

Figure S1 Study design. Grey areas indicate actual outcome and dose reduction of this study. BID, administered twice daily; DLTs, dose limiting toxicities; RD, recommended dose; MTD, maximum tolerated dose. This figure was from the reference (25).

Table S1 List of patients in phase 1

Cohort (alectinib dose)	Case	Age	Sex	Smoking status	Type of RET fusion	PS	Body weight (kg)	Previous RET-TKI treatment	Previous ICI treatment	No. of previous regimens	DLTs
Cohort 1 (600 mg BID)	S1-1	53	F	Never	KIF5B- RET	0	67	–	–	2	–
	S1-2	64	F	Former	KIF5B- RET	1	45	Vandetanib	–	3	–
	S1-3	47	F	Never	KIF5B- RET	1	60	–	Nivolumab	5	Rash, AST increased
	S1-4	39	F	Never	KIF5B- RET	1	55	–	Nivolumab	8	Erythema multiforme, Thromboembolic event
	S1-5	61	F	Never	KIF5B- RET	1	46	Vandetanib	–	3	–
	S1-6	73	M	Former	Unknown	1	54	–	–	2	CPK Increased
Cohort 2 (450 mg BID)	S1-7	68	F	Never	KIF5B- RET	0	58	–	–	1	–
	S1-8	58	M	Never	KIF5B- RET	0	53	–	–	4	–
	S1-9	75	M	Former	KIF5B- RET	0	63	–	–	2	–

PS, performance status; ICI, immune checkpoint inhibitor; DLTs, dose-limiting toxicities; F, female; M, male.

Table S2 List of patients in phase 2

Case	Age	Sex	Smoking status	Type of RET fusion	ECOG PS	Body weight	Previous RET-TKI treatment	Previous ICI treatment	Number of previous regimens
S2-1	69	M	Former	KIF5B-RET	1	48	-	-	1
S2-2	67	F	Never	Unknown	1	48	-	-	2
S2-3	66	F	Never	KIF5B-RET	1	56	-	-	3
S2-4	47	F	Never	CCDC6-RET	1	59	Vandetanib, lenvatinib	-	5
S2-5	36	M	Never	CCDC6-RET	1	56	-	Avelumab	3
S2-6	61	M	Former	KIF5B-RET	1	87	-	-	1
S2-7	46	M	Former	KIF5B-RET	0	82	-	-	1
S2-8	52	M	Never	Unknown	0	70	-	-	1
S2-9	67	F	Former	CCDC6-RET	0	75	-	-	2
S2-10	33	F	Never	KIF5B-RET	1	54	-	-	1
S2-11	44	M	Former	CCDC6-RET	0	73	Vandetanib, lenvatinib	-	5
S2-12	46	F	Never	KIF5B-RET	0	73	-	-	2
S2-13	54	F	Never	Unknown	1	62	-	-	3
S2-14	30	M	Never	CCDC6-RET	1	65	-	-	3
S2-15	39	F	Never	KIF5B-RET	1	69	-	-	2
S2-16	44	F	Former	CCDC6-RET	0	57	-	-	1
S2-17	78	F	Never	KIF5B-RET	1	52	-	-	2
S2-18	59	F	Never	KIF5B-RET	0	80	-	Nivolumab	3
S2-19	30	M	Former	CCDC6-RET	1	90	-	-	2
S2-20	34	M	Former	KIF5B-RET	0	86	-	Pembrolizumab	2
S2-21	57	F	Former	CCDC6-RET	0	41	Vandetanib	-	4
S2-22	70	F	Never	KIF5B-RET	1	51	-	Pembrolizumab	2
S2-23	53	M	Never	KIF5B-RET	1	63	-	-	3
S2-24	37	F	Never	KIF5B-RET	0	55	-	Nivolumab	3
S2-25	44	M	Never	CCDC6-RET	1	63	-	Nivolumab	5

PS, performance status; ICI, immune checkpoint inhibitor; M, male; F, female.

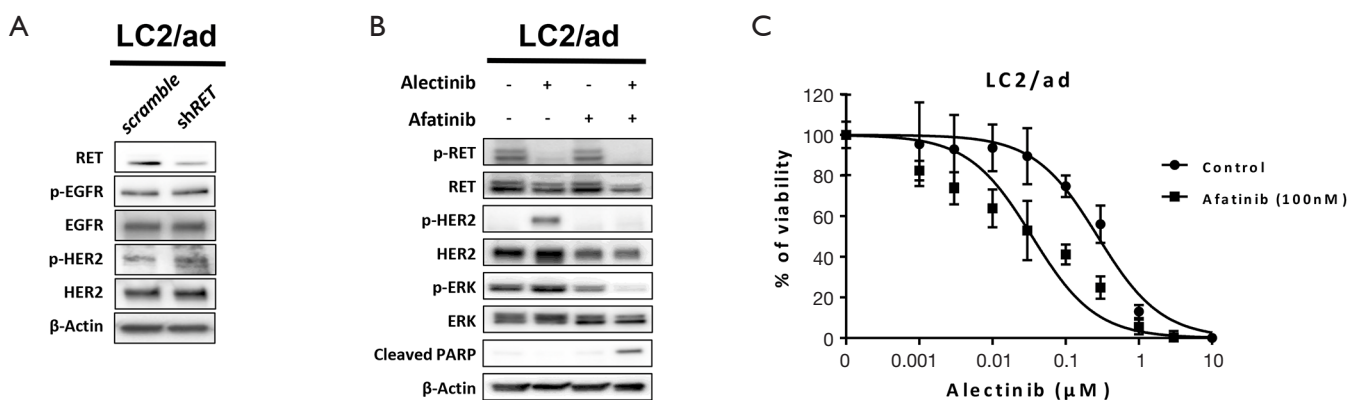


Figure S2 Alectinib exposure induced activation of HER2 in the RET-fusion positive NSCLC cell line LC2/ad. (A) Western blotting of LC2/ad cells treated with shRNA targeting RET. (B) Protein expression by western blotting in LC2/ad cells treated with alectinib (1 μmol/L) and/or afatinib (100 nmol/L) for 72 h. (C) Cell viability determined by MTT assay in LC2/ad cells after 72 h treatment with combination of alectinib and afatinib. Data shown are representative of at least three independent experiments. The data shown are the mean ± SD of triplicate cultures. RET, rearranged during transfection; NSCLC, non-small cell lung cancer.