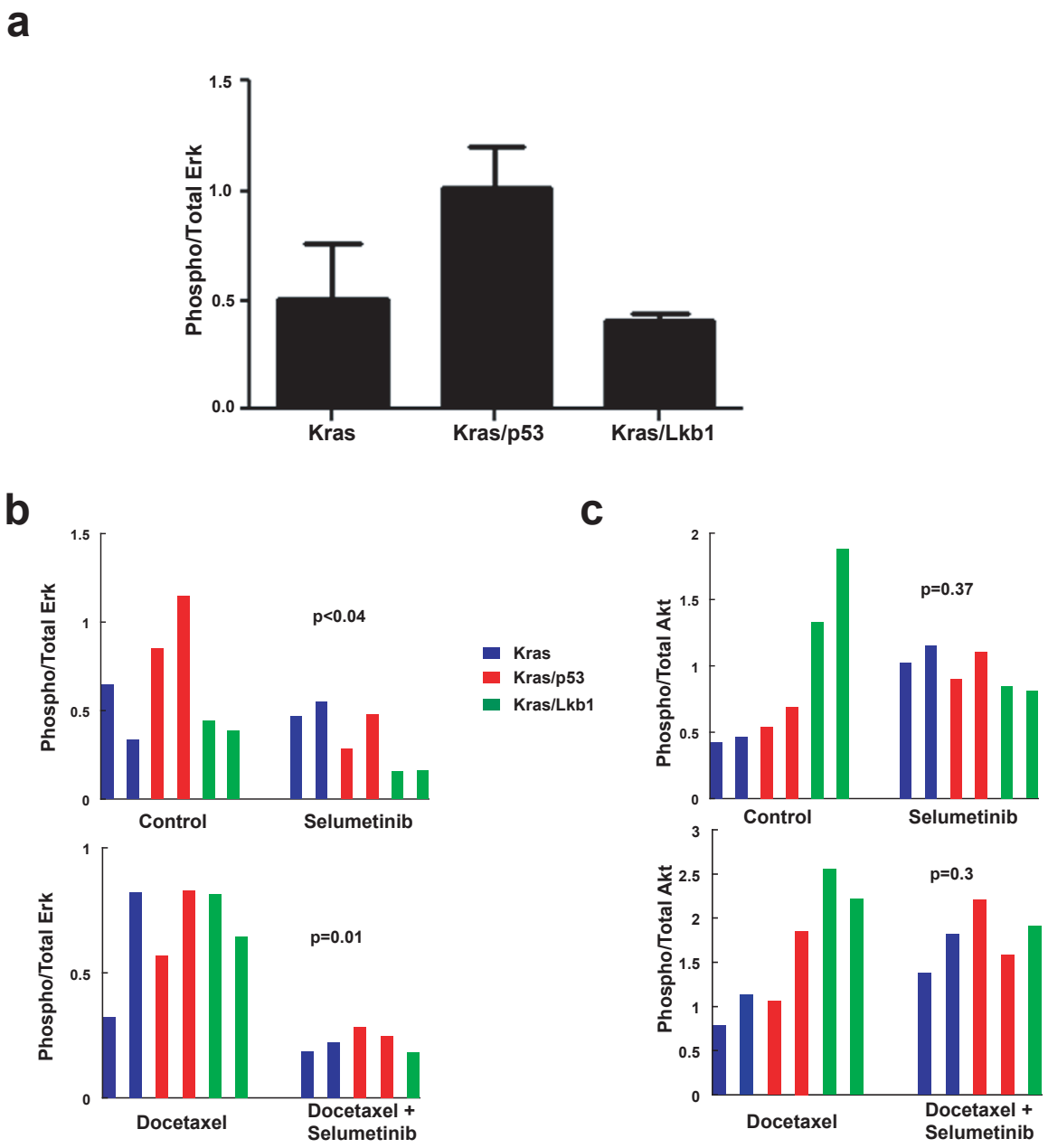


Supplementary Figure 2. Docetaxel and selumetinib combination treatment increases activated caspase-3 and reduces Ki-67 staining in the *Kras* and *Kras/p53* mouse tumors compared to docetaxel alone.

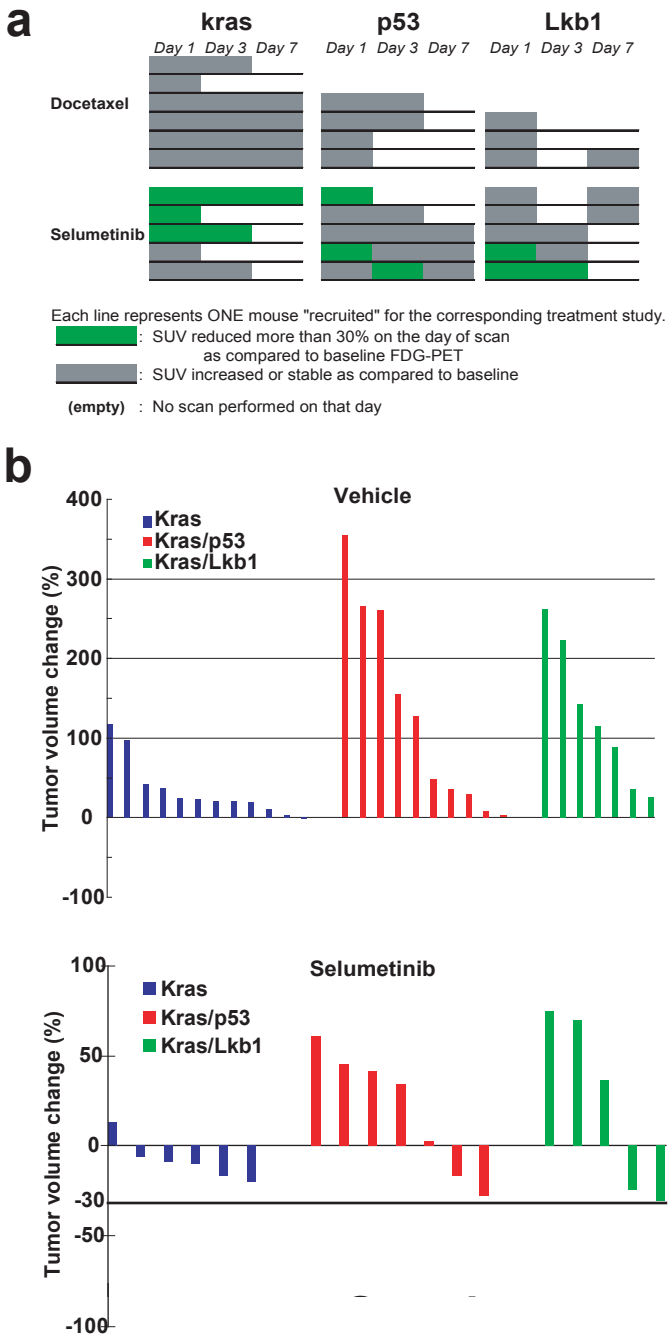
a, Immunohistochemistry (IHC) staining of activated caspase-3. Scale bar, 50μm. **b,** IHC staining of Ki-67. Scale bar, 50μm.



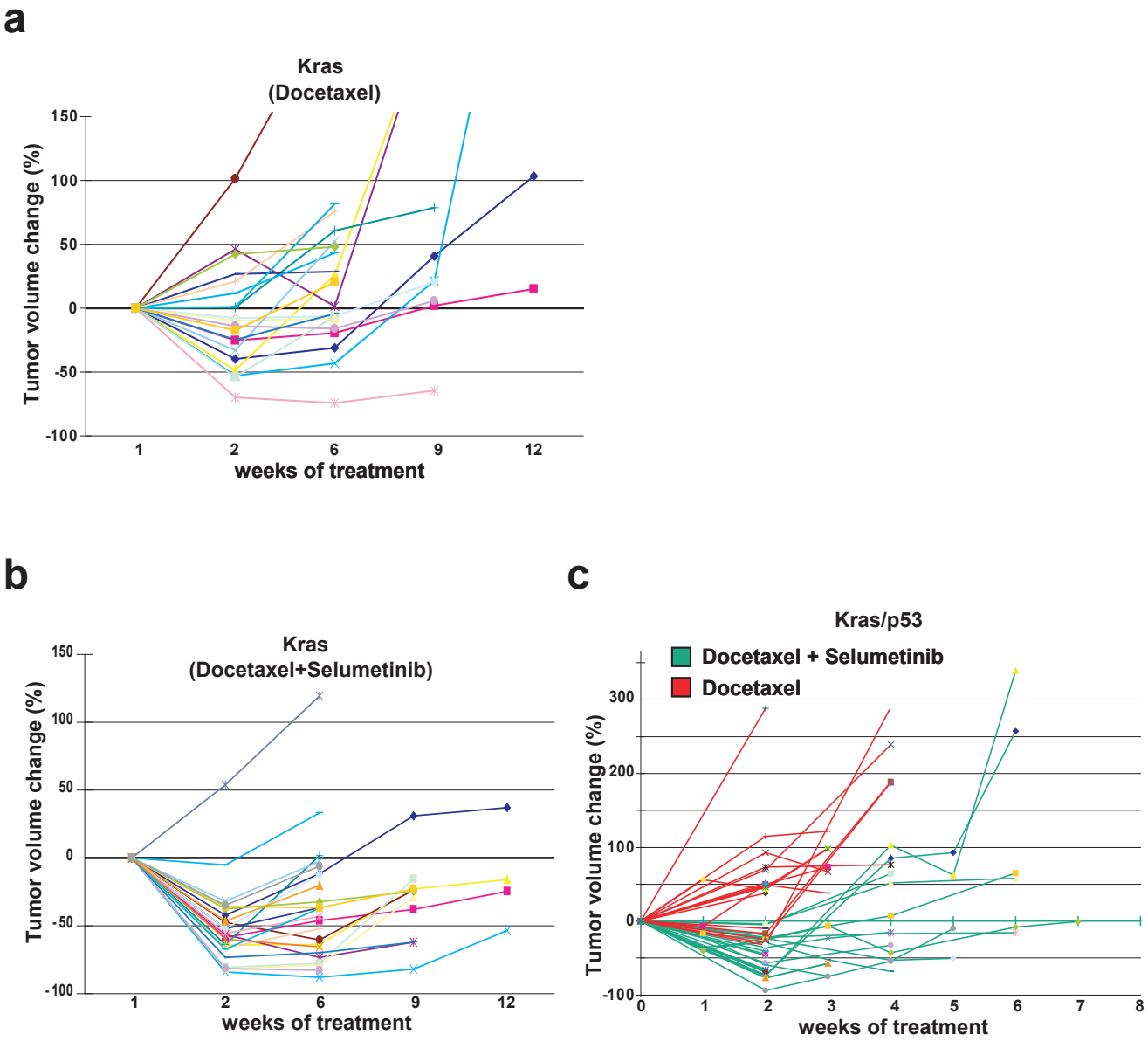
Supplementary Figure 3. Signaling pathways active in Kras/Lkb1 tumors.
a, Western blot analysis comparing Akt and Src activity, as well as determinants of glucose metabolism in *Kras*, *Kras/p53*, and *Kras/Lkb1* tumors. **b**, Densitometric quantification of Akt and Src activity shown in panel a, normalized to total Akt or total Src.



Supplementary Figure 4. Quantification of Erk and Akt activity in mouse tumor nodules after treatment. **a,** Densitometric quantification of phospho-Erk levels in untreated *Kras, Kras/p53,* and *Kras/Lkb1* mouse tumor nodules (Fig. 3c, n=2 for each genotype), normalized to total Erk (Image J, NCBI) +/- SD. **b**, Quantification of Erk activity for individual samples in Fig. 3c. **c**, Individual quantification of Akt activity for samples in Fig. 3c.



Supplementary Figure 5. Selumetinib as a single agent in *Kras*, *Kras/p53* and *Kras/Lkb1* tumor bearing mice. **a**, FDG-PET response for individual mice treated with either docetaxel or selumetinib as single agent. **b,** Top, MRI tumor volume changes in vehicle-treated mice with tumors of the indicated genotypes. Bottom, response of mice to treatment with selumetinib at 25mg/kg daily via oral gavage. Treatment effects were evaluated 2 weeks after baseline MR imaging. Each column represents a single mouse. Partial response threshold (-30%) is shown.



Supplementary Figure 6. Longitudinal analysis of tumor volume in response to treatment. **a,** Tumor volumes were serially determined by MRI in *Kras* mice treated with either docetaxel or **b,** with docetaxel plus selumetinib. **c,** *Kras/p53* mice treated with either docetaxel or docetaxel plus selumetinib. Each line represents an individual mouse. Each data point represents tumor volume change normalized to the baseline tumor volume for each individual mouse.

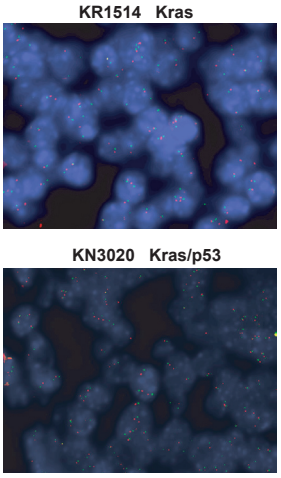
a

	p-ERK positive	p-ERK negative
Kras	94	16
Kras/p53	38	11

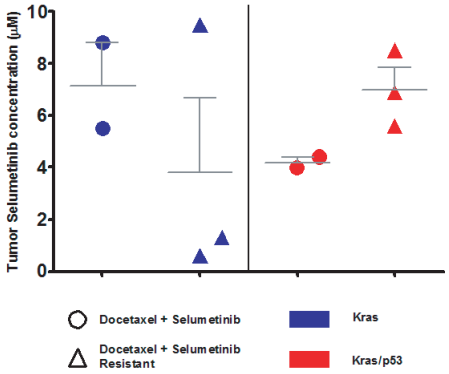
p-ERK activity grade score (%)

	0	1	2	3
Kras	14.5%	15.5%	56.4%	13.6%
Kras/p53	22.4%	44.9%	18.4%	14.3%

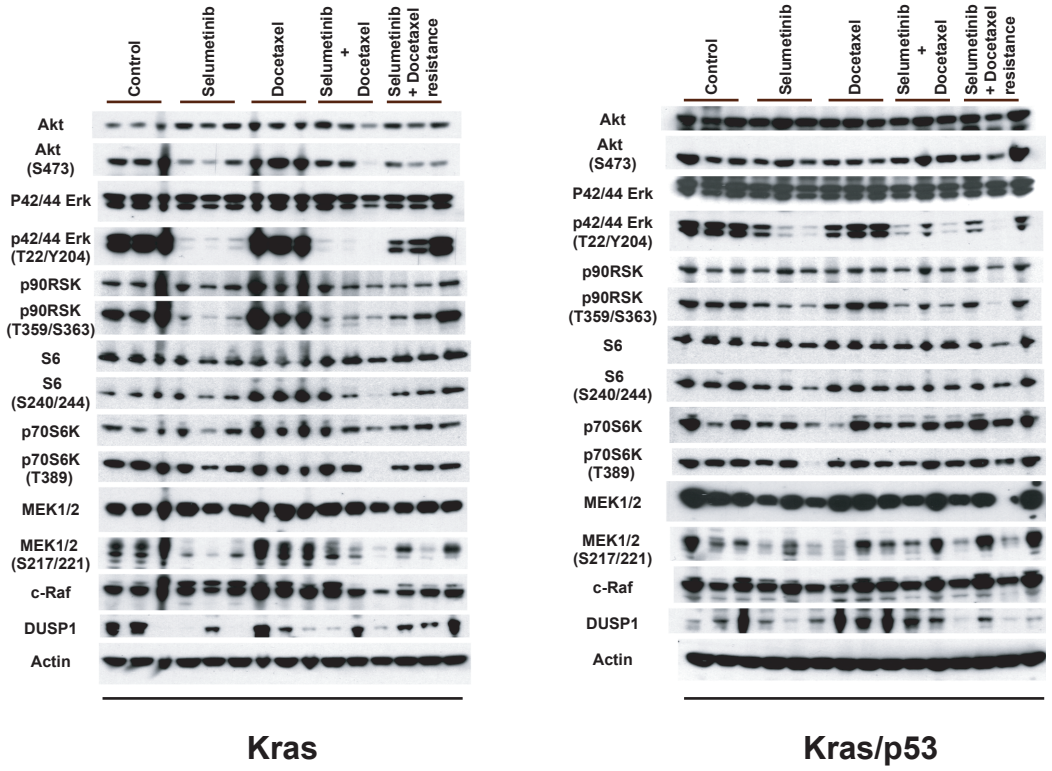
b



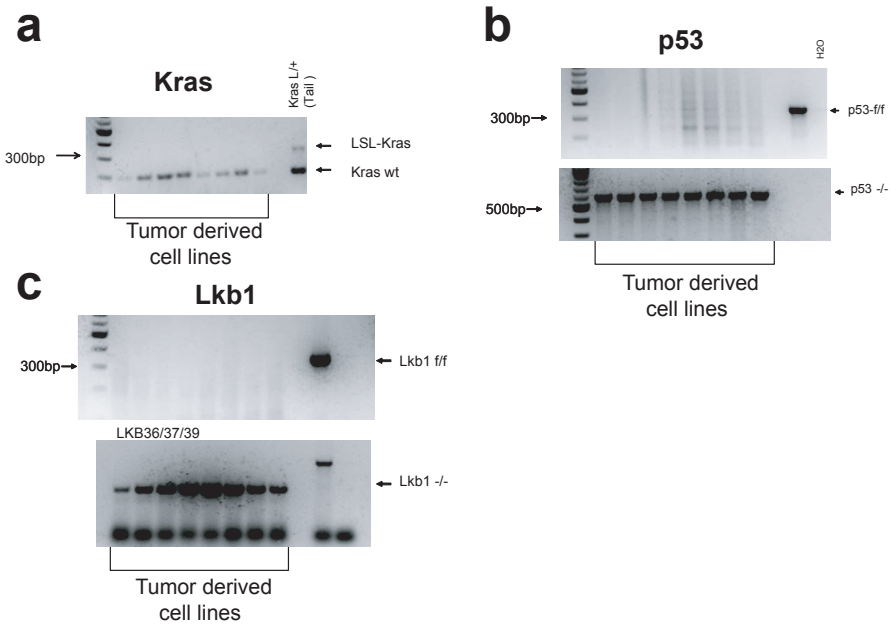
d



c



Supplementary Figure 7. Study of signaling and mechanisms of acquired resistance in *Kras* and *Kras/p53* tumors treated with docetaxel and selumetinib. **a**, Erk activity in *Kras* and *Kras/p53* tumors with acquire resistance to treatment with docetaxel and selumetinib. Individual nodules were scored for intensity of p-Erk staining. Total numbers of nodules scored (top), and percentage of each intensity grade (bottom) are shown. **b**. FISH staining of Erk genomic locus revealed no amplification in both *Kras* and *Kras/p53* acquired resistant nodules. **c**, Western blotting comparing Erk upstream/downstream (Raf, MEK, p90) and parallel (Akt, p70, S6) pathways. Potential changes in dual specific phosphatase 1 (DUSP1) was also evaluated. **d**, Pharmacokinetics (PK) study of selumetinib concentrations in naive and combination resistant tumor nodules. Nodules were collected from mice with confirmed tumor progression by MRI scans after long-term docetaxel/selumetinib treatment. Mean+/-SEM are shown.



Supplemental Figure 8. Confirmation of genotypes in *Kras* tumors with concurrent tumor suppressors loss. *Kras/p53* and *Kras/p53/Lkb1* cell lines were derived from individual tumor nodules after tissue dissection, digestion, and propagation *in vitro* to remove contaminating stromal cells.

a, PCR genotyping of activated *Kras* allele. *Lox-stop-lox Kras* (*LSL-Kras*) allele before and after activation. PCR shows *Kras-LSL* heterozygous tumor derived cell lines lose the *LSL* allele after activation. **b**, PCR genotyping of *p53* deletion. *Lox P*-flanked *p53* allele (*p53f/f*) before Cre recombinase mediated deletion. Tumor cell lines all lose the *p53f/f* allele, and demonstrate conversion to *p53-/-* after CRE recombinase mediated deletion. **c**, PCR genotyping of *Lkb1* deletion. *LoxP*-flanked *Lkb1* (*Lkb1f/f)* is converted to *Lkb1-/-* after Cre recombinase mediated deletion.

Supplementary Table 1

24 hrs (μM)

	Docetaxel/8mpk	*Docetaxel/16mpk*	*Docetaxel/8mpk +Selumetinib*	*Docetaxel/16mpk +Selumetinib*
plasma	43.7	46	18.3	66.2
lung	2587	2760.3	1237.8	5830.1
tumor	3490.6	4493.2	N/D	4555.1

2 weeks (μM)

	Docetaxel/8mpk	*Docetaxel/16mpk*	*Docetaxel/8mpk +Selumetinib*	*Docetaxel/16mpk +Selumetinib*	*Docetaxel/16mpk +Selumetinib*
plasma	100.8	8.9	14.2	433.2	96.4
lung	3057.4	1955.7	308.2	7600.1	2537.5
tumor	2426.1	2680.6	N/D	N/D	2648.9

Supplementary Table 2. Tumor progression in different genotypes

Treatment	Genotype	number of mice evaluated for tumor burden	number of mice treated	Death before 2wk MRI	tumor progression 2 weeks after treatment	Death before 6wk MRI	Tumor progression 6 weeks after treatment (including death)
Docetaxel	Kras	23	21	1/21	5/20	1/21	15/20
Selumetinib + Docetaxel	Kras	30	28	3/28	0/25	3/28	13/25
						Death before 4wk MRI	Tumor progression 4 weeks after treatment (including death)
Docetaxel	Kras/Lkb1	10	9*	5/9	3/4	7/9	4/4
Selumetinib + Docetaxel	Kras/Lkb1	17	17	5/17	2/12	15/17	12/12
Docetaxel	Kras/p53	22	20	2/20	12/18	14/20	18/18
Selumetinib + Docetaxel	Kras/p53	29	26	3/26	0/23	13/26	17/23

*Additional 5 mice were evaluated for 2 weeks treatment only, but not included in this table, as they were not followed for long-term changes.

Supplementary Table 3. Pharmacokinetics of selumetinib in mice

		Selumetinib concentration (μM)		
Treatment	*Genotype*	*Serum*	*Lung*	*Tumor*
DS	*Kras*	*12.5*	*3.9*	*5.1*
DS	*Kras*	*N/D*	*N/D*	*8.8*
DS	*Kras/p53*	*17.6*	*3.9*	*4.4*
DS	*Kras/p53*	*14.1*	*1.7*	*4*
S	*Kras*	*3.4*	*0.9*	*0.7*
S	*Kras*	*7.7*	*1.9*	*1.5*
S	*Kras/p53*	*2.9*	*0.6*	*0.6*
S	*Kras/p53*	*N/D*	*N/D*	*0.5*

S=selumetinib
DS=docetaxel + selumetinib
N/D, Not Determined
Tumor bearing mice are treated for 2 weeks.

Supplementary Table 4. Mice used in treatment study

Mouse	Genotype	Treatment	Sex	DOB	Adeno-Cre	Age at Adeno-Cre(weeks)	Treatment Start Date	Induction Length at treatment start(weeks)
KN3018	Kras/p53	DS	F	2010-7-28	2010-9-14	6.9	2010-11-11	8.3
KN3019	Kras/p53	DS	F	2010-7-28	2010-9-14	6.9	2010-11-11	8.3
KN3020	Kras/p53	DS	M	2010-7-28	2010-9-14	6.9	2010-11-11	8.3
KN2996	Kras/p53	DS	F	2010-6-27	2010-8-13	6.7	2010-11-10	12.7
KN3021	Kras/p53	DS	F	2010-8-17	2010-10-1	6.4	2010-12-1	8.7
KN3023	Kras/p53	DS	F	2010-8-17	2010-10-1	6.4	2010-12-1	8.7
KN3027	Kras/p53	DS	F	2010-8-17	2010-10-1	6.4	2010-12-1	8.7
KN3049	Kras/p53	DS	F	2010-8-15	2010-10-1	6.7	2010-12-1	8.7
KN3059	Kras/p53	DS	M	2010-8-22	2010-10-6	6.4	2010-12-8	9
KN3060	Kras/p53	DS	M	2010-8-22	2010-10-6	6.4	2010-12-8	9
KN3068	Kras/p53	DS	M	2010-8-19	2010-10-15	8.1	2010-12-15	8.7
KN3072	Kras/p53	DS	F	2010-8-24	2010-10-15	7.4	2010-12-15	8.7
KN3075	Kras/p53	DS	M	2010-8-24	2010-10-15	7.4	2010-12-15	8.7
KN3078	Kras/p53	DS	M	2010-8-24	2010-10-15	7.4	2010-12-15	8.7
KN3077	Kras/p53	DS	F	2010-8-24	2010-10-15	7.4	2010-12-15	8.7
KN2535	Kras/p53	DS	F	2009-9-10	2009-10-30	7.1	2009-12-30	8.7
KN2568	Kras/p53	DS	F	2009-9-15	2009-10-30	6.4	2009-12-30	8.7
KN2453	Kras/p53	DS	M	2009-8-8	2009-10-9	8.9	2009-12-18	10
KN2499	Kras/p53	DS	M	2009-8-16	2009-10-9	7.7	2009-12-18	10
KN2455	Kras/p53	DS	M	2009-8-8	2009-10-9	8.9	2009-12-18	10
KN2477	Kras/p53	DS	M	2009-8-17	2009-10-9	7.6	2009-12-18	10
KN2569	Kras/p53	DS	F	2009-9-15	2009-10-30	6.4	2009-12-30	8.7
KN2539	Kras/p53	DS	F	2009-9-10	2009-10-30	7.1	2009-12-30	8.7
KN3010	Kras/p53	D	M	2010-7-27	2010-9-10	6.4	2010-11-11	8.9
KN24	Kras/p53	D	M	2010-8-17	2010-10-1	6.4	2010-12-1	8.7
KN38	Kras/p53	D	M	2010-8-14	2010-10-1	6.9	2010-12-1	8.7
KN3050	Kras/p53	D	M	2010-8-19	2010-10-6	6.9	2010-12-8	9
KN3062	Kras/p53	D	M	2010-8-22	2010-10-6	6.4	2010-12-8	9
KN3069	Kras/p53	D	F	2010-8-24	2010-10-15	7.4	2010-12-15	8.7
KN3073	Kras/p53	D	F	2010-8-24	2010-10-15	7.4	2010-12-15	8.7
KN3051	Kras/p53	D	F	2010-8-19	2010-10-15	8.1	2010-12-15	8.7
KN3061	Kras/p53	D	F	2010-8-22	2010-10-15	7.7	2010-12-15	8.7
KN3077	Kras/p53	D	F	2010-8-24	2010-10-15	7.4	2010-12-15	8.7
KN2419	Kras/p53	D	F	2009-7-27	2009-9-17	7.4	2009-11-27	10.1
KN2548	Kras/p53	D	F	2009-9-8	2009-10-30	7.4	2009-12-30	8.7
KN2421	Kras/p53	D	F	2009-7-27	2009-9-17	7.4	2009-11-27	10.1
KN2537	Kras/p53	D	F	2009-9-10	2009-10-30	7.1	2009-12-30	8.7
KN2471	Kras/p53	D	F	2009-8-17	2009-10-9	7.6	2009-12-18	10
KN2550	Kras/p53	D	F	2009-9-8	2009-10-30	7.4	2009-12-30	8.7
KN2423	Kras/p53	D	F	2009-7-23	2009-9-17	8	2009-11-27	10.1
KN2474	Kras/p53	D	F	2009-8-17	2009-10-9	7.6	2009-12-18	10
KN2010	Kras/p53	D	M	2009-10-8	2009-11-20	6.1	2010-1-22	9.0
KN3118	Kras/p53	D	F	2010-9-10	2010-11-24	10.7	2011-2-1	9.9
KN2013	Kras/p53	D	M	2009-10-16	2009-11-20	5.0	2010-1-22	9.0
KN3093	Kras/p53	D	F	2010-9-4	2010-11-24	11.6	2011-2-1	9.9
KN3129	Kras/p53	D	F	2010-9-17	2010-11-24	9.7	2011-2-1	9.9
KN3132	Kras/p53	D	F	2010-9-17	2010-11-24	9.7	2011-2-1	9.9
KN3128	Kras/p53	D	F	2010-9-17	2010-11-24	9.7	2011-2-1	9.9
KR1531	Kras	DS	F	2010-1-13	2010-2-24	6	2010-5-12	11
KR1672	Kras	DS	F	2010-6-11	2010-8-2	7.4	2010-12-8	18.3
KR6204	Kras	DS	F	2010-6-28	2010-8-11	6.3	2010-12-8	17
KR1519	Kras	DS	F	2010-1-13	2010-2-24	6	2010-5-12	11
KR1513	Kras	DS	M	2010-1-13	2010-2-24	6	2010-5-12	11
KR1512	Kras	DS	M	2010-1-13	2010-2-24	6	2010-5-12	11

KR6085	Kras	DS	F	2010-5-11	2010-6-29	7	2010-10-13	15.1
KR1514	Kras	DS	F	2010-1-13	2010-2-24	6	2010-5-29	13.4
KR1715	Kras	DS	M	2010-7-2	2010-8-17	6.6	2010-12-1	15.1
KR1718	Kras	DS	M	2010-7-2	2010-8-17	6.6	2010-12-1	15.1
KL6198	Kras	DS	F	2010-6-27	2010-8-11	6.4	2010-12-8	17
KL3915	Kras	DS	F	2009-11-23	2010-1-6	6.3	2010-4-22	15.1
KR1713	Kras	DS	M	2010-7-2	2010-8-17	6.6	2010-12-1	15.1
KL6093	Kras	DS	F	2010-5-11	2010-6-29	7	2010-10-13	15.1
KR1515	Kras	DS	F	2010-1-13	2010-2-24	6	2010-5-29	13.4
KR1716	Kras	DS	M	2010-7-2	2010-8-17	6.6	2010-12-1	15.1
KL6099	Kras	DS	F	2010-5-18	2010-7-6	7	2010-10-13	14.1
KR1503	Kras	DS	F	2010-1-10	2010-2-24	6.4	2010-5-29	13.4
KR1510	Kras	DS	M	2010-1-10	2010-2-24	6.4	2010-5-29	13.4
KR1509	Kras	DS	F	2010-1-10	2010-2-24	6.4	2010-5-29	13.4
KR6199	Kras	DS	F	2010-6-27	2010-8-11	6.4	2010-12-8	17
KR6200	Kras	DS	F	2010-6-27	2010-8-11	6.4	2010-12-8	17
KL3928	Kras	DS	M	2009-11-23	2010-1-6	6.3	2010-4-22	15.1
Kr1645	Kras	DS	F	2010-5-18	2010-7-19	8.9	2010-10-20	13.3
kr1678	Kras	D	M	2010-6-11	2010-8-2	7.4	2010-11-11	14.4
Kr1656	Kras	D	M	2010-5-25	2010-7-19	7.9	2010-10-20	13.3
KR1539	Kras	D	F	2010-1-13	2010-2-24	6	2010-5-12	11
KR1712	Kras	D	M	2010-7-2	2010-8-17	6.6	2010-12-1	15.1
KR1511	Kras	D	M	2010-1-10	2010-2-24	6.4	2010-5-29	13.4
KR1685	Kras	D	F	2010-6-11	2010-8-2	7.4	2010-12-8	18.3
KR1530	Kras	D	F	2010-1-13	2010-2-24	6	2010-5-12	11
kr1679	Kras	D	M	2010-6-11	2010-8-2	7.4	2010-11-11	14.4
KR1714	Kras	D	M	2010-7-2	2010-8-17	6.6	2010-12-1	15.1
KR1502	Kras	D	M	2010-1-10	2010-2-24	6.4	2010-5-29	13.4
KR1508	Kras	D	M	2010-1-10	2010-2-24	6.4	2010-5-29	13.4
kR1542	Kras	D	F	2010-1-13	2010-2-24	6	2010-5-12	11
KR1517	Kras	D	M	2010-1-13	2010-2-24	6	2010-5-12	11
KL6103	Kras	D	F	2010-5-18	2010-7-6	7	2010-10-13	14.1
KR1504	Kras	D	M	2010-1-10	2010-2-24	6.4	2010-5-29	13.4
KL6102	Kras	D	F	2010-5-18	2010-7-6	7	2010-10-13	14.1
Kr1642	Kras	D	F	2010-5-18	2010-7-19	8.9	2010-10-20	13.3
Kr1644	Kras	D	M	2010-5-18	2010-7-19	8.9	2010-10-20	13.3
KL3920	Kras	D	M	2009-11-23	2010-1-6	6.3	2010-4-22	15.1
KR1507	Kras	D	M	2010-1-10	2010-2-24	6.4	2010-5-29	13.4
KBc89_27	Kras	S	M	2011-5-5	2011-7-1	8.1	2011-10-14	15.0
KBc89_28	Kras	S	M	2011-5-5	2011-7-1	8.1	2011-10-14	15.0
KBc92_39	Kras	S	F	2011-5-29	2011-7-12	6.3	2011-10-14	13.4
KBc93_44	Kras	S	M	2011-5-29	2011-7-12	6.3	2011-10-14	13.4
KBc93_45	Kras	S	M	2011-5-29	2011-7-12	6.3	2011-10-14	13.4
KBc95_51	Kras	S	M	2011-5-30	2011-7-12	6.1	2011-10-14	13.4
KL405	Kras/Lkb1	DS	M	2010-5-29	2010-7-19	7.3	2010-9-3	6.6
KL407	Kras/Lkb1	DS	M	2010-5-29	2010-7-19	7.3	2010-9-3	6.6
KL409	Kras/Lkb1	DS	M	2010-5-29	2010-7-19	7.3	2010-9-3	6.6
KL6091	Kras/Lkb1	DS	F	2010-6-2	2010-7-19	6.7	2010-9-3	6.6
KL6165	Kras/Lkb1	DS	F	2010-6-9	2010-7-26	6.7	2010-10-5	10.1
KL6219	Kras/Lkb1	DS	M	2010-7-17	2010-8-30	6.3	2010-10-20	7.3
KL6220	Kras/Lkb1	DS	F	2010-7-17	2010-8-30	6.3	2010-10-20	7.3
KL6222	Kras/Lkb1	DS	F	2010-7-17	2010-8-30	6.3	2010-10-20	7.3
KL6224	Kras/Lkb1	DS	M	2010-7-17	2010-8-30	6.3	2010-10-20	7.3
KL6225	Kras/Lkb1	DS	M	2010-7-17	2010-8-30	6.3	2010-10-20	7.3
KL6271	Kras/Lkb1	DS	F	2010-8-15	2010-9-29	6.4	2010-11-17	7
KL6274	Kras/Lkb1	DS	F	2010-8-15	2010-9-29	6.4	2010-11-17	7
KLM28-03	Kras/Lkb1	D	F	2010-7-3	2010-8-23	7.3	2010-10-20	8.3

KLM28-05	Kras/Lkb1	D	F	2010-7-3	2010-8-23	7.3	2010-10-20	8.3
KLM28-06	Kras/Lkb1	D	F	2010-7-3	2010-8-23	7.3	2010-10-20	8.3
KL6270	Kras/Lkb1	D	F	2010-8-15	2010-9-29	6.4	2010-11-17	7
KR6706	Kras/Lkb1	D	M	2011-5-20	2011-7-8	7.0	2011-10-12	13.7
KR6707	Kras/Lkb1	D	M	2011-5-20	2011-7-8	7.0	2011-10-12	13.7
KR6809	Kras/Lkb1	D	F	2011-6-15	2011-8-12	8.3	2011-10-19	9.7
KR6932	Kras/Lkb1	D	M	2011-8-12	2011-9-15	4.9	2011-10-19	4.9
KBC-81 #0	Kras/Lkb1	D	F	2011-4-16	2011-5-22	5.1	2011-7-12	7.3
KR6703	Kras/Lkb1	S	M	2011-5-20	2011-7-8	7.0	2011-10-12	13.7
KR6704	Kras/Lkb1	S	M	2011-5-20	2011-7-8	7.0	2011-10-12	13.7
KR6817	Kras/Lkb1	S	F	2011-6-18	2011-8-12	7.9	2011-10-12	8.7
KR6929	Kras/Lkb1	S	M	2011-8-12	2011-9-15	4.9	2011-10-19	4.9
KR6931	Kras/Lkb1	S	M	2011-8-12	2011-9-15	4.9	2011-10-19	4.9

Legends: D, docetaxel; S, selumetinib; DS: docetaxel + Selumetinib; M, male; F, female.

Supplementary Table 5. Mice used in PET-CT study.

Label	Mouse ID	Genotype	Imaging Date	Treatment	Days R.X.	SUV_max	% Change	Liver SUV mean	Liver SUV STD
KBC53	6	kras	2011-3-28	(Baseline)	0		(Baseline)		
KBC52	11	kras	2011-3-24	(Baseline)	0		(Baseline)		
KBC34#37 (D1)	37	lkb	2010-11-17	Taxotere	0	1.2	(Baseline)	0.29	0.03
KBC34#37 (D1)	37	lkb	2010-11-18	Taxotere	1	0.9	-25%	0.25	0.025
KBC34#38 (D1)	38	lkb	2010-11-17	Taxotere+AZD	0	2.5	(Baseline)	0.32	0.0545
KBC34#38 (D1)	38	lkb	2010-11-18	Taxotere+AZD	1	3.4	36%	0.316	0.023
KBC41#60 (D1)	60	lkb	2010-12-20	AZD	0	3.4	(Baseline)	0.445	0.47
KBC41#60 (D1)	60	lkb	2010-12-22	AZD	1	3.4	0%	0.43	0.042
KBC41#60 (D1)	60	lkb	2010-12-28	AZD	7	1.6	?	0.2	0.022
KBC42#62 (D1, D	62	lkb	2010-12-20	AZD	0	1.9	(Baseline)	0.5	0.028
KBC42#62 (D1, D	62	lkb	2010-12-22	AZD	1	1.9	0%	0.4	0.03
KBC42#62 (D1, D	62	lkb	2010-12-28	AZD	7	2.9	53%	0.4	0.028
KBC43#68 (D1)	68	lkb	2010-12-20	Taxotere	0	3.5	(Baseline)	0.7	0.08
KBC43#68 (D1)	68	lkb	2010-12-22	Taxotere	1	3.1	-11%	0.66	0.055
KBC43#68 (D1)	68	lkb	2010-12-28	Taxotere	7	(n/a)	(n/a)	(n/a)	(n/a)
KBC43#71 (D1, D	71	lkb	2010-12-20	Taxotere	0	0.9	(Baseline)	0.56	0.027
KBC43#71 (D1, D	71	lkb	2010-12-22	Taxotere	1	1.1	22%	0.65	0.07
KBC43#71 (D1, D	71	lkb	2010-12-28	Taxotere	7	7.3		0.88	0.037
KBC42#73 (D1, D	73	lkb	2010-12-20	Taxotere+AZD	0	0.5	(Baseline)	0.31	0.028
KBC42#73 (D1, D	73	lkb	2010-12-22	Taxotere+AZD	1	0.56	0%	0.4	0.02
KBC42#73 (D1, D	73	lkb	2010-12-28	Taxotere+AZD	7	0.5	0%	0.35	0.01
KBC42#74 (D1, D	74	lkb	2010-12-20	Taxotere+AZD	0	2.4	(Baseline)	0.54	0.024
KBC42#74 (D1, D	74	lkb	2010-12-22	Taxotere+AZD	1	2.3	-4%	0.52	0.0255
KBC42#74 (D1, D	74	lkb	2010-12-28	Taxotere+AZD	7	1.6	-33%	0.45	0.028
KBC46#88 (D1, D	88	kras	2011-3-15	Taxotere+AZD	0	1.5	(Baseline)	0.34	0.03
KBC46#88 (D1, D	88	kras	2011-3-16	Taxotere+AZD	1	0.9	-40%	0.24	0.028
KBC46#88 (D1, D	88	kras	2011-3-18	Taxotere+AZD	3	0.7	-53%	0.23	0.019
KBC46#88	88	kras	2011-4-5	(Baseline)	20	2.7	(Baseline)	0.37	0.023
KBC46#89 (D1, D	89	kras	2011-3-15	Taxotere	0	2.4	(Baseline)	0.23	0.028
KBC46#89 (D1, D	89	kras	2011-3-16	Taxotere	1	3.4	42%	0.28	0.038
KBC46#89 (D1, D	89	kras	2011-3-18	Taxotere	3	4.1	71%	0.34	0.024
KR#1942 (D1, ...)	1942	kras	2011-5-10	Taxotere	0	1.3	(Baseline)	0.6	0.04
KR#1942 (D1, ...)	1942	kras	2011-5-11	Taxotere	1	1.5	15%	0.64	0.025
KR#1942	1942	kras	2011-5-24	Taxotere	14	1.7	31%	0.49	0.027
#1945 (D1,D3, D7	1945	kras	2011-5-17	AZD	0	1.9	(Baseline)	0.3	0.019
#1945 (D1,D3, D7	1945	kras	2011-5-18	AZD	1	1.2	-37%	0.42	0.025
#1945 (D1,D3, D7	1945	kras	2011-5-20	AZD	3	1.2	-37%	0.38	0.032
#1945 (D1,D3, D7	1945	kras	2011-5-24	AZD	7	0.9	-53%	0.29	0.02
#1946 (neg)	1946	kras	2011-5-10	(Baseline)	0		(Baseline)		
#1946 (neg)	1946	kras	2011-5-18	(Baseline)	0		(Baseline)		
#1951 (D1,D3, D7	1951	kras	2011-5-17	Taxotere	0	0.76	(Baseline)	0.29	0.018
#1951 (D1,D3, D7	1951	kras	2011-5-18	Taxotere	1	0.79	0%	0.44	0.032
#1951 (D1,D3, D7	1951	kras	2011-5-20	Taxotere	3	0.7	0%	0.42	0.032
#1951 (D1,D3, D7	1951	kras	2011-5-24	Taxotere	7	0.58	0%	0.29	0.022
KR#1952 (D1)	1952	kras	2011-5-10	AZD	0	0.9	(Baseline)	0.46	0.025
KR#1952 (D1)	1952	kras	2011-5-11	AZD	1	0.6	-33%	0.5	0.03
#1953 (neg)	1953	kras	2011-5-17	(Baseline)	0		(Baseline)		
KR#1956 (D1,D3,	1956	kras	2011-4-26	Taxotere	0	1.3	(Baseline)	0.45	0.011
KR#1956 (D1,D3,	1956	kras	2011-4-27	Taxotere	1	1.7	31%	0.4	0.033
KR#1956 (D1,D3,	1956	kras	2011-4-29	Taxotere	3	1.4	8%	0.32	0.02
KR#1956 (D1,D3,	1956	kras	2011-5-3	Taxotere	6	2.1	62%	0.45	0.05
#1957 (neg)	1957	kras	2011-5-2	(Baseline)	0	0.65	(Baseline)	0.32	0.023
#1957	1957	kras	2011-5-3	(Baseline)	0	0.79	(Baseline)	0.51	0.036
#1957(D1,D3)	1957	kras	2011-5-24	AZD	0	1.1	(Baseline)	0.54	0.023
#1957(D1,D3)	1957	kras	2011-5-25	AZD	1	0.44	-60%	0.33	0.026
#1957(D1,D3)	1957	kras	2011-5-27	AZD	3	0.45	-59%	0.29	0.018
#1959 (neg)	1959	kras	2011-5-2	(Baseline)	0		(Baseline)		
#1959	1959	kras	2011-5-3	(Baseline)	0		(Baseline)		
KR59	1960	kras	2011-4-26	Taxotere+AZD	0	1.9	(Baseline)	0.376	0.022
KR59	1960	kras	2011-4-27	Taxotere+AZD	1	0.8	-58%	0.5	0.04
KR59	1960	kras	2011-4-29	Taxotere+AZD	3	0.7	-63%	0.45	0.022
KR#1975 (D1,D3,	1975	kras	2011-4-26	Taxotere	0	1.2	(Baseline)	0.47	0.019
KR#1975 (D1,D3,	1975	kras	2011-4-27	Taxotere	1	1.6	33%	0.38	0.025
KR#1975 (D1,D3,	1975	kras	2011-4-29	Taxotere	3	1.8	50%	0.35	0.04
KR#1975 (D1,D3,	1975	kras	2011-5-3	Taxotere	7	1.7	42%	0.35	0.026

KR#1975 (D1,D3,	1975 kras	2011-5-13	Taxotere	17	1.5	25%	0.3	0.034
KN1150#3203 (D	3203 p53	2011-4-18	Taxotere	0	2.3	(Baseline)	0.52	0.032
KN1150#3203 (D	3203 p53	2011-4-19	Taxotere	1	2.6	13%	0.55	0.026
KN1150#3203 (D	3203 p53	2011-4-21	Taxotere	3	2.6	13%	0.53	0.027
KN1150#3203 (D	3203 p53	2011-5-12	AZD	0	5.1	(Baseline)	0.65	0.058
KN1150#3203 (D	3203 p53	2011-5-13	AZD	1	3.2	-37%	0.64	0.05
KN1150#3211 (D	3211 p53	2011-4-18	Taxotere	0	0.78	(Baseline)	0.33	0.0316
KN1150#3211 (D	3211 p53	2011-4-19	Taxotere	1	1	28%	0.496	0.029
KN1150#3211 (D	3211 p53	2011-4-21	Taxotere	3	0.93	19%	0.43	0.037
KN1146#3284	3284 p53	2011-4-18	Taxotere+AZD	0	6	(Baseline)	0.6	0.038
KN1146#3284 (D	3284 p53	2011-4-19	Taxotere+AZD	1	3	-50%	0.43	0.037
KN1146#3284 (D	3284 p53	2011-4-21	Taxotere+AZD	3	2.3	-62%	0.36	0.046
KN1146#3284 (D	3284 p53	2011-5-12	BKM+AZD	0	2.8	(Baseline)	0.46	0.04
KN1146#3284 (D	3284 p53	2011-5-13	BKM+AZD	1	1.1	-61%	0.23	0.028
KN1150#3286 (D	3286 p53	2011-4-18	AZD	0	0.5	(Baseline)	0.21	0.014
KN1150#3286 (D	3286 p53	2011-4-19	AZD	1	0.6	0%	0.053	0.023
KN1150#3286 (D	3286 p53	2011-4-21	AZD	3	0.4	0%	0.39	0.019
KN1146#3305 (D	3305 p53	2011-4-18	Taxotere+AZD	0	1.8	(Baseline)	0.31	0.019
KN1146#3305 (D	3305 p53	2011-4-19	Taxotere+AZD	1	1	-44%	0.4	0.02
KN1146#3305 (D	3305 p53	2011-4-21	Taxotere+AZD	3	0.87	-52%	0.43	0.0255
#3313 (D1, D3)	3313 p53	2011-5-19	AZD	0	0.92	(Baseline)	0.35	0.026
#3313 (D1, D3)	3313 p53	2011-5-20	AZD	1	1	0%	0.556	0.031
#3313 (D1, D3)	3313 p53	2011-5-23	AZD	3	1	0%	0.33	0.028
#3314 (neg)	3314 p53	2011-5-19	(Baseline)	0		(Baseline)		
#3318 (D1, D2)	3318 p53	2011-5-25	AZD	0	1.8	(Baseline)	0.34	0.046
#3318 (D1, D2)	3318 p53	2011-5-26	AZD	1	1.5	-17%	0.32	0.026
#3318 (D1, D2)	3318 p53	2011-5-27	AZD	2	1.6	-11%	0.38	0.023
#3318 (D1, D2)	3318 p53	2011-5-31	AZD	6	2	11%	0.34	0.03
#3318 (D1, D2)	3318 p53	2011-5-31	AZD	6	2.1	17%	0.49	0.02
#3320 (D1, D2)	3320 p53	2011-5-25	AZD	0	1	(Baseline)	0.2	0.022
#3320 (D1, D2)	3320 p53	2011-5-26	AZD	1	0.3	-70%	0.13	0.014
#3320 (D1, D2)	3320 p53	2011-5-27	AZD	2	0.74	-26%	0.35	0.025
#3320 (D6)	3320 p53	2011-5-31	AZD	6	0.9	-10%	0.26	0.0186
#3321 (neg)	3321 p53	2011-5-19	(Baseline)	0		(Baseline)		
#3323 (D1, D4)	3323 p53	2011-5-19	Taxotere	0	0.94	(Baseline)	0.39	0.023
#3323 (D1, D4)	3323 p53	2011-5-20	Taxotere	1	1	6%	0.457	0.0286
#3323 (D1, D4)	3323 p53	2011-5-23	Taxotere	4	0.52	-45%	0.29	0.016
KN1152	3326 p53	2011-5-31	AZD	0	1.4	(Baseline)	0.485	0.028
KN1152	3326 p53	2011-6-1	AZD	1	1	-29%	0.45	0.0186
KN1152	3326 p53	2011-6-3	AZD	3	0.88	-37%	0.46	0.026
KN1152	3328 p53	2011-5-31	Taxotere+AZD	0	3.9	(Baseline)	0.493	0.021
KN1152	3328 p53	2011-6-1	Taxotere+AZD	1	2.1	-46%	0.4	0.018
KN1152	3328 p53	2011-6-3	Taxotere+AZD	3	4.3	10%	0.42	0.04
#3329	3329 p53	2011-5-10	(Baseline)	0	0.73	(Baseline)	0.4	0.023
KN1152	3329 p53	2011-5-31	Taxotere	0	1.7	(Baseline)	0.4	0.018
KN1152	3329 p53	2011-6-1	Taxotere	1	1.9	12%	0.32	0.018
KLM#6358	6358 kras	2011-5-2	(Baseline)	0		(Baseline)		
KN1152	3328 p53	2011-6-7	Taxotere+AZD	7	4.4	13%	0.36	0.014
KLM#6359 (D1,D	6359 kras	2011-5-2	Taxotere+AZD	0	1.6	(Baseline)	0.46	0.021
KLM#6359 (D1,D	6359 kras	2011-5-3	Taxotere+AZD	1	1.2	-25%	0.62	0.03
KLM#6359 (D1,D	6359 kras	2011-5-18	AZD	0	1.4	(Baseline)	0.34	0.03
KLM#6359 (D1,D	6359 kras	2011-5-19	AZD	1	1.3	-7%	0.42	0.023
KLM#6359 (D1,D	6359 kras	2011-5-5	Taxotere+AZD	3	1	-29%	0.55	0.028
KLM#6359 (D1,D	6359 kras	2011-5-23	Taxotere+AZD	0	1.8	(Baseline)	0.49	0.038
#6368 (neg)	6368 kras	2011-4-26	(Baseline)	0	0.6	(Baseline)	0.27	0.204
#6368 (D1,D3)	6368 kras	2011-5-24	AZD	0	1.1	(Baseline)	0.44	0.034
#6368 (D1,D3)	6368 kras	2011-5-25	AZD	1	1	-9%	0.39	0.027
#6368 (D1,D3)	6368 kras	2011-5-27	AZD	3	1.1	0%	0.46	0.014
KLM#6369 (D1,D	6369 kras	2011-4-26	Taxotere	0	0.76	(Baseline)	0.4	0.018
KLM#6369 (D1,D	6369 kras	2011-4-27	Taxotere	1	1.2	0%	0.49	0.026
KLM#6369 (D1,D	6369 kras	2011-4-29	Taxotere	3	1.2	0%	0.48	0.034
KLM#6369 (D1,D	6369 kras	2011-5-3	Taxotere	7	1.4	0%	0.54	0.028
KLM#6369 (D1,D	6369 kras	2011-5-13	Taxotere	17	1.2	0%	0.58	0.021
#6529 (neg)	6529 lkb	2011-5-17	(Baseline)	0	0.54	(Baseline)	0.3	0.02
#6531 (D1, D2, …	6531 lkb	2011-5-25	AZD	0	0.98	(Baseline)	0.18	0.023
#6531 (D1, D2, …	6531 lkb	2011-5-26	AZD	1	1	0	0.23	0.023
#6531 (D1, D2, …	6531 lkb	2011-5-27	AZD	2	0.7	?	0.15	0.014
#6532 (D1, D3, …	6532 lkb	2011-5-17	AZD	0	1.5	(Baseline)	0.61	0.026
#6532 (D1, D3, …	6532 lkb	2011-5-18	AZD	1	1	-33%	0.65	0.04

#6532 (D1, D3, …	6532 lkb	2011-5-20	AZD	3	1.2	-20%	0.72	0.04
KLM#6359 (D1,D2	6359 kras	2011-5-24	Taxotere+AZD	1	0.6	-50%	0.39	0.026
#6533	6533 lkb	2011-5-17	Taxotere+AZD	0	1.5	(Baseline)	0.39	0.026
#6535 (D1, D2, …	6535 lkb	2011-5-25	AZD	0	2.9	(Baseline)	0.2	0.025
#6535 (D1, D2, …	6535 lkb	2011-5-26	AZD	1	1.5	-48%	0.22	0.019
#6535 (D1, D2, …	6535 lkb	2011-5-27	AZD	2	1.4	-52%	0.23	0.016
KN1152	3326 p53	2011-6-7	AZD	7	1	-29%	0.47	0.019
#6533	6533 lkb	2011-5-18	Taxotere+AZD	1	1.2	-20%	0.65	0.04

Supplementary Table 6. Mice used in pharmacodynamic studies

Mouse	Genotype	Treatment	Sex	DOB	Adeno-Cre	Age at Adeno-Cre(weeks)	Treatment Start Date	Induction Length at treatment start(weeks)	Pathology
MKL512	Kras/Lkb1	WT	M	2005-8-19	2005-10-28	10.0	N/D	N/D	Adenocarcinoma, poor differentiation with squamous component
MKL515	Kras/Lkb1	WT	M	2005-8-19	2005-10-28	10.0	N/D	N/D	Mixed adeno/squamous carcinoma
KL6348	Kras/Lkb1	WT	M	2010-10-22	2010-11-30	5.6	2011-1-19	7.1	Mixed adeno/squamous carcinoma
KL6350	Kras/Lkb1	D	M	2010-10-22	2010-11-30	5.6	2011-1-19	7.1	Adenocarcinoma, poor differentiation with squamous component
KL6053	Kras/Lkb1	D	F	2010-5-3	2010-6-24	7.4	2010-8-21	8.3	Mixed adeno/squamous carcinoma
KL6047	Kras/Lkb1	DS	F	2010-5-3	2010-6-24	7.4	2010-8-21	8.3	Adenocarcinoma, poor differentiation with squamous component
KR6193	Kras	WT	M	2010-6-19	2010-8-3	6.4	2010-12-2	17.3	Adenocarcinoma
KR15	Kras	DS	M	2010-6-28	2010-8-11	6.3	2010-12-2	16.1	Adenocarcinoma
KR09	Kras	DS	M	2010-6-28	2010-8-11	6.3	2010-12-2	16.1	Adenocarcinoma
KR10	Kras	D	F	2010-6-28	2010-8-11	6.3	2010-12-2	16.1	Adenocarcinoma
KR12	Kras	D	M	2010-6-28	2010-8-11	6.3	2010-12-2	16.1	Adenocarcinoma
KN2182	Kras/p53	WT	M	2009-3-29	2009-5-14	6.6	2009-8-10	12.6	Adenocarcinoma , poor differentiation
KN2261	Kras/p53	WT	M	2009-5-10	2009-6-24	6.4	2009-9-1	9.9	Adenocarcinoma , poor differentiation
KN2256	Kras/p53	D	M	2009-5-10	2009-6-24	6.4	2009-9-1	9.9	Adenocarcinoma , poor differentiation
KN2259	Kras/p53	D	M	2009-5-10	2009-6-24	6.4	2009-9-1	9.9	Adenocarcinoma , poor differentiation
KN2247	Kras/p53	DS	M	2009-5-10	2009-6-24	6.4	2009-9-1	9.9	Adenocarcinoma , poor differentiation
KN2567	Kras/p53	DS	F	2009-9-15	2009-11-5	7.3	2010-1-7	9.0	Adenocarcinoma , poor differentiation

Supplementary Table 7. DFCI Patient Information

	Sex	Race	Smoking History, pack-years	Histology	Biopsy Site	Status of biosied lesion at time of Bx	KRAS mutation Status	LKB1 Staining	PET SUVmax
1	F	White	15	NSCLC NOS	Lung	Untreated, growing	G12V	Negative	8.83
2	F	White	24	Adenocarcinoma	Lung	On chemo, responding	G12A	Negative	7.51
3	M	White	40	Adenosquamous	Lung	Untreated, growing	G12D	Negative	4.6
4	M	White	71	Adenocarcinoma	LN	Untreated, growing	G12A	Negative	18.7
5	F	White	35	NSCLC NOS	LN	Untreated, growing	G12C	Negative	6.49
6	F	White	3	Adenocarcinoma	Lung	Untreated, growing	G12D	Negative	6.34
7	F	White	74	Adenocarcinoma	Lung	Untreated, growing	G12V	Positive	0.38
8	F	Asian	0	Adenocarcinoma	Lung	Untreated, growing	G12V	Positive	0.41
9	F	White	30	Adenocarcinoma	Liver	On chemo, growing	G12C	Positive	6.2

Supplementary Table 8. UNC Patients Information

KWong_pERK_Project_Identifier	LKB1 Status	KRAS Status	TP53 Status	AgeatDiagnosis	Race	Sex	CancerType	TumorHistology	Grade	SourceCancer	FinalStage
KW_pERK_01	mutation	mutation	no mutation	53.78	White	Female	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IA
KW_pERK_02	mutation	mutation	no mutation	81.75	White	Male	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IB
KW_pERK_03	mutation	no mutation	mutation	79.81	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IIB
KW_pERK_04	mutation	no mutation	no mutation	63.75	White	Male	Non-small cell lung cancer	Adenosquamous Carcinoma	Moderately differentiated	Primary	IA
KW_pERK_05	no mutation	mutation	mutation	67.19	White	Male	Non-small cell lung cancer	Large Cell Carcinoma	Poorly differentiated	Primary	IA
KW_pERK_06	no mutation	mutation	mutation	57.27	White	Female	Non-small cell lung cancer	Adenocarcinoma	Poorly differentiated	Primary	IB
KW_pERK_07	no mutation	mutation	mutation	74.42	White	Male	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IB
KW_pERK_08	no mutation	mutation	no mutation	63.59	White	Male	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IIA
KW_pERK_09	no mutation	mutation	no mutation	41.93	White	Female	Non-small cell lung cancer	Adenosquamous Carcinoma	Not evaluated	Primary	IB
KW_pERK_10	no mutation	no mutation	mutation	73.36	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IB
KW_pERK_11	no mutation	no mutation	mutation	73.94	White	Male	Non-small cell lung cancer	Adenosquamous Carcinoma	Moderately differentiated	Primary	IB
KW_pERK_12	no mutation	no mutation	mutation	41.05	Black	Female	Non-small cell lung cancer	Squamous Cell Carcinoma	Poorly differentiated	Primary	IB
KW_pERK_13	no mutation	no mutation	mutation	63.05	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IIB
KW_pERK_14	no mutation	no mutation	mutation	81.16	White	Female	Non-small cell lung cancer	Squamous Cell Carcinoma	Poorly differentiated	Primary	IB
KW_pERK_15	no mutation	no mutation	mutation	48.46	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IIB
KW_pERK_16	no mutation	no mutation	mutation	74.74	White	Female	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IB
KW_pERK_17	no mutation	no mutation	mutation	64.52	White	Male	Non-small cell lung cancer	Adenosquamous Carcinoma	Poorly differentiated	Primary	IIB
KW_pERK_18	no mutation	no mutation	mutation	79.82	White	Male	Non-small cell lung cancer	Large Cell Carcinoma	Poorly differentiated	Primary	IIB
KW_pERK_19	no mutation	no mutation	mutation	55.49	Black	Male	Non-small cell lung cancer	Large Cell Carcinoma	Poorly differentiated	Primary	IB
KW_pERK_20	no mutation	no mutation	mutation	64.11	White	Female	Non-small cell lung cancer	Adenocarcinoma	Poorly differentiated	Primary	IA
KW_pERK_21	no mutation	no mutation	mutation	75.80	White	Female	Non-small cell lung cancer	Adenocarcinoma	Poorly differentiated	Primary	IB
KW_pERK_22	no mutation	no mutation	mutation	72.67	White	Female	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IA
KW_pERK_23	no mutation	no mutation	mutation	64.89	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Poorly differentiated	Primary	IB
KW_pERK_24	no mutation	no mutation	mutation	69.52	White	Male	Non-small cell lung cancer	Adenosquamous Carcinoma	Poorly differentiated	Primary	IA
KW_pERK_25	no mutation	no mutation	no mutation	41.29	White	Female	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IIB
KW_pERK_26	no mutation	no mutation	no mutation	63.11	Black	Male	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IIIA
KW_pERK_27	no mutation	no mutation	no mutation	61.27	White	Female	Non-small cell lung cancer	Large Cell Carcinoma	Poorly differentiated	Primary	IIB
KW_pERK_28	no mutation	no mutation	no mutation	72.99	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IB
KW_pERK_29	no mutation	no mutation	no mutation	83.13	White	Female	Non-small cell lung cancer	Squamous Cell Carcinoma	Poorly differentiated	Primary	IIB
KW_pERK_30	no mutation	no mutation	no mutation	59.45	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Poorly differentiated	Primary	IIB
KW_pERK_31	no mutation	no mutation	no mutation	66.78	White	Female	Non-small cell lung cancer	Adenocarcinoma	Poorly differentiated	Primary	IA
KW_pERK_32	no mutation	no mutation	no mutation	61.87	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Poorly differentiated	Primary	IIB
KW_pERK_33	no mutation	no mutation	no mutation	81.04	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IIB
KW_pERK_34	no mutation	no mutation	no mutation	76.98	White	Male	Non-small cell lung cancer	Adenocarcinoma	Poorly differentiated	Primary	IIIA
KW_pERK_35	no mutation	no mutation	no mutation	52.15	White	Female	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IA
KW_pERK_36	no mutation	no mutation	no mutation	67.66	Asian	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IB
KW_pERK_37	no mutation	no mutation	no mutation	75.26	White	Female	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IA
KW_pERK_38	no mutation	no mutation	no mutation	54.98	Black	Male	Non-small cell lung cancer	Large Cell Carcinoma	Poorly differentiated	Primary	IIB
KW_pERK_39	no mutation	no mutation	no mutation	66.41	White	Female	Non-small cell lung cancer	Adenocarcinoma	Poorly differentiated	Primary	IB
KW_pERK_40	no mutation	no mutation	no mutation	65.12	White	Male	Non-small cell lung cancer	Adenosquamous Carcinoma	Poorly differentiated	Primary	IA
KW_pERK_41	no mutation	no mutation	no mutation	73.50	White	Female	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IIIA
KW_pERK_42	no mutation	no mutation	no mutation	68.17	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IIIA
KW_pERK_43	no mutation	no mutation	no mutation	49.41	White	Male	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IB
KW_pERK_44	no mutation	no mutation	no mutation	64.23	White	Male	Non-small cell lung cancer	Adenosquamous Carcinoma	Moderately differentiated	Primary	IB
KW_pERK_45	no mutation	no mutation	no mutation	86.33	White	Female	Non-small cell lung cancer	Large Cell Carcinoma	Poorly differentiated	Primary	IV
KW_pERK_46	no mutation	no mutation	no mutation	75.57	White	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Poorly differentiated	Primary	IB
KW_pERK_47	no mutation	no mutation	no mutation	60.96	White	Female	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IB
KW_pERK_48	no mutation	no mutation	no mutation	77.72	White	Female	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IA
KW_pERK_49	no mutation	no mutation	no mutation	66.68	White	Male	Non-small cell lung cancer	Adenocarcinoma	Poorly differentiated	Primary	IIIA
KW_pERK_50	no mutation	no mutation	no mutation	70.62	Black	Male	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IB
KW_pERK_51	no mutation	no mutation	no mutation	47.05	Asian	Female	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IB
KW_pERK_52	no mutation	no mutation	no mutation	59.53	White	Female	Non-small cell lung cancer	Adenosquamous Carcinoma	Poorly differentiated	Primary	IIIA
KW_pERK_53	no mutation	no mutation	no mutation	48.79	Black	Male	Non-small cell lung cancer	Large Cell Carcinoma	Poorly differentiated	Primary	IIB
KW_pERK_54	no mutation	no mutation	no mutation	49.02	Black	Male	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IV
KW_pERK_55	no mutation	no mutation	no mutation	57.59	White	Male	Non-small cell lung cancer	Adenocarcinoma	Poorly differentiated	Primary	IA
KW_pERK_56	no mutation	no mutation	no mutation	78.36	White	Female	Non-small cell lung cancer	Adenocarcinoma	Moderately differentiated	Primary	IB
KW_pERK_57	no mutation	no mutation	no mutation	58.17	White	Female	Non-small cell lung cancer	Squamous Cell Carcinoma	Moderately differentiated	Primary	IB

Methods

Mice: Mouse strains harboring conditional activating mutation (G12D) at the endogenous Kras locus, conditional *Lkb1* knockout, and conditional *p53* knockout were activated by nasal instillation of $5x10^6$ pfu of adenovirus encoded CRE recombinase administered between 6-8 weeks of age under isoflurane anesthesia. Virus was diluted in alpha-MEM and activated by calcium chloride. Kras only mice had a latency of 13-15 weeks after induction. Kras/p53 and Kras/Lkb1 mice had a latency of 8-10 weeks and 6-7 weeks respectively.

MRI quantification: Mouse lung cancer MRI scans were quantified by 3D Slicer software. Threshold intensity was obtained by calculating background intensity for each scan. Potential tumor bearing areas in the scans were selected manually. Potential tumors with higher intensity value than preset threshold intensity were segmented by the software automatically. Reconstruction and calculation of total tumor volume was performed using 3D Slicer.

Therapeutics: Docetaxel was diluted in PBS and administered by IP injection at 15ul/gram body weight. The dosing of the various therapeutics are described in the text. After the initial 2 weeks of treatment with 16mpk of docetaxel every other day, the dose was adjusted to 8 mpk every 3 days thereafter for chronic treatment studies. Selumetinib was resuspended in 0.5% methylcellulose with 0.1% Tween-80, and administered by oral gavage at 20ul/gram body weight.

PET/CT:

For FDG-PET/CT studies, each mouse was fasted overnight (~ 12 to 16 hours) while allowing free access to water. Mice were warmed for at least one hours, then injected with ~ 14 MBq@250uL of ^{18}F-FDG through intraperitoneal administration. Mice were subjected to an one-hour awake uptake period before being anesthetized by inhaling a mixture of sevoflurane and oxygen. Mice were scanned with a low-dose CT acquisition protocol (80 kVp, 0.5 mA, 220 degree rotation, 600 ms/degree exposure time, 80 μm reconstruction pixel size), followed

by a PET data acquisition protocol (350-650 kev energy window, 10 minutes listmode acquisition, 3D rebinning followed by OSEM-MAP reconstruction) on a multi-modality preclinical imaging system (Inveon, Siemens Healthcare). Reconstructed PET/CT images were visualized and analyzed using Inveon Research Workplace (Siemens Healthcare), where lung tumors were identified and quantified by their standardized uptake values (SUVs). The percentage differences of SUV max for the same tumor between the baseline and post-treatment images were then calculated. For human PET/CT images, the maximum standard uptake value (SUVmax) of lung tumors was determined by a thoracic radiologist, who was blinded to the patients' tumor LKB1 or p53 status.

Immunohistochemistry Staining:

Immunohistochemical analyses were performed using standard protocols with the following antibodies: p-ERK, activated caspase-3 (Cell Signaling), and Ki-67 (Dako). Briefly, sections were deparaffinized using Xylene for 30 min and antigen retrieval was performed by boiling in 10 mM sodium citrate with 0.05% Tween-20 for 15 min, or by pressure cooking. Primary antibodies were incubated overnight at 4°C and secondary antibodies for 2 hr at room temperature. Signals were detected using the ABC kit for immunoperoxidase staining (Vector Laboratories). Scoring of the staining was done by our consulting pathologist, using the same parameters used for scoring human specimens.

Pharmacokinetics:

For short-term analysis, tumor bearing mice were treated with one dose of docetaxel on day one. Selumetinib was administered daily (2 doses total). Mice were sacrificed 3 hours after the second dose of selumetinib on day 2. For long-term analysis, the last dose of selumetinib was administered 3 hours before sacrifice. Collected tumor nodules, serum and lung tissues were snapped frozen. All samples were analyzed using an API 4000 Q-Trap^{TM} mass spectrometer interfaced with an Agilent 1200 HPLC. Plasma proteins were removed by addition of 100 µl acetonitrile to 25 µl plasma. Tissue samples were mixed with 10-fold water (10 µl water per mg tissue) and sonicated with a probe tip sonicator to break up the tissue.

After sonication, 25 µl of tissue solution was mixed with 100 µl acetonitrile. Samples were allowed to agitate for approximately ten minutes and centrifuged through a Millipore Multiscreen Solvinter 0.45 micron low binding PTFE hydrophilic filter plate. Concentrations were determined using standard curves prepared in mouse plasma or mouse lung over a concentration of 2 – 2000 ng/ml. Samples outside the linear range of the curve were 20-fold diluted using blank mouse plasma or blank mouse lung homogenate and reanalyzed. Positive ion multiple reaction monitoring MS/MS methods using the peak area of the transition m/z 457→395 (decluster potential=40, collision energy=24) for AZ624 and 808.4→527.4 (decluster potential=40, collision energy=24) for taxotere. Tissue concentrations were corrected for dilution and converted to ng analyte per mg tissue. Assuming a density of 1 mg tissue equals 1 µl allowed the tissue levels to be expressed as µM for easy comparison to plasma values. LC settings are provided in the table below.

LC (Agilent 1200) conditions of AZ624 or Taxotere

Compound	AZ624	Taxotere
Column	Thermo Betasil C18, 50x2.1 mm, 5u	
Mobile phase	A: Water with 0.1% Formic Acid B: Acetonitrile with 0.1% Formic Acid	
Flow rate(ml/min)	0.375	
Temperature(°C)	25	
Injection volume(µl)	10	
Elution time (min)	4.3	4.7

Gradient elution conditions:

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	90	10
0.5	90	10
2.0	5	95
3.0	5	95
4.0	90	10
7.0	90	10

Statistical Analysis:

The statistical analyses of tumor volume changes in Kras, Kras/p53 and Kras/Lkb1 mice after 2 weeks of treatment were performed using the likelihood ratio method to determine significant interactions between treatment and genotype. Our null hypotheses assumed the treatment difference to be zero for mice in the different genotypes. Statistical tests used for other data are as indicated in the text and figure legends.

Western Blotting:

Snap frozen tumor samples were processed using 1 x Lamelli loading buffer with the presence of protease and phosphatase inhibitors. Pre-cast gradient SDS-PAGE gels (Invitrogen) were used and all antibodies were from Cell Signaling Technology Inc., except the GLUT1 antibody, which was from Abcam.