

Characteristics	<i>KEAP1/NFE2L2/CUL3</i>		<i>P</i> -value
	mutant (<i>n</i> = 10)	wild-type (<i>n</i> = 30)	
Age, mean (years)	64	61	0.77
Sex			
Male	3	11	1.0
Female	7	19	
Race			
White	4	13	1.0
Asian	6	17	
Smoking History			
Current	0	0	0.1
Previous	3	10	
Never	7	20	
EGFR mutation			
L858R	6	11	0.11
Exon 19 deletion	2	18	
Other*	2	1	
TKI Therapy			
Erlotinib	7	26	0.57
Osimertinib	2	3	
Other*	1	1	

*Other: exon 21 mutation, exon 20 insertion. +: afatinib, TKI on clinical trial.

Supplementary Table S2. NSCLC cohort generation from the Stanford Solid Tumor Actionable Mutation Panel (STAMP).

Demographic data from the STAMP cases of patients with stage IV non-small cell lung cancer (NSCLC), oncogenic *EGFR* and *TP53* mutations included in the study. Data including sex, age at diagnosis, race, smoking history, type of *EGFR* mutation and TKI therapy are reported. The cohort was matched to a *KEAP1/NFE2L2/CUL3* wild-type cohort and no significant difference was observed based on the matched variables.

	Hazard Ratio	95% CI	<i>P</i> -value
<i>KEAP1</i> mutation	2.6	1.05-6.43	0.04*
Age at diagnosis	1.0	0.97-1.03	0.99
Sex	1.5	0.79-2.65	0.23
Tobacco Use	1.3	0.54-3.11	0.57
Race	0.9	0.41-1.77	0.67

Supplementary Table S3. Impact of confounding variables on time to treatment failure with TKIs.

Even after adjustment for potential confounders such as age, sex, race and smoking status, the multivariate analysis shows that *KEAP1* mutations significantly reduced time on treatment with TKIs. **P*-value is significant after adjustment for potential confounders.

Characteristics	<i>EGFR</i> mutant (<i>n</i> = 29)
Age, mean (years)	59
Sex	
Male	11
Female	18
Race	
Black	2
White	25
Asian	2
Smoking History	
Current	0
Previous	16
Never	13
EGFR mutation	
L858R	12
Exon 19 deletion	15
G719X	2
TKI Therapy	
Erlotinib	26
Gefitinib	1
Afatinib/Cetuximab	2

Supplementary Table S4. NSCLC cohort from the Yale Lung Rebiopsy Program (YLR).

Demographic data from the available YLR cases of patients with stage IV NSCLC and mutant *EGFR* included in the study. Data including sex, age at enrollment, race, smoking history, type of *EGFR* mutation and TKI therapy are reported.

Vectors for Lenti-sgTS ^{Pool} /Cre	sgRNA Sequence	Target Exon [Total # of Exons]	Adjacent to SA/SD	Upstream of Functional Domain [Functional Domain]	References
Lenti-sgApc/Cre	TTGAGCGTAGTTTCACTCCG	Exon 4 [16]	No	Yes [Eb1]	Rogers <i>et al.</i> , 2017
Lenti-sgArid1a/Cre	TATGGGTTAGTCCCACCATA	Exon 2 [20]	No	Yes [ARID]	Rogers <i>et al.</i> , 2017
Lenti-sgAtm/Cre	GCTAAGATGTGACTTAAGCC	Exon 7 [64]	No	Yes [FAT, PI3K/PI4K, FATC]	Rogers <i>et al.</i> , 2017
Lenti-sgCdkn2a/Cre	GCGCTGCGTCGTGCACCGGG	Exon 2 [3]	No	N/A	Rogers <i>et al.</i> , 2017
Lenti-sgKeap1/Cre	CCTGCACGTGATGAACGGGG	Exon 2 [6]	No	Yes [BACK]	Rogers <i>et al.</i> , 2017
Lenti-sgLkb1/Cre	GTGGTGGGCCGCGAGTCACAA	Exon 6 [10]	No	Yes [Protein Kinase]	Rogers <i>et al.</i> , 2017
Lenti-sgp53/Cre	AGGAGCTCCTGACACTCGGA	Exon 4 [8]	No	Yes [DNA-binding, Tetramer]	Rogers <i>et al.</i> , 2017
Lenti-sgRb1/Cre	TCTTACCAGGATTCCATCCA	Exon 2 [26]	No	N/A	Rogers <i>et al.</i> , 2017
Lenti-sgRbm10/Cre	GTATTTCTGAACAGATCCG	Exon 5 [24]	Yes	Yes [RRM1, RRM2, G-Patch]	Rogers <i>et al.</i> , 2017
Lenti-sgSetd2/Cre	TCTCTAATCCATCTTCCCAG	Exon 3 [21]	No	Yes [AWS, SER, Post-SET, WW]	Rogers <i>et al.</i> , 2017
Lenti-sgSmad4/Cre	GGTGGCGTTAGACTCTGCCG	Exon 5 [12]	No	Yes [MH2]	Rogers <i>et al.</i> , 2017
Lenti-sgNeo1/Cre	TCATGGCTGATGCAATGCGG	N/A	N/A	N/A	Rogers <i>et al.</i> , 2017
Lenti-sgNeo2/Cre	GATATTGCTGAAGAGCTTGG	N/A	N/A	N/A	Rogers <i>et al.</i> , 2017
Lenti-sgNeo3/Cre	GAATAGCCTCTCCACCCAAG	N/A	N/A	N/A	Rogers <i>et al.</i> , 2017
Lenti-sgNT/Cre	GCGAGGTATTCGGCTCCGCG	N/A	N/A	N/A	Rogers <i>et al.</i> , 2017

Supplementary Table S5. List of sgRNAs targeting candidate tumor suppressor genes.

Vectors designed to initiate tumors with Lenti-TS^{Pool}/Cre virus. All vectors were published in Rogers *et al.*, 2017.

Vectors for Lenti-sgTS/Cre	sgRNA Sequence	Target Exon [Total # of Exons]	Adjacent to SA/SD	Upstream of Functional Domain [Functional Domain]	References
Lenti-sgApc/Cre	TTGAGCGTAGTTTCACTCCG	Exon 4 [16]	No	Yes [Eb1]	Rogers <i>et al.</i> , 2017
Lenti-sgRbm10/Cre	GTATTTCTGAACAGATCCG	Exon 5 [24]	Yes	Yes [RRM1, RRM2, G-Patch]	Rogers <i>et al.</i> , 2017
Lenti-sgRbm10#2/Cre	CTGTCTCCAGGTCAGAGCCG	Exon 6 [24]	No	Yes [RRM1, RRM2, G-Patch]	Rogers <i>et al.</i> , 2017
Lenti-sgKeap1/Cre	CCTGCACGTGATGAACGGGG	Exon 2 [6]	No	Yes [BACK]	Rogers <i>et al.</i> , 2017
Lenti-sgNeo2/Cre	GATATTGCTGAAGAGCTTGG	N/A	N/A	N/A	Rogers <i>et al.</i> , 2017

Supplementary Table S6. List of sgRNAs used to validate the role of tumor suppressor gene inactivation on tumor growth and therapeutic sensitivity.

Vectors designed to initiate tumors with individual Lenti-sgTS/Cre virus.