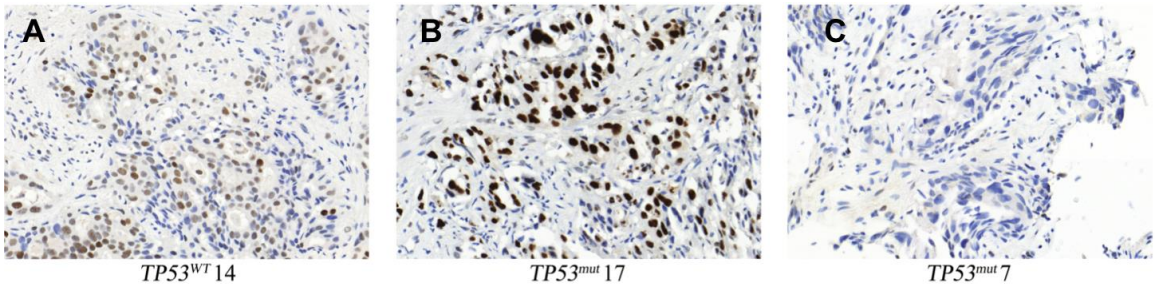

Figure S1. Three immunohistochemical staining patterns of p53 in *ALK*+ patients *TP53*^{WT} 14, *TP53*^{mut} 17, and *TP53*^{mut} 7. (A) Pattern suggestive of a wild-type *TP53* gene showing patchy positivity in some tumour cell nuclei and negativity in others. (B) Pattern suggestive of a missense mutation resulting in a non-functional protein accumulating in the tumour cell nuclei. (C) Pattern suggestive of a truncating mutation resulting in the complete loss of the protein in the tumour cell nuclei. Images were taken at 400 × original magnification.

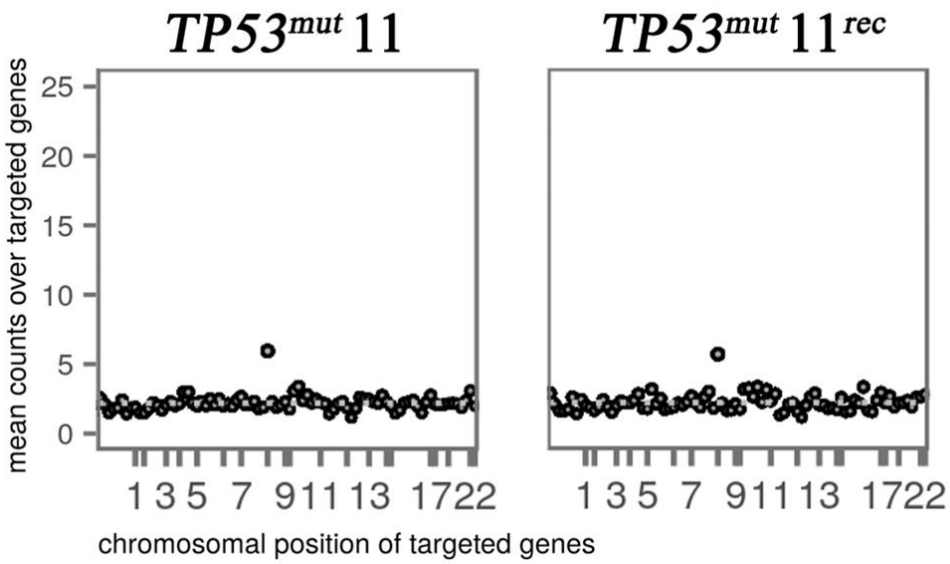

Figure S2. Copy number plots of primary tumour (*TP53*^{mut} 11, left) and local recurrence (*TP53*^{mut} 11^{rec}, right) of the same *ALK+/TP53*^{mut} patient. Copy numbers of 87 genes were determined by means of NanoString nCounter technology. Absolute copy numbers (*Y*-axis) for each gene are plotted according to their chromosomal location (*X*-axis). rec = recurrence.

Gene	Early	CI 90%	Late	CI 90%
APC	0.43	(0.1–1)	0.64	(0–0.95)
ATM	1.00	(1–1)	0.00	(0–0)
CDKN2A	1.00	(0.05–1)	0.00	(0–0.98)
EGFR	1.00	(0.71–1)	0.00	(0–0.36)
EPHA3	0.14	(0–1)	0.89	(0–1)
EPHA5	0.13	(0–1)	0.92	(0.55–1)
EPHA7	0.12	(0–1)	0.91	(0–1)
ERBB4	0.12	(0.02–0.35)	0.90	(0.68–0.99)
FGFR4	0.10	(0–0.4)	0.93	(0.67–1)
INHBA	0.39	(0–1)	0.63	(0–1)
KDR	0.04	(0–1)	0.97	(0–1)
KRAS	1.00	(0.57–1)	0.00	(0–0.62)
LRP1B	0.27	(0.06–1)	0.79	(0–0.97)
LTK	0.05	(0–1)	0.97	(0–1)
MYO3B	0.22	(0–1)	0.79	(0–1)
NF1	0.19	(0.04–0.4)	0.90	(0.76–0.99)
NRAS	1.00	(0–1)	0.00	(0–1)
NTRK1	0.17	(0.04–1)	0.88	(0–0.98)
NTRK2	0.27	(0–1)	0.76	(0–1)
NTRK3	1.00	(0.11–1)	0.00	(0–0.92)
PAK3	0.06	(0–1)	0.95	(0–1)
PTEN	1.00	(0.22–1)	0.00	(0–0.81)
PTPRD	0.65	(0.12–1)	0.39	(0–0.92)
RB1	0.09	(0–1)	0.96	(0–1)
STK11	1.00	(1–1)	0.00	(0–0.32)
TFDP1	1.00	(1–1)	0.00	(0–0.91)
TP53	0.89	(0.68–1)	0.27	(0–0.66)
ZMYND10	1.00	(1–1)	0.00	(0–0)

Figure S3. *TP53* mutation is an early event during tumourigenesis in *ALK*-driven tumours. The *TP53* mutation was estimated to be an early event (i.e. one of the first three mutations to occur) with a probability of 89%, given a 90% confidence interval (CI) ranging from 68% to 100% (penultimate line).

Table S1. NGS results from the *EML4–ALK*-translocated cell line H2888, sequenced using gene panels comprising lung cancer relevant genes

Gene	Exon	Mutation status
AKT1	4	wild type
ALK	21–25	wild type
BRAF	11, 15	wild type
CTNNB1	3	wild type
DDR2	3–18	wild type
EGFR	18, 19, 21	wild type
EGFR	20	wild type
ERBB2	19, 20	wild type
KRAS	2, 3	wild type
MAP2K1	2	wild type
MET	14	wild type
NRAS	2, 3	wild type
PIK3CA	9, 20	wild type
PTEN	1–8	wild type
TP53	5–8	wild type

Table S2. NGS results from the *EML4–ALK*-translocated cell line H3122, sequenced using gene panels comprising lung cancer relevant genes

Gene	Exon	Mutation status	Freq. %	Function of mutation
AKT1	4	wild type		
ALK	21–25	wild type		
BRAF	11, 15	wild type		
CTNNB1	3	wild type		
DDR2	3–18	wild type		
EGFR	18, 19, 21	wild type		
EGFR	20	wild type		
ERBB2	19, 20	wild type		
KRAS	2, 3	wild type		
MAP2K1	2	wild type		
MET	14	wild type		
NRAS	2, 3	wild type		
PIK3CA	10, 21	wild type		
PTEN	1–8	wild type		
TP53	5–8	EX8: c.854A>T p.E285V	99.39	non-functional protein*

*http://p53.iarc.fr/TP53GeneVariations.aspx

Table S3. NGS results from the *EML4–ALK*-translocated cell line A549$^{EML4–ALK}$, sequenced using gene panels comprising lung cancer relevant genes

Gene	Exon	Mutation status	Freq. %	Function of mutation
AKT1	4	wild type		
ALK	21–25	wild type		
BRAF	11, 15	wild type		
CTNNB1	3	wild type		
DDR2	3–18	wild type		
EGFR	18, 19, 21	wild type		
EGFR	20	wild type		
ERBB2	19, 20	wild type		
KRAS	2, 3	EX2: c.34G>A p.G12S	99.39	Activating*
MAP2K1	2	wild type		
MET	14	wild type		
NRAS	2, 3	wild type		
PIK3CA	10, 21	wild type		
PTEN	1–8	wild type		
TP53	5–8	wild type		

*http://oncokb.org

Table S4. Characteristics of patients (*TP53*^{WT})

Patient	Age	Sex	Translocation partner	Tumour cells harbouring *ALK* translocation (%)	p53 immunohistochemical staining pattern
TP53^{WT} 1	35	M	*EML4*	90	–
TP53^{WT} 2	60	F	*EML4*	80	–
TP53^{WT} 3	86	M	unknown	88	–
TP53^{WT} 4	71	F	unknown	80	WT
TP53^{WT} 5	32	M	*EML4*	100	–
TP53^{WT} 6	51	M	*EML4*	78	WT
TP53^{WT} 7	88	F	unknown	36	WT
TP53^{WT} 8	76	F	*EML4*	66	–
TP53^{WT} 9	44	M	*EML4*	85	WT
TP53^{WT} 10	76	F	*EML4*	35	WT
TP53^{WT} 11	73	M	*EML4*	81	WT
TP53^{WT} 12	74	F	*EML4*	24	–
TP53^{WT} 13	50	M	*EML4*	80	WT
TP53^{WT} 14	43	F	*EML4*	90	WT
TP53^{WT} 15	71	M	*EML4*	55	WT
TP53^{WT} 16	80	F	*EML4*	52	WT
TP53^{WT} 17	30	M	*EML4*	85	–
TP53^{WT} 18	38	F	*EML4*	51	WT
TP53^{WT} 19	69	F	*EML4*	27	WT
TP53^{WT} 20	54	M	*EML4*	84	WT
TP53^{WT} 21	56	F	*EML4*	30	WT
TP53^{WT} 22	73	M	*EML4*	62	WT
TP53^{WT} 23	30	F	*EML4*	98	–
TP53^{WT} 24	70	F	*EML4*	85	–
TP53^{WT} 25	75	M	*EML4*	90	–
TP53^{WT} 26	72	F	*EML4*	50	WT
TP53^{WT} 27	47	F	*EML4*	48	–
TP53^{WT} 28	69	F	*EML4*	78	–
TP53^{WT} 29	73	F	*EML4*	65	WT
TP53^{WT} 30	56	M	*EML4*	70	–
TP53^{WT} 31	53	M	*EML4*	88	–
TP53^{WT} 32	51	F	*EML4*	22	WT

– = patient material not available.

Table S5. Characteristics of patients (*TP53*^{mut})

Patient	Age	Sex	Trans-location partner	Tumour cells harbouring *ALK* translocation (%)	Type of *TP53* mutation	Function of *TP53* mutation	p53 immunohistochemical staining pattern
TP53^{mut} 1	28	M	*EML4*	43	EX6: c.586C>T p.R196*	truncated protein	–
TP53^{mut} 2	60	M	*EML4*	100	EX5: c.486_493del p.Y163Vfs*15 EX7: c.701A>G p.Y234C	truncated protein non-functional protein*	–
TP53^{mut} 3	49	M	*EML4*	91	EX8: c.856G>A p.E286K	non-functional protein*	overexpressed
TP53^{mut} 4	50	M	unknown	25	EX8: c.844C>T p.R282W	non-functional protein*	overexpressed
TP53^{mut} 5	82	F	*EML4*	100	EX5: c.396G>T p.K132N	non-functional protein*	–
TP53^{mut} 6	59	M	unknown	52	EX6: c.584T>C p.I195T	non-functional protein*	overexpressed
TP53^{mut} 7	37	M	*EML4*	90	EX6: c.586C>T p.R196*	truncated protein	loss
TP53^{mut} 8	35	M	*EML4*	71	EX5: c.532_533insC p.H178fs*3	truncated protein	–
TP53^{mut} 9	37	M	*EML4*	80	EX7: c.715_716insT p.N239Ifs*25	truncated protein	–
TP53^{mut} 10	58	M	unknown	21	EX8: c.818G>A p.R273H	non-functional protein*	–
TP53^{mut} 11	55	M	*EML4*	55	EX7: c.761T>G p.I254S	non-functional protein*	overexpressed
TP53^{mut} 12	38	F	*EML4*	36	EX5: c.524G>A p.R175H	non-functional protein*	overexpressed
TP53^{mut} 13	73	F	*EML4*	77	EX5: c.455C>G p.P152R	non-functional protein*	overexpressed
TP53^{mut} 14	45	M	*EML4*	80	EX7: c.742C>T p.R248W	non-functional protein*	–
TP53^{mut} 15	52	M	*EML4*	80	EX7: c.715A>G p.N239D	non-functional protein*	–

TP53^{mut} 16	62	F	*EML4*	97	EX6: c.641A>G p.H214R	non-functional protein*	–
TP53^{mut} 17	68	F	unknown	43	EX7: c.743G>A p.R248Q	non-functional protein*	overexpressed
TP53^{mut} 18	53	F	*EML4*	20	EX8: c.817C>T p.R273C	non-functional protein*	–
TP53^{mut} 19	50	M	*EML4*	95	EX6: c.580C>T p.L194F	non-functional protein*	overexpressed
TP53^{mut} 20	59	M	*EML4*	71	EX5: c.423C>G p.C141W	non-functional protein*	overexpressed
TP53^{mut} 21	60	F	*EML4*	32	EX6: c.568C>T p.P190S	non-functional protein*	–

*http://p53.iarc.fr/TP53GeneVariations.aspx

– = patient material not available.